

OXFORD MEDICAL PUBLICATIONS

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PRICE'S TEXTBOOK  
OF THE  
PRACTICE OF MEDICINE

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OF THE  
PRACTICE OF MEDICINE

BY VARIOUS AUTHORS

EDITED BY  
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# NEW CONTRIBUTIONS

## SECTION II

Tropical Eosinophilia  
Q Fever  
Syphilis  
Gonorrhœa

Non-specific Urethritis  
Chancroid  
Rheumatic Fever

## SECTION IV

Epidemic Dropsy  
Poisoning by Beryllium, Cadmium,  
Chromium, Phosphorus, Methyl  
Alcohol, Barbiturates, Tri-ortho-  
cresyl Phosphate, Dinitro-ortho-  
cresol and Dinitrophenol

Plant Poisons  
Effects of Tobacco  
Corrosive Poisons

## SECTION V

Spontaneous Hypoglycæmia  
Galactosuria

Disorders of Porphyrin Metabolism  
Disturbances of Water and Electrolytes

## SECTION VI

Kwashiorkor  
The Fanconi Syndrome  
Riboflavin Deficiency  
Nicotinamide Deficiency  
Pyridoxine Deficiency

Pantothenic Acid Deficiency  
Protein Deficiency  
Vitamin B<sub>12</sub> (Cyanocobalamin)

## SECTION VII

Phæochromocytoma  
Neuroblastoma

Ganglioneuroma

## SECTION VIII

Halitosis  
Dental Caries  
Hiatus Hernia  
Benign Hypertrophy of the Pylorus  
Duodenal Ileus  
Diverticula of the Stomach and Small  
Intestine

Intestinal Lipodystrophy  
Visceroptosis  
Subacute Appendicitis  
Bile Peritonitis  
Tests of Liver Function  
Marasmus

## SECTION IX

Iron Deficiency Anæmia  
Pernicious Anæmia  
Leukæmia

Hæmolytic Anæmias  
Hæmorrhagic Diseases  
Blood Coagulation

## SECTION X

Hypersplenism  
Thrombosis of the Splenic Vein

Lipoid Deposit Diseases

## SECTION XI

Reticulum Cell Sarcoma

## SECTION XII

Anticoagulant Therapy  
 Cardiac Neurosis  
 Emphysema Heart Disease  
 Cardiac Surgery  
 Massive Pulmonary Embolism  
 Acute Benign Pericarditis  
 Tuberculous Pericarditis  
 Electrocardiography : Unipolar and  
 Routine Chest Leads  
 Angiocardiography

Systemic Arterial Hypertension  
 Essential Hypertension  
 Benign Hypertension  
 Malignant Essential Hypertension  
 Pulmonary Hypertension  
 Postural Hypotension  
 Peripheral Arteriosclerosis  
 Acrocyanosis  
 Lymphatic Obstruction

## SECTION XIII

Acute Laryngo-Tracheo-Bronchitis  
 Minimal Tuberculosis  
 Sarcoidosis  
 Treatment of Tuberculosis  
 Treatment of Pneumonia  
 Treatment of Lung Abscess  
 Treatment of Empyema  
 Silicosis  
 Pneumoconiosis of Coal Miners

Pneumoconiosis due to Sillimanite,  
 Sericite, Mica, Fuller's Earth and  
 Kaolin  
 Asbestosis  
 Aluminosis  
 Pneumoconiosis in Bauxite Smelters  
 The Benign Pneumoconioses  
 Byssinosis  
 Farmer's Lung  
 Bagassosis

## SECTION XIV

Congenital Abnormalities of the Kidney  
 Diabetic Glomerulosclerosis  
 Type I Nephritis

Type II Nephritis  
 Nephrosclerosis without Hypertension  
 Renal Vascular Disease

## SECTION XV

Use in Arthritis of :  
 Corticotrophin  
 Phenylbutazone

Cortisone  
 Hydrocortisone  
 Probenamid

## SECTION XVII

Diseases of the Hair  
 Diseases of the Nails

Diseases of the Lips  
 Diseases of the Mouth

## SECTION XVIII

Abnormalities of the Pupil  
 Recurrent Vertigo  
 Thrombosis of the Internal Carotid  
 Artery  
 Angiomatous Malformations of the  
 Brain  
 The Carpal Tunnel Syndrome

Acroparæsthesia  
 Dysphasia  
 Tuberculous Meningitis  
 Encephalitis Lethargica  
 Inclusion Body Encephalitis  
 Infantile Hemiplegia

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# CONTENTS

## SECTION I

### INFECTION AND ANTI-BACTERIAL AGENTS

Infection	page 1	Sulphonamides	page 17
Antibiotics	6		

## SECTION II

### INFECTIOUS DISEASES

Bacterial	page 30	Protozoal	page 245
Viral	146	Rickettsial	285
Mycotic	193	Of Doubtful Ætiology	304
Spirochætal	202		

## SECTION III

### DISEASES DUE TO METAZOA AND ANIMAL POISONS AND VENOMS

Trematodes	page 316	Injurious Arthropods	page 336
Cestodes	322	Snakes and Poisonous Fishes	340
Nematodes	325		

## SECTION IV

### DISEASES DUE TO CHEMICAL AND PHYSICAL AGENTS

CHEMICAL		CHEMICAL—continued	
Plant Poisons	page 344	Poisoning by Coal-Tar Derivatives	page 388
Effects of Tobacco	346	Poisoning by Halogenated Hydrocarbons	393
Argemone Poisoning (Epidemic Dropsy)	348		
Lathyrism	349	PHYSICAL	
Ackee Poisoning	350	Decompression Sickness	395
Acute Morphine Poisoning	351	Anoxæmia	399
Cocaine Poisoning	352	Travel Sickness	401
Atropine Poisoning	352	Electrical Injuries	403
Alcoholism	353	The Effects of Heat	406
Methyl Alcohol Poisoning	357	Injuries from X-rays	409
Carbon Monoxide Poisoning	357	Injuries from Radioactive Substances	411
Poisoning by Barbiturates	360	Injuries from Fission Products	413
Corrosive Poisons	362		
Metallic Poisons	363		

## SECTION V

### DISEASES OF METABOLISM

Basal Metabolic Rate	page 415	Gout	page 444
Disturbances of Water and Electrolytes	415	Obesity	449
Diabetes Mellitus	422	Lipodystrophia Progressiva	451
Spontaneous Hypoglycæmia	443	The Lipomatoses	452
Hyperinsulinism	443	Glycogen Disease	452
		Disorders of Porphyrin Metabolism	452

## SECTION VI

## DEFICIENCY DISEASES

The Vitamins	<i>page</i> 454	Pellagra	<i>page</i> 472
Scurvy	461	Nutritional Macrocytic Anæmia	475
Infantile Scurvy	463	Protein Deficiency	477
Rickets	465	Kwashiorkor	478
Beriberi	468		

## SECTION VII

## DISEASES OF THE ENDOCRINE GLANDS

The Pituitary Gland	<i>page</i> 483	The Suprarenal Glands	<i>page</i> 506
The Thyroid Gland	491	The Sex Glands	520
The Parathyroid Glands	501		

## SECTION VIII

## DISEASES OF THE DIGESTIVE SYSTEM

The Mouth	<i>page</i> 525	The Intestines	<i>page</i> 599
The Salivary Glands	530	The Liver	658
The Tonsils	533	The Gall-Bladder and Bile-Ducts	689
The Pharynx	538	The Pancreas	700
The Œsophagus	541	The Peritoneum	711
The Stomach	553		

## SECTION IX

## DISEASES OF THE BLOOD

The Blood Volume	<i>page</i> 725	Leucocytosis	<i>page</i> 752
The Red Blood Cells	726	Eosinophilia	753
The Symptomatic Anæmias	729	Lymphocytosis	754
The Deficiency Dyshæmopoietic Anæmias	731	Monocytosis	755
Aplastic Anæmia	738	Basophilia	755
Hæmolytic Anæmia	740	Leucopenia	755
Leuco-Erythroblastic Anæmia	747	Leukæmia	757
Anæmia in Pregnancy	747 *	Blood Coagulation	765
Polycythæmia	749	The Hæmorrhagic Diseases	767

## SECTION X

## DISEASES OF THE SPLEEN AND RETICULO-ENDOTHELIAL SYSTEM

The Spleen	<i>page</i> 777	The Reticulo-Endothelial System	<i>page</i> 783
------------	-----------------	---------------------------------	-----------------

## SECTION XI

## DISEASES OF THE LYMPHATIC SYSTEM

The Thoracic Duct	<i>page</i> 787	Neoplastic Disease	<i>page</i> 788
The Lymphatic Vessels and Glands	787	Hodgkin's Disease	789
Lymphædema	788	Lymphosarcoma	791
		Reticulum Cell Sarcoma	792

## SECTION XII

## DISEASES OF THE CARDIO-VASCULAR SYSTEM

## DISEASES OF THE HEART

General Considerations	page 793
Circulatory Failure	806
Cardiac Arrhythmia	819
Ischæmic Heart Disease	834
Hypertensive Heart Disease	850
Pulmonary Heart Disease	851
Syphilitic Heart Disease	858
Chronic Valvular Disease	862
Diseases of the Pericardium	878
Diseases of the Endocardium	884
Diseases of the Myocardium	890

DISEASES OF THE HEART—*continued*

Congenital Heart Disease	page 893
The Heart in Miscellaneous Con- ditions	900

## DISEASES OF THE BLOOD VESSELS

Hypertension and Hypotension	907
Peripheral Vascular Disease	917
Embolism and Thrombosis	925
Lymphatic Obstruction	928
Arterial Aneurysm	929
Collagen Diseases	930

## SECTION XIII

## DISEASES OF THE RESPIRATORY SYSTEM

The Nose	page 938
The Naso-Pharynx	941
The Larynx	943
The Trachea	954
The Bronchi	963

The Lungs	page 986
The Pleura	1063
The Diaphragm	1087
The Mediastinum	1089

## SECTION XIV

## DISEASES OF THE KIDNEY

The Characters of Normal Urine	page 1098
The Estimation of Renal Function	1100
Abnormalities of the Urinary Secretion	1102
Circulatory Disturbances	1107
Uremia	1108
Bright's Disease	1114
Lardaceous Disease	1131
Pyelitis	1132

Chronic Pyelonephritis	page 1136
Perinephritis and Perinephric Abscess	1137
Tuberculosis of the Kidney	1139
Renal Calculi	1140
Hydronephrosis	1142
Pyonephrosis	1144
Tumours of the Kidney	1144
Cysts of the Kidney	1146
Movable Kidney	1147

## SECTION XV

## DISEASES OF THE JOINTS, FIBROUS TISSUES AND MUSCLES

Arthritis	page 1150
Pseudo-Arthritis	1165

Non-Articular Rheumatism	page 1165
Myositis	1169

## SECTION XVI

## DISEASES OF THE SKELETON

Diseases of the Bone	page 1171
Diseases of the Endochondral Ossification	1182

Diseases of Bone Marrow	page 1184
-------------------------	-----------

## SECTION XVII

## DISEASES OF THE SKIN

Sensory Disorders	page 1189	Dermatoses	page 1270
Secretory Disorders	1198	Chronic Bullous Eruptions	1286
Pigmentary Anomalies	1201	Scleroderma and Allied Condi- tions	1291
Vasomotor Disorders	1205	Atrophy and Hypertrophy	1295
Dermatitis	1209	Degenerative Conditions	1298
Coccal Infections	1224	Epidermal Tumours	1301
Fungous Infections	1232	Tumours of the Dermis	1310
Cutaneous Tuberculosis	1240	Cutaneous Reticuloses	1316
Virus Infections	1246	Diseases of the Hair	1317
Parasitic Infections	1250	Diseases of the Nails	1321
Erythematous Conditions	1254	Diseases of the Lips and Mouth	1324
Drug Eruptions	1265	Tropical Skin Diseases	1327
Erythroderma	1268		

## SECTION XVIII

## DISEASES OF THE NERVOUS SYSTEM

Disorders of the Cranial Nerves	page 1338	Syphilis of the Central Nervous System	page 1454
The Signs of Local Lesions within the Skull and Brain	1357	The Demyelinating Diseases	1472
Aphasia and Other Defects of Speech	1367	Hereditary and Familial Diseases	1479
The Cerebrospinal Fluid	1377	Paroxysmal Disorders of the Central Nervous System	1492
Intracranial Tumours	1380	Disorders Characterised by In- voluntary Movements	1511
Meningitis	1391	Local Lesions of the Spinal Cord	1527
Hydrocephalus	1399	Other Diseases of the Spinal Cord	1545
Encephalitis	1404	Disorders of the Peripheral Nerves	1567
Virus Diseases of the Nervous System	1414	Muscular Diseases	1596
Vascular Disorders of the Nerv- ous System	1435		

## SECTION XIX

## PSYCHOLOGICAL MEDICINE

Introduction	page 1608	Hysteria	page 1669
Classification	1622	Anxiety State	1677
Organic Disorders	1624	Obsessional Disorder	1677
Affective Disorder	1645	Psychopathic Personality	1680
Schizophrenia	1656	Mental Deficiency	1682
Paranoia and Allied States	1668		

## APPENDIX

Histoplasmosis	page i	Toxoplasmosis	page v
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## INDEX

page 1689



## SECTION I

### INFECTION

Of the three main varieties of disease, infective, degenerative and neoplastic, infective is perhaps the commonest. It is certainly of such frequent occurrence and exhibits so much variety that a brief general account of its origins and nature should precede those of its individual manifestations.

Infection is defined as the successful invasion of the tissues by micro-organisms. "Infective" is an adjective applicable to any such process: "infectious", although used by some writers in the same broad sense, is so often used to denote ready communicability that it is better restricted to this meaning. The micro-organisms responsible belong for the most part to the vegetable kingdom (bacteria) although some to the animal (protozoa), and are the smallest and most primitive forms of life known. It may seem strange that man, the most complex and highly developed of creatures, should be subject to attack by those at the other extreme of the scale of development. It appears less so when one remembers that the principal function of bacteria is to cause the decomposition of dead animal and vegetable material, so releasing their constituents for further use by other living things. In view of this it is not so surprising that some bacteria have evolved the capacity to attack living tissue as well as dead, and have so become "pathogenic".

The stage reached in this evolutionary process varies in different species. Some are "obligatory pathogens", incapable of existence in the body except as causes of disease: such are the virus of small-pox and the bacilli causing tuberculosis and plague. There are other highly pathogenic species to which this definition does not apply, because they may be found in "carriers": these are individuals who have usually recovered from an attack of the disease and are in any case immune to it, but have failed to rid themselves of the micro-organism. Other bacteria are only "facultatively" pathogenic: these include species inhabiting exposed surfaces of the body and the alimentary tract, where they normally lead a purely "saprophytic" existence—i.e., they multiply in secretions, dying superficial epithelial cells and food residues without invading the tissues or causing any harm. In certain circumstances, particularly if they gain access to other parts of the body, such bacteria may assume pathogenic activity.

Another commonly used term requiring definition is "virulence". This is used of pathogenic species to denote the *degree* of their capacity to produce disease, and it may be measured in terms of the numbers of bacteria required to establish infection or to produce fatal infection. Thus the minimum number of hemolytic streptococci with which a mouse must be inoculated to cause death may be millions or only about five. Virulence in this species is subject to rapid change, and an increase is caused by transference from one host to another, and particularly by a series of such transfers. The same effect operates, although less strikingly, in other species: apart from this, greater or lesser degrees of virulence may be an inherent property of individual strains within a species (the term "strain" is used to denote an individual example of a micro-organism, and is often known by the name of the patient in whom it was found).

### FACTORS PREDISPOSING TO INFECTION

It is usually said that if bacteria gain access to the tissues, the outcome depends on their numbers and virulence on one hand, and on the resistance or "immunity" of the host on the other. In connection with some infections, specific immunity,

the nature of which will be considered shortly, is all-important. There are many diseases, such as the common childhood fevers, chicken-pox, measles and mumps, which almost everyone must acquire on first exposure to infection, regardless of any other factor whatever: specific immunity, usually permanent, follows. The degree of immunity—for this may sometimes be relative and not absolute—is a factor in connection with all infection, but it is often overshadowed in importance by others. Indeed many examples of bacterial infection would not have occurred at all had there not been some other condition predisposing to it. Examples of these are the following.

*Injury.*—The interior of the body is normally free of bacteria, and some parts are ill-equipped to deal with them. Perhaps the most defenceless tissue is the surface of the central nervous system: hence when the base of the skull is fractured, and bacteria from the naso-pharynx are enabled to enter, meningitis, almost always due to a pneumococcus, commonly results. Similarly a perforating wound of the abdomen is followed by peritonitis due to the escape of intestinal bacteria. Any wound is liable to be contaminated with bacteria from the skin or from the outer world, and much of its treatment is directed to preventing the infection which may otherwise result.

*Fluid retention.*—Another purely mechanical cause of infection, although usually brought about in quite different ways, is obstruction to the escape of some fluid with resulting stagnation. The urinary tract affords the best examples of this: retention in the bladder due to prostatic enlargement or in the renal pelvis due to constriction of the ureter is eventually followed by infection, and although this may be eliminated for the time being by treatment it will regularly recur unless the obstruction is relieved. Retained bronchial secretion in bronchiectatic cavities is inevitably infected for the same reason.

*Malnutrition.*—A generally ill-nourished person is thereby rendered more susceptible to many infections, and particularly to tuberculosis. There are more specific forms of malnutrition; deficiency of vitamin A leads to metaplasia of the epithelium of the air passages, which in its turn predisposes to infection. In a sense, malnutrition may be local, the effect of an inadequate blood supply: thus circulatory stasis is the underlying cause of a varicose ulcer and pressure, producing ischaemia, that of a bedsore.

*Other diseases.*—There are many examples of diseases predisposing to others of an infective nature. Diabetes mellitus, cirrhosis of the liver and silicosis predispose to tuberculosis, and hydræmic nephritis to pyogenic infections of serous cavities. Infection, often taking the form of broncho-pneumonia, is a common terminal event in many progressive and incurable conditions, and is particularly liable to develop in old people immobilised in bed, as for the treatment of a fractured femur.

*Agranulocytosis.*—A gross deficiency or actual absence of granular leucocytes in the blood, which occasionally follows the use of certain drugs, deprives the body of a defence whereby its bacterial inhabitants are evidently kept in check, since they then attack the surfaces of the throat and mouth, producing a condition known as agranulocytic angina.

These are only some of the main examples of the causes which underlie many infections, and it will be clear that prevention and treatment should be directed to removal of these causes, when possible, as well as directly to eliminating the infection itself.

## RESULTS OF BACTERIAL INFECTION

The tissue changes resulting from infection are in the province of the morbid anatomist, and a textbook of pathology should be consulted for their details. The following account suffices only to define the terms used elsewhere in this book. *Inflammation* is the first result of bacterial invasion, and its cardinal features are the

dilatation of capillaries and the escape from them of fluid and leucocytes. In connective tissue the inflammatory oedema so produced is known as cellulitis; in a serous cavity the result will be an effusion; in a mucous membrane the result is *catarrh*, the most obvious effect, apart from swelling, being an increased flow of secretion.

Some forms of inflammation proceed to tissue destruction. This is of two principal kinds, *necrosis*, or death of an area of tissue, which may be caused by poisonous bacterial products or indirectly, as in syphilis, by vascular changes reducing the blood supply, and *suppuration*, in which tissue is liquefied and the cavity so formed occupied by pus, a fluid containing mainly dead leucocytes and bacteria.

Infection may remain localised, or may spread in any of three ways, by direct tissue continuity, via lymphatics or via the blood. The presence of certain types of bacteria in the blood is called *septicæmia*; in *pyæmia*, fragments of infected clot from veins bordering the focus of infection escape into the circulation and cause septic infarcts elsewhere. *Bacteriæmia* is a term used to denote the presence of bacteria in the blood when this is of not such grave import. It is a constant and merely incidental feature of typhoid fever, occurs in most patients with cerebrospinal fever, and in severe cases of lobar pneumonia. A transient bacteriæmia has been shown to result even from such simple operations as dental extraction and tonsillectomy.

#### THE RESPONSE OF THE BODY TO INFECTION

The body has two means of repelling bacterial invasion which to a large extent are interdependent. One is by the activity of leucocytes and other phagocytic cells which ingest and may destroy the micro-organisms. The other is by the formation of *antibodies*: these are globulins found in the plasma which have a specific action on bacteria or their products. In this connection a distinction has to be drawn between two different kinds of infection. In one, of which the best examples are diphtheria and tetanus, the bacteria form a potent *exotoxin*—i.e., a toxin or poison which is discharged by the growing bacterium into its surroundings and is carried to parts of the body where it causes damage remote from the focus of infection. The whole of the damage to tissue in these diseases is caused by this toxin, and the response of the body is the formation of an antibody, antitoxin, which neutralises this. Most bacteria form no such toxin, although they contain an *endotoxin* which is liberated when they are destroyed: these produce their effects directly by their presence and multiplication in infected tissue. Infection due to such bacteria extends much more widely, and is sometimes described as *invasive* in contradistinction to the localised exotoxin-forming type. The response to such infection is the formation of antibodies with a direct action on the bacteria themselves: these are agglutinin, which clumps and immobilises them—an important factor in checking spread—opsonin, which enables phagocytes to attack them, and bacteriolysin, which can actually cause their dissolution.

Antibodies act only on the bacteria in response to which they are formed. Their development is an essential factor in natural recovery, and subsequent immunity depends on their continued presence in the blood.

#### IMMUNISATION

Specific immunity having this basis not only results from an attack of the disease but may be produced artificially with much less disturbance or none. Artificial immunisation is of two kinds:

*Passive*.—This is the administration of serum, either of an immune human being or, more commonly, of an animal rendered highly immune by the second of these methods. The necessary antibody is thus supplied ready-made, and the term "passive" denotes the fact that the recipient takes no part in its formation. This is an

emergency measure, and its effect is of short duration, the extraneous globulin introduced being lost, as are other labile constituents of the body, within a short time. It may be used in either prevention or treatment. Its preventive use is certain of effect when the serum is one containing antitoxin. This type of antibody is accurately measurable and its unit is the subject of an International Standard. An adequate dose of diphtheria or tetanus antitoxin protects absolutely against these diseases for about 10 to 30 days, according to the amount given. Antitoxic sera are less consistently effective in treatment because they cannot repair damage already done by toxin to susceptible tissue cells, but they achieve their purpose if given early, before this damage is too extensive. Antibacterial sera have been used almost exclusively for the treatment of established infection, and are in general less effective, although the antipneumococcal serum formerly used in pneumonia was an exception. It so happens that most infections originally treated in this way are now amenable to chemotherapy.

*Active.*—The object of active immunisation is to stimulate specific antibody formation by the recipient: when this process has been initiated, it continues as it does after a natural attack of the disease, although usually not for so long. The only stimulus which will serve is the toxin or the micro-organism itself, according to the class to which the infection belongs, and either must be rendered relatively harmless before it can be injected. Toxin can be rendered harmless without loss of immunising capacity by conversion to toxoid, and diphtheria and tetanus toxoids are used, the former in several different forms, for active immunisation against these diseases. For invasive infections, the micro-organism must be used. It can be rendered harmless by being first killed by heat or chemical treatment (typhoid vaccine), by being deprived of virulence by prolonged artificial cultivation under abnormal conditions (B.C.G. vaccine for tuberculosis) or by habituation to growth in another animal species (vaccination against small-pox affords an example of this). Whether dead or living but "attenuated" by either of these processes, it elicits a reaction similar to that of the natural disease, antibody being formed. The resulting protection against some diseases, including small-pox, is absolute for several years: in connection with others it can only be said that the likelihood of developing the disease is substantially reduced.

These methods are not applicable to all infections. Some, like chicken-pox, are not worth preventing: for others, either because a variety of immunologically distinct micro-organisms can cause them, or because no technique for preparing a harmless but effective vaccine has yet been devised, we are unable to produce immunity.

#### ANAPHYLAXIS

Anaphylaxis is a shock-like state rapidly produced by the parenteral injection of foreign protein, usually a therapeutic horse serum, in a "sensitised" individual. Apart from its anti-infective action, serum from another animal is itself a foreign material to which antibody (a precipitin) is formed. Hence if a second injection of horse serum is given more than 10 days after a first, or at any time afterwards for a period which may extend to several years, it reacts immediately with antibody, the result in the human subject being a state of profound shock, although in other animal species it takes somewhat different forms. The degree of the effect depends on the dose of serum and the route of administration, the intravenous being the most dangerous. The "sensitive" state, produced by a previous injection, or sometimes, it appears, accompanying conditions such as asthma, may be detected by the intradermal injection of a small amount of the serum, such as 0.1 ml. of a 1 in 10 dilution: an urticarial wheal then develops within 30 minutes. Such a patient, if serum treatment must nevertheless be proceeded with, can be desensitised by a series of subcutaneous injections of serum at half-hour intervals, starting with about 0.02 ml.

and doubling the dose each time until a therapeutic quantity is reached : the principle of this method is that free antibody is progressively neutralised until, by the time a large dose of serum is given, none is left to combine with it.

The risk involved in sensitisation affords a strong reason for not administering therapeutic serum of animal origin except for clear indications, although the highly refined antitoxic sera now available, consisting largely of antibody globulin, are certainly less dangerous than the cruder products of the past. Whenever foreign serum is administered, adrenaline and a hypodermic syringe should be instantly available, and 1 ml. of a 1 in 1000 solution should be injected forthwith if signs of shock develop.

*Serum sickness* is a delayed and much less serious effect of administering foreign serum, and is believed to be due to reaction between antibody formed to it and the small amount of foreign protein still circulating at this stage. The usual time of onset is about the eighth day after injection, and the features are urticaria with itching and moderate fever, sometimes with swollen and painful joints. Only symptomatic treatment is necessary.

#### ALLERGY

Allergy was defined by von Pirquet, who coined the word, simply as "altered reactivity", and to accept this definition is to condone an indiscriminate use of the term which has rendered it almost meaningless. Confusion would be avoided if its use were more restricted : the following are two distinct phenomena to which the term definitely applies.

*Bacterial allergy.*—In various microbic infections and parasitic infestations the tissues become sensitised to the causal agent of the disease, and react to it, or to an extract of it, with inflammation and oedema. The change responsible is in tissue cells, and is not dependent on the presence of an antibody in the blood : thus although anaphylactic sensitivity is transferable from one individual to another by serum, allergic is not. The usefulness of this state in resisting infection is the subject of very divergent views ; it is certainly distinct from immunity, although degrees of both may co-exist. Its usefulness to the physician is indisputable, since it is the basis of diagnostic tests, the best known of which is the tuberculin reaction. There are similar tests for the diagnosis of undulant fever, glanders, lymphogranuloma inguinale, hydatid disease and trichiniasis.

Some authorities take the view that a reaction of this type may be the basis of naturally occurring disease ; rheumatic fever, for example, is regarded by some as representing an allergic reaction to the hæmolytic streptococcus or its products. Some forms of nephritis and even pneumonia have been credited with a similar basis. It is much easier to postulate such an origin for a disease than to prove it.

*Allergy to inanimate foreign material.*—A common variety of asthma and some skin diseases appears to be the result of sensitisation to elements, usually proteins and often of animal origin, contained in foods, dust, etc. ; the responsible material can be identified by skin tests with extracts. Sensitivity to drugs may be of the same nature. Comparatively simple chemical compounds are incapable of acting alone as the inciting agents of such reactions, but they can do so when they combine with plasma protein : a substance which, when combined with a protein, confers such specificity on it is known as a haptene. Penicillin, to which such reactions are being seen with increasing frequency, is known to circulate in the blood partly in such a combined form.

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## ANTIBIOTICS

Antibiosis, the antithesis of symbiosis, may be defined in broad terms as the formation by one living thing of a substance detrimental to another. The word is used chiefly in reference to such antagonism within the plant kingdom and more particularly of relationships between species of micro-organisms, both bacteria and fungi. That some micro-organisms produce substances antagonistic to the growth of others has been well recognised for over 70 years, the first observation on this subject having been made by Pasteur himself. Many attempts were made during this period to exploit such products in therapeutics, with little success, owing chiefly to the gross impurity of the materials used. The first antibiotic to be purified and shown to exert a systemic as well as a local action was gramicidin (tyrothricin), isolated from *Bacillus brevis* by Dubos of New York. The example set by his work was largely responsible for the isolation and therapeutic study of penicillin and hence indirectly for the further developments of which this chapter is an account.

## PENICILLIN

Penicillin, the product of a green mould, *Penicillium notatum*, was discovered by Fleming in 1929. Early attempts at purification failed, and it was not until 11 years later that Florey and Chain overcame the difficulties imposed by the instability of the natural product, and extracted from cultures material suitable for experimental, and later clinical, study. The properties thus revealed were so astonishing that immense efforts were concentrated during the latter part of the War of 1939-1945 on producing enough penicillin for the treatment of battle casualties. Supplies became adequate for this purpose in 1944, and civilian use was also expanded until a free market was established in 1946.

*Nature and properties.*—Penicillin is an organic acid of unique structure, the synthesis of which on a commercial scale is impracticable: it is therefore still obtainable only by extraction from cultures of *P. notatum*. The commercial product is the sodium or other salt of the naturally formed acid, a colourless crystalline material freely soluble in water. The dry powder in a sealed ampoule is stable; solutions deteriorate, and should be freshly made and stored in the cold if kept for more than a day or two during use. It is moderately heat-stable, but not sufficiently so for heat to be employed for sterilising solutions; aseptic dispensing is therefore necessary. Penicillin is destroyed by acids and alkalis, by certain heavy metals and their salts and by strong solutions of alcohols. It is also rapidly destroyed by an enzyme, penicillinase, formed by certain bacteria, which consequently possess a high degree of resistance to the drug.

The only possible measure of penicillin in the early days was in terms of anti-bacterial activity. The original Oxford unit has been perpetuated as an International Standard, and dosage is measured in terms of this unit. Pure penicillin has an activity of 1667 units per mg. Here it must be made clear that there are different forms of penicillin, of which the earliest to be recognised were known as F, G, X and K in the United States and I, II, III and K in England. Which of these are formed and in what proportions depends on the strain of *P. notatum* or *P. chrysogenum* used and the composition of the medium. They differ only in the structure of a side chain attached to the molecule. Their antibacterial activity varies somewhat, as does the rate of their excretion. The commercial product is a mixture, but usually consists predominantly of penicillin G (benzyl penicillin): the International Standard consists of this form and has the activity stated.

*Action on Bacteria.*—Unlike the sulphonamides, which are purely bacteriostatic

(growth-preventing), penicillin is actively bactericidal (lethal). Like them, however, it can exert this action only on multiplying bacteria, the more rapidly multiplying the better. This explains the dramatic effect of both forms of chemotherapy on acute infections, and their lesser efficacy in the treatment of chronic infections and carrier states. These facts indicate that penicillin, like the sulphonamides, arrests some vital process in bacterial metabolism; the precise mechanism is not yet known. The action of penicillin is unique in being exerted fully in any environment found in the body; that of many antiseptics, as is well known, is diminished in the presence of various body fluids, and even that of the sulphonamides is neutralised by substances occurring in pus. There are no such limitations to the action of penicillin; unless its environment is such as actually to destroy it (as by acid in the stomach or bacterial enzymes in the lower bowel) its antibacterial power is constant.

Susceptibility to the action of penicillin varies very widely among different bacterial species. It follows that only those infections due to more susceptible bacteria are suitable for treatment, and that the nature of the infection should preferably be known before treatment is begun. This may be self-evident, as in gonorrhœa or carbuncle; in conditions such as pneumonia, septicæmia or meningitis it probably will not, and specimens for bacteriological examination should always be obtained before treatment is begun.

The following table gives a list of the principal pathogenic micro-organisms classified in the hitherto conventional manner as sensitive or resistant to penicillin:

Sensitive	Resistant
Gram-negative cocci	<i>Strep. faecalis</i> .
<i>N. gonorrhœæ</i>	Gram-negative bacilli generally, including the whole of the genera <i>Hæmophilus</i> , <i>Bacterium</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Pseudomonas</i> , <i>Proteus</i> , <i>Brucella</i> and <i>Pasteurella</i> .
<i>N. meningitidis</i>	
Gram-positive cocci	<i>Myco. tuberculosis</i> .
<i>Strep. pyogenes</i>	Yeasts and moulds.
<i>Staph. aureus</i>	Viruses generally.
<i>Strep. pneumoniae</i>	
<i>viridans</i>	
Gram-positive bacilli	
<i>B. anthracis</i>	
<i>C. diphtheriæ</i>	
<i>Clostridia (welchii, etc.)</i>	
Spirochætes	
<i>T. pallidum</i>	
<i>T. vincenti</i>	
<i>L. icterohæmorrhagiæ</i> .	
Miscellaneous:	
<i>Fusiformis</i> and related organisms	
<i>Actinomyces</i>	
<i>Streptobacillus moniliformis</i>	
<i>Erysipelothrix rhusiopathiæ</i>	
Ornithosis virus	

The matter is not quite so simple as such a list makes it appear, because there are many degrees of resistance and susceptibility; an arbitrary line has to be drawn somewhere, and in this the line chosen is inhibition of growth by a concentration of about

1 unit per ml. The following is a list of important species in order of diminishing susceptibility.

				Approximate concentration of penicillin in units per ml. required to inhibit growth
<i>N. gonorrhœæ</i> ..	..	..	..	0.002-0.005
<i>Strep. pyogenes</i> ..	..	..	..	0.01
<i>Staph. aureus</i> ..	..	..	..	0.02
<i>Cl. welchii</i> ..	..	..	..	0.1
<i>H. influenza</i> ..	..	..	..	0.5-5.0
<i>Strep. faecalis</i> ..	..	..	..	2.0-5.0
<i>Proteus vulgaris</i> ..	..	..	..	8.0
<i>Salm. typhi</i> ..	..	..	..	5.0-20.0
<i>Bact. coli</i> ..	..	..	..	30.0->100.0
<i>Shigellas</i> ..	..	..	..	>100
<i>Ps. pyocyanea</i> ..	..	..	..	>1000
<i>Myc. tuberculosis</i> ..	..	..	..	>1000

The importance of recognising these grades of susceptibility is that in certain situations a very high local concentration of penicillin can be attained, which is capable of destroying bacteria ordinarily classed as resistant. Thus, intrathecal injection will produce in the cerebrospinal fluid a concentration adequate for the treatment of meningitis due to *H. influenza*. The same is true of the urinary tract: penicillin is excreted in the urine in high concentration, and may cure an infection due to any organism inhibited by 50 units per ml. or less.

Although the susceptibility of some bacterial species is constant within narrow limits, in others it varies from strain to strain. This is particularly true of staphylococci, which sometimes possess naturally a high degree of resistance. Variations in susceptibility are also seen among strains of *Strep. viridans* and *Actinomyces*. It is often advisable to test susceptibility in the laboratory before embarking on treatment, if only to decide on dosage. Sometimes the result with a staphylococcus will indicate that treatment is likely to be useless.

The clinical indications for the use of penicillin are too numerous to be detailed here, and frequent references to them will be found in the chapters on individual diseases.

*Principles of administration.*—The first cardinal principle in penicillin treatment is to determine that the infection is susceptible; the second is to ensure that the drug is brought into full and sufficiently prolonged contact with the infecting micro-organism. There are two ways of doing this, systemic (parenteral) administration and local application or injection.

*Systemic administration.*—When a solution of penicillin is injected intramuscularly, most of it is absorbed within 15 minutes and produces a high concentration in the blood. It passes thence into most of the other body fluids, including glandular secretions, but a therapeutic concentration is not attained in the cerebrospinal fluid unless very large doses are given. It is also rapidly excreted by the kidneys, with the result



intervals, which is now more common practice than giving smaller doses at short intervals, produces wide fluctuations in the blood level, alternating with periods during which an effective level is absent. This is at least theoretically undesirable in some conditions, but the high levels immediately following a dose are believed to promote diffusion into tissue fluids in areas of inflammation and particularly into isolated foci of infection: in these, penicillin persists much longer than in the circulation.

When a continuous effect is required, a different form of penicillin may be preferred. The history of "repository" preparations, from the injection sites of which the drug is slowly absorbed, began with the suspension of soluble penicillin in an oil medium, but made a great advance with the introduction of procaine penicillin, an equimolecular compound of the two substances which has a much lower solubility. This is usually administered as a watery suspension, and although the size and shape of the crystals determine their rate of solution, which can also be further delayed by suspending them in oil, a dose of 300,000 units of any such preparation should maintain a therapeutic concentration in the blood for at least 24 hours and will often do so for longer. The maximum concentration is reached with such preparations in about 4 hours and is much lower than that produced by sodium penicillin. For still more prolonged effects—extending even to several weeks after a large dose—preparations of N, N'-dibenzylethylenediamine dipenicillin may be used.

Another method of prolonging effect, but more often used to sustain a higher blood level than the dosage would otherwise produce, is to administer a substance which impedes renal penicillin excretion. Those used successively have been sodium p-aminohippurate, 4'-carboxyphenyl-methane-sulphonanilide (Caronamide), and probenecid (Benemid): the latter is now usually preferred.

Oral administration is an alternative particularly suitable for young children, and may be used in adults if the infecting organism is highly sensitive and the condition not dangerous. When penicillin is swallowed, much of it is destroyed by the gastric acid, and thereafter absorption is erratic and incomplete; even in patients with achlorhydria only a variable amount, not often exceeding one-fifth of the dose, appears in the urine. Various special forms of penicillin manufactured for this purpose have little of the advantage claimed for them: recent observations have shown that simple tablets of soluble penicillin, possibly including a buffer, are absorbed as well as anything else. They are better absorbed if taken before meals than after.

It is difficult to lay down any general rule about the duration of treatment, except that it should be continued until the infection is overcome. The duration varies from a few hours for gonorrhoea to 6 weeks or more for subacute bacterial endocarditis. The subsidence of fever is often the surest guide, but is not infallible. A recurrence may take place if treatment is stopped too soon after the temperature falls; this often occurs in pneumonia and acute streptococcal throat infections. The explanation of such recurrences is that penicillin destroys most of the micro-organisms before the ordinary immunity mechanism has come into play; a few survivors will thus multiply without restraint and the attack is repeated.

**Local administration.**—If the site of infection is an accessible surface or body cavity, local administration may be indicated, either alone or combined with systemic. Technique is all-important, and must be such as to secure persistence of effect. Thus skin infections or superficial wounds or burns may be treated with a cream made up with a suitable base from which penicillin is slowly liberated and absorbed. Infections of the nose and naso-pharynx, including carrier states, are susceptible to the action of a snuff containing 5000 units of calcium penicillin per gramme of sulphathiazole. Mouth and throat infections can be treated by the continuous sucking of penicillin pastilles, preferably in a gelatin base. Inhalation of a solution is useful for certain infections of the bronchi. Lamellae or solution frequently instilled are used in conjunctivitis.

Closed body cavities afford special opportunities for effective treatment; a solution can be injected into them which will exert not only a prolonged and powerful local effect, but even a systemic one if the dose is large enough, since slow absorption takes place through inflamed serous and other surfaces. Such injections may be made into inflamed serous sacs, joints and abscess cavities generally. Intrathecal injection may be indicated in meningitis: 10,000 units daily by this route will maintain a cerebrospinal fluid concentration adequate for the treatment of susceptible infections. Some authorities now prefer to enable penicillin to traverse the blood-brain barrier by giving very large and frequent doses intramuscularly, such as 2,000,000 units every 2 hours.

**Toxic effects.**—Penicillin is by far the least toxic chemotherapeutic agent known; this is its most astonishing property, and an important factor in its therapeutic success. Enormous doses—such as 40,000,000 units a day—have been given without ill effect. There are no recorded instances of damage to the bone-marrow, liver or kidney, such as has occasionally to be feared following the use of many other potent antimicrobial drugs. On the other hand, *sensitivity* to penicillin is increasing in frequency, and causing difficulty in administration. In patients sensitised by previous treatment—or, it is said, by suffering from skin mycoses—an injection of penicillin may produce urticaria and fever. Occasionally it may result immediately in vasomotor collapse, which has even been fatal. Sensitised patients may be recognised by injecting a small dose intradermally, which causes wheal formation within a few minutes. It is a wise precaution to apply this test to any patient giving a history of previous reactions or suffering from asthma or other allergic condition. Such reactions can be prevented in sensitised patients by adding an anti-histamine compound to the penicillin to be injected.

### STREPTOMYCIN

Streptomycin, extracted from *Actinomyces griseus*, the antibacterial properties of which were first described by Waksman and his colleagues in 1944, was the first successful product of a world-wide and systematic search for further antibiotics which began when the value of penicillin was first recognised. It is of more complex chemical structure than penicillin; the commercial product is a salt of the natural base. This is a white powder, freely soluble in water, although not soluble in as high a concentration, in terms of its activity, as penicillin. It is measured by weight, 1 g. of pure streptomycin being equivalent to 1,000,000 units as originally defined.

**Action on bacteria.**—Streptomycin, like penicillin, is actively lethal to bacteria. The mechanism of its action is certainly different, but so far unknown. A neutral or alkaline medium is necessary for it, whereas penicillin is at least equally active a little on the acid side of neutrality.

The merit of streptomycin is that it is effective against certain bacteria which are resistant to penicillin. The most important species among these is the tubercle bacillus; the rest are chiefly Gram-negative bacilli, including most of the intestinal pathogens, *Haemophilus influenzae* and *pertussis*, the *Brucella* group, *Pasteurella* (plague) and *Pseudomonas*. It is also active in lesser degree against most of the Gram-positive species which are also sensitive to penicillin.

The main drawback of streptomycin is that bacteria originally sensitive to it may rapidly acquire a high degree of resistance during treatment. This resistance may be acquired within 2 days or even less, and is of such a degree that further treatment is quite useless.

**Administration.**—Streptomycin given by intramuscular injection is absorbed and excreted rather more slowly than penicillin; it is therefore usually administered at intervals of 6 or 8 hours or once daily during prolonged treatment, as for tuberculosis. The total daily dose is usually 1 g. for a long course, but larger amounts may be

given for short periods. Distribution in the body is similar to that of penicillin; the drug does not enter the cerebrospinal fluid, and is excreted by the kidneys. There is a striking difference from penicillin in the behaviour of the drug when given orally. It is not destroyed in the stomach, but neither is it absorbed; it is excreted almost quantitatively in the faeces, and acts as a powerful intestinal antiseptic, almost completely suppressing the coliform flora.

Streptomycin can also be administered locally in various ways; intrathecal injection is the most notable example of this. The local treatment of large collections of pus, such as empyema, is disappointing; the acid reaction of the exudate probably explains this.

**Indications.**—Tuberculosis in its more acute forms and some of its more chronic is the outstanding indication for this drug. This is not the place to enter into any further detail on this subject, but it should be added that the present practice is never to give streptomycin alone, but to administer at the same time either isoniazid or sodium aminosalicylate, either of which has an independent action on the tubercle bacillus.

Formerly many infections of various kinds due to Gram-negative bacilli were indications for streptomycin treatment. Its use for these purposes has diminished for two reasons: many strains of such bacteria are now completely resistant to it, and other antibiotics have been introduced which produce a similar effect with less trouble. The former consideration does not apply to tularæmia or plague, since these are acquired from animals in which previous contact with the drug will not have occurred; both are unequivocal indications, unless one of the later antibiotics be preferred for the treatment of tularæmia. In any other infection the sensitivity of the causative organism should be tested. If the result of this test is satisfactory, streptomycin may be used for infections by coliform bacilli (*Bact. coli*, *Bact. aerogenes*, *Pr. pyocyanea*) wherever situated: these may take the form of a septicæmia, meningitis or a urinary tract infection. For the latter it is important to render the urine constantly alkaline before treatment is started. Pneumonia due to Friedländer's bacillus is another strong, if uncommon, indication. Streptomycin acts synergically with penicillin against some bacteria, notably *Str. faecalis*: endocarditis due to this organism calls for treatment with both drugs. This should be no excuse for administering this combination indiscriminately on the general principle that it is superior to penicillin: much harm can be done by such unnecessary use.

**Toxic effects.**—Excessive doses of streptomycin can cause liver degeneration and various nervous system effects, but dosage has to be kept within strict limits mainly because of possible damage to the eighth nerve. There is little danger of this from a course of treatment lasting a week or less, and it does not often result from a longer course if the dose is restricted to 1 g. daily. There are exceptions to these rules, some at least of which have been patients with unrecognised or unheeded impairment of renal function: excretion of the drug is then delayed and a given dose produces higher and more sustained blood levels. Streptomycin more often damages the vestibular branch, although the auditory may also be affected, and the consequent vertigo or deafness develops during administration. Dihydrostreptomycin, originally thought to be non-toxic, causes damage to the auditory branch which may not betray itself until well after the course is finished. Since the damage is usually permanent, this danger affords a very strong reason for not using this drug except for clear and serious indications. The suggestion that a combination of both forms is safer has yet to be fully verified.

#### CHLORAMPHENICOL

Two further important antibiotics, also derived from soil actinomycetes, were discovered in 1948: of these it is convenient first to deal with Chloromycetin. This is a product of *Streptomyces venezuelæ*, and was at first manufactured from cultures

of this mould. It was then found possible to synthesise it on a commercial scale, and the synthetic product, indistinguishable in every way from the natural, is known as chloramphenicol. It is the only antibiotic of therapeutic importance which can be produced in this way. Its solubility in water is low, and its action, like that of the tetracyclines, mainly bacteriostatic.

This drug opened a new chapter in antibiotic treatment by virtue of its mode of administration. Like its principal successors, it is simply administered in capsules

SENSITIVITY OF PRINCIPAL PATHOGENS TO SIX ANTIBIOTICS

	Minimum Inhibitory Concentration ( $\mu\text{gm./ml.}$ )						
	Penicillin.	Streptomycin.	Chlortetracycline	Chloramphenicol.	Erythromycin.	Bacitracin.	Poly-myxin.
<i>Staph. pyogenes</i> ..	0.02	5	0.2	5	0.3	2	>250
<i>Strep. pyogenes</i> (A) ..	0.01	50	0.5	3	0.02	0.3	>400
" <i>viridans</i> ..	0.02	50	3	3	0.06	2	>200
" <i>faecalis</i> ..	5	50	3	12	2.0	3	>200
" <i>pneumoniae</i> ..	0.01	25	0.8	3	0.02	6	>800
<i>N. gonorrhoea</i> ..	0.003	6	0.8	0.8	0.04	6	>300
<i>H. influenza</i> ..	1	2	1.3	0.8	1.6	>750	0.8
<i>Bact. coli</i> ..	75	10	10	5	>100	>1000	2.5
<i>Bact. aerogenes</i> ..	>1000	6	10	6	>100	>1000	2.5
<i>Bact. friedländeri</i> ..	10	1	5	3	12	>1000	1
<i>Proteus vulgaris</i> ..	8	50	200	25	>100	>1000	>1000
<i>Ps. pyocyanea</i> ..	>1000	50	200	500	>100	>1000	1
<i>Salmon. typhi</i> ..	10	5	3	2			
<i>Br. abortus</i> ..	20	2.5	3	2			
<i>Cl. welchii</i> ..	0.1	>500	0.1	2			
<i>Mycob. tuberculosis</i> ..	>1000	0.1	10	10			
<i>Actinomyces israeli</i> ..	0.075	8	4	2			
Average concentration attained in blood on ordinary dosage ( $\mu\text{gm./ml.}$ ) ..	0.3	10	4	10	4	2	2

The inhibitory concentrations stated are those normal for the species; in many cases they are subject to wide variation particularly in the direction of greater resistance.

*Oxytetracycline* behaves very similarly to chlortetracycline: it is somewhat more active against *Ps. pyocyanea*.

*Carbomycin* behaves similarly to erythromycin, but is less active against some organisms and attains lower blood concentrations.

by the mouth. Absorption from the alimentary tract is satisfactory if not complete, and excretion (mainly by the kidney, and mainly also in an inactive acetylated form) is comparatively slow: hence 4 daily doses of 0.5 g. will maintain an adequate concentration in the blood continuously. Chloramphenicol appears in glandular secretions, particularly those of the air passages, and regularly attains concentrations in the cerebrospinal fluid equal to about one-third of those in the blood, an advantage possessed in this degree by no other antibiotic.

**Indications.**—The most striking advance achieved by the discovery of this and other antibiotics is the provision of specific and regularly effective treatment for all forms of typhus. The remarkable efficacy of chloramphenicol was first demonstrated in the treatment of scrub typhus in Malaya: there is now evidence that this applies

to all rickettsial infections, including Q fever. Chloramphenicol is also effective against the viruses of psittacosis, lymphogranuloma inguinale and "primary atypical pneumonia".

By its action on bacteria also chloramphenicol qualifies as one of the "broad spectrum" antibiotics: a variety of both Gram-positive and Gram-negative species are susceptible to it. The susceptibilities of some important species to this and other antibiotics are stated in the Table. The minimum inhibitory concentrations given are necessarily only approximate; these depend on the conditions of the test determining them and vary also with the strain of organism used. In general, chloramphenicol is less active than penicillin or chlortetracycline against Gram-positive organisms, but more so against Gram-negative. Thus its principal sphere of usefulness is for treating infections due to certain Gram-negative bacilli. An outstanding example is typhoid fever: although other antibiotics might be expected from their *in vitro* performance to have some effect in this disease, chloramphenicol far exceeds them in therapeutic activity. Another strong indication is *H. influenzae* meningitis, because both of the extreme susceptibility of this organism and of the relatively high concentration which the drug attains in the cerebrospinal fluid. It may also be used successfully for undulant fever. Its choice for a variety of other purposes for which alternatives exist will depend on the view taken with regard to its toxicity.

**Toxic effects.**—Like other orally administered antibiotics, chloramphenicol is liable to cause nausea or vomiting and diarrhoea, especially if given in full doses for more than a few days. Unlike any other, it can also cause aplasia of the bone marrow, and a consequent deficiency of all formed elements in the blood: such patients exhibit hæmorrhages and rapidly progressive anaemia which are usually fatal, although the marrow recovers in some after a series of transfusions. Occasionally the only effect produced is agranulocytosis, red cell and platelet formation being unaffected.

The true frequency of this complication is still unknown: in some hospitals or practices several examples have been seen, suggesting a fairly high incidence, whereas others profess to have treated thousands of patients with no ill effect. Nor is there any unequivocal information about the system of treatment most liable to cause marrow damage. Excessive doses, prolonged treatment or repeated courses have sometimes preceded it: in other cases a quite small total dose has been responsible, and it seems necessary to assume that idiosyncrasy is a factor. Whatever view may be taken of this risk, it undoubtedly exists, and chloramphenicol should certainly not be prescribed except for some definite and serious indication. To pay with one's life for the doubtful benefit conferred by this drug in the common cold, as some patients have done, is asking too much.

## THE TETRACYCLINES

### CHLORTETRACYCLINE

Chlortetracycline (Aureomycin), also discovered in 1948, is a golden yellow substance formed by *Streptomyces aureofaciens*. Chlortetracycline hydrochloride, the form chiefly used in therapeutics, gives highly acid solutions which are much less stable than those of other antibiotics. The intramuscular injection of such a solution causes severe pain, but the drug can be suitably dissolved in a large volume of buffered solution for intravenous injection. The ordinary method of administration is in capsules by the mouth, and dosage and pharmacological behaviour are similar to those of chloramphenicol, with the following differences: the blood levels attained are rather lower, and those in the cerebrospinal fluid distinctly so, the drug is excreted in the urine in active form and, owing either to excretion in the bile or to incomplete absorption, has a greater suppressive effect on the bowel flora.

**Indications.**—Chlortetracycline has a comparable effect to that of chloramphenicol in all rickettsial and certain virus infections and in undulant fever. It is more active than chloramphenicol against Gram-positive cocci, and thus a particularly valuable substitute for penicillin in staphylococcal infections resistant to the latter. Its action on pneumococci, streptococci, *H. influenzae* and the pneumotropic viruses enables it to be used indiscriminately for any form of pneumonia. It has also been successfully used for gonorrhœa, syphilis, peritonitis, gas gangrene, urinary infections and actinomycosis.

**Toxic effects.**—These are limited to gastro-intestinal disturbances, unless excessive doses are given, particularly by the intravenous route, when there may be some damage to the liver.

#### OXYTETRACYCLINE

Oxytetracycline (Terramycin), formed by *Streptomyces rimosus*, and introduced in 1950, closely resembles chlortetracycline both in chemical structure and in therapeutic activity. It is colourless, less soluble and more stable than chlortetracycline, administered by the mouth or, if necessary, intravenously in similar dosage, and attains blood levels for a given dose intermediate between those produced by chloramphenicol and chlortetracycline. Indications for its use are almost identical to those for chlortetracycline. Gastro-intestinal disturbances have been the only toxic effects observed.

#### TETRACYCLINE

It is known that the molecular structures of chlortetracycline and oxytetracycline are identical, but for the presence of a Cl atom in the former and an OH group in the latter. The same molecule without either of these additions is tetracycline, which can be prepared from one of the other drugs and is also formed directly by a recently discovered mould. It has a very similar therapeutic action, but is said to be much less liable to cause nausea or vomiting and diarrhœa, an important advantage in some patients, including any who have to take such a drug for some length of time, as, for instance, in the treatment of brucellosis.

#### ERYTHROMYCIN AND CARBOMYCIN

Erythromycin (Ilotycin) and carbomycin (Magnamycin) are recently introduced antibiotics of as yet unknown structure. From their antibacterial spectra and the completeness of cross-resistance between them it is evident that they must be closely related: erythromycin is the more therapeutically active of the two in infections which have hitherto been studied. Their spectrum resembles that of penicillin, streptococci, staphylococci and other Gram-positive organisms being highly susceptible and Gram-negative species except of the genera *Haemophilus* and *Neisseria* relatively resistant. The therapeutic activity particularly of erythromycin, has been confirmed clinically in pneumococcal infections (pneumonia), hæmolytic streptococcal (acute sore throat) and staphylococcal (various). Since penicillin will usually serve for the two former, it seems that these antibiotics will be mainly useful in staphylococcal infections unresponsive to other drugs. They are administered by the mouth and behave pharmacologically in much the same way as the tetracyclines: gastro-intestinal disturbances are the only toxic effects hitherto noted.

#### ANTIBIOTICS FROM BACILLI

The genus *Bacillus* (aerobic Gram-positive sporogenous rods) includes several species which form powerful antibiotics; indeed the first such substance ever shown to exert a systemic antibacterial effect was gramicidin, derived from *Bacillus brevis*.

Antibiotics formed by *Bacilli* are polypeptides, and all are toxic in some way and to some degree, often so much so as to preclude their systemic use, although local application may be useful and is harmless. The most promising are bacitracin and polymyxin, the antibacterial activities of which are stated in the Table. It is strange that two substances of like derivation and similar structure should have such different action.

*Bacitracin* is chiefly active against streptococci and other Gram-positive cocci. Since penicillin and other safer antibiotics will usually deal with these organisms, its use is not often indicated, but may be so, for example, in subacute bacterial endocarditis due to an atypical streptococcus resistant to other drugs. Bacitracin is liable to cause renal tubular degeneration, and many patients given it develop albuminuria: this is said usually to disappear after administration has ceased. Oliguria and nitrogen retention have occurred in patients given large doses or having previously damaged kidneys.

*Polymyxin*.—There are now known to be five forms of polymyxin: those designated B and E are the most suitable for therapeutic use, and are less liable to cause renal damage than bacitracin. Polymyxin has little action on Gram-positive organisms, but is highly active against some Gram-negative species including *Ps. pyocyanea*, which is notoriously resistant to most other forms of chemotherapy. Meningitis due to this organism is a strong indication for polymyxin, and intrathecal injection is safe. Urinary infections due to this or similar bacteria resistant to other drugs may also call for it.

Bacitracin and polymyxin have both to be administered by injection.

#### COMBINED TREATMENT

It is sometimes advisable to give two antibiotics together, but the indications for this should be precise and clearly understood. Such treatment may be required for any of three reasons. The infection may be mixed, and hence unresponsive to any single drug, as in peritonitis, which may be treated with penicillin and streptomycin. It may be important, particularly during prolonged treatment, to prevent the acquisition of resistance by the bacteria to the drug used, and the simultaneous action of a second drug tends to prevent this: the best example is tuberculosis, where the administration of a second drug—not in this case usually an antibiotic—is now considered imperative. Thirdly, two drugs together may exert a synergic effect, *i.e.*, one greater than the sum of their separate effects. An example of this is the action of penicillin with streptomycin in *Str. faecalis* endocarditis: this combination alone is completely bactericidal to this organism, and in order to cure this infection, nothing short of total extermination of the streptococci in the vegetations will suffice.

Unfortunately the effect of combining two antibiotics may sometimes be quite the opposite. The bactericidal drugs (penicillin and streptomycin) exert this effect only on multiplying bacteria, and the bacteriostatic (chloramphenicol, chlortetracycline and oxytetracycline) prevent multiplication. Hence in a combination of one from each of these groups, the action of the bactericidal drug may be inhibited. It is uncertain how far this effect operates under clinical conditions, but a clear example of it has been seen in the unsuccessful treatment of cases of pneumococcal meningitis with chlortetracycline and penicillin, when a series treated with the same dose of penicillin alone had a much lower mortality. In general such combinations should be avoided, and in difficult cases an elaborate form of *in vitro* test may be necessary to decide what drugs will exert the desired effect.

#### ACQUIRED BACTERIAL RESISTANCE

Several references have already been made to the fact that bacteria formerly susceptible to an antibiotic may become resistant to it, sometimes to a degree

rendering further treatment useless. This may be considered from the point of view of the individual patient in whom it occurs, but its effect on the population at large is more important, because such resistant bacteria usually retain this character, and are liable to be disseminated, with the result that fresh infections in other individuals are insusceptible to the treatment from the outset.

Penicillin resistance is only a general problem in connection with staphylococci, and here the prevalence of resistant strains is not due to acquisition of this character, but to the breeding out of an originally resistant race which owes this property to forming penicillinase. Resistance to streptomycin can be acquired by any organism very rapidly, and resistant strains of originally sensitive species have become steadily commoner throughout the world since the introduction of this drug. To chloramphenicol and the tetracyclines any organism can develop resistance, but the process is a slower one. Resistance to one of the tetracyclines is usually accompanied by resistance to the others. Erythromycin stands apart, and resistance to it is so far rare, but it can be acquired readily and rapidly and will doubtless become a problem wherever the drug is widely used.

The capacity of staphylococci in particular and of various Gram-negative bacilli to become resistant to antibiotics which have been in general use for some time is one of the chief incentives in the search for new drugs. Staphylococcal resistance to penicillin and sometimes to all antibiotics except—at present—erythromycin is most frequent in hospitals where cross-infection takes place among patients and by way of nasal carriers among the staff. The stage of this process which has been reached in the United States, where the newer drugs have been available far longer than elsewhere, is much more advanced than in this country. It serves as a powerful argument against indiscriminate use. Whenever bacterial resistance is a possibility, laboratory tests should be made to determine which is the most suitable drug to use.

#### SUPERINFECTIONS

It has long been recognised that during treatment with penicillin the original infecting organism may be replaced at the site of infection by another belonging to a naturally resistant species. More recently, and mainly in consequence of the use of the modern broad spectrum antibiotics, "superinfections" have been seen to develop, not necessarily at the site of infection, but in the air passages or alimentary tract, due often to *Candida (Monilia) albicans*, and sometimes to a staphylococcus resistant both to the antibiotic in use and to others. *Candida albicans* is completely resistant to all antibiotics. These organisms are presumably enabled to proliferate by the elimination of the normal flora of the area; there is some evidence that they may be actually stimulated by the drug. Thrush in the mouth and pruritus ani are common results of *Candida* infection: staphylococci may cause a severe enteritis and either or both organisms have been known to cause severe and even fatal infection of the bronchi and lungs.

This complication should be watched for; if serious it demands immediate cessation of the treatment producing it. There is no specific treatment for *Candida* infection; staphylococcal infection so caused will usually respond to erythromycin.

LAWRENCE P. GARROD.



# THE SULPHONAMIDES

## INTRODUCTION

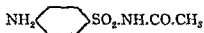
The demonstration by Domagk that streptococcal septicaemia could be prevented by the use of sulphonamido-chrysoidin opened a new era in chemotherapy. The activity of this compound was found to be due to the liberation of sulphanilamide in the body.

Sulphanilamide and its derivatives have been widely used therapeutically, and it has been customary to speak of this group of compounds as sulphonamides, and used in this sense it refers to various substituted compounds as well as the parent substance.

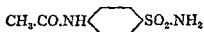
Sulphanilamide is the parent substance and the simplest of the group.



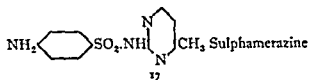
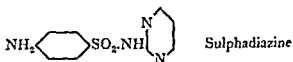
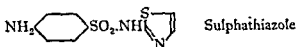
Acetylation of the sulphonamido group yields sulphacetamide.

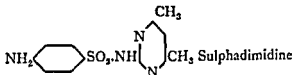


This compound must not be confused with the derivative produced in the body by the acetylation of the *p*-amino group which is therapeutically inert.



Substitution in the sulphonamido group with pyridine, thiazole, pyrimidine, methylpyrimidine and dimethylpyrimidine gives rise to the compounds known as sulphapyridine, sulphathiazole, sulphadiazine, sulphamerazine and sulphadimidine.



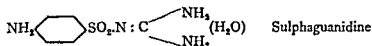


These substances are all suitable for administration by mouth and are absorbed well from the small intestine. The absorption, however, of sulphapyridine is somewhat irregular.

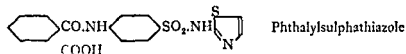
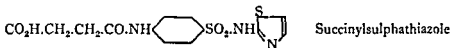
With the exception of sulphacetamide, and to a less degree sulphanilamide, these compounds are very sparingly soluble in water, but sodium compounds are made which are very soluble in water and can be administered either intravenously or intramuscularly, although their great alkalinity renders them very damaging to the tissues and great caution must be exercised in their use.

Another group of sulphonamides are absorbed poorly from the intestinal tract.

Sulphaguanidine is produced by substitution in the sulphonamido group with guanidine.



Others are made by acetylation of the *p*-amino group with succinic and phthalic acids. These compounds are known as succinylsulphathiazole and phthalylsulphathiazole.



Sulphaguanidine is absorbed somewhat better than the other two, and although it exerts its major effects in the intestinal tract, up to 60 per cent. may be absorbed and its systemic effects, toxic reactions and insolubility in the urine cannot be ignored. In the case of succinylsulphathiazole and phthalylsulphathiazole absorption is negligible, less than 5 per cent., and toxic manifestations are rare. A greater concentration can therefore be produced in the intestinal tract.

## THE ACTION OF SULPHONAMIDES

The presence of an adequate concentration of sulphonamide prevents the growth of susceptible bacteria. Bacterial destruction does not occur from the action of the sulphonamides but is brought about by the normal body defence mechanism.

The bacterial stasis produced by sulphonamides is the basis of their great therapeutic usefulness but for an adequate clinical response not only must the organism be susceptible to the concentration produced but at the same time the body defences must be adequate to destroy the remaining bacteria and to overcome the effects of the bacterial toxæmia.

This antibacterial action is believed to be due to an effect on the bacterial enzyme system. Bacteria require *p*-aminobenzoic acid for their growth, and it has been shown that sulphanilamide and *p*-aminobenzoic acid are competitive antagonists, competing for the same enzyme receptors. The bacteriostatic action of sulphonamides can be prevented by the addition of *p*-aminobenzoic acid even in small quantities and suggests that the bacteria have a high affinity in their enzyme systems for this substance and this presumably accounts for the relatively great concentration of sulphonamide required to produce its effects.

The antagonism of *p*-aminobenzoic acid to the antibacterial action of the sulphonamides is not however entirely specific and can be produced by a wide range of chemical compounds containing a similar nucleus. Procaine and allied substances used for local anaesthesia possess this quality, and this fact must be borne in mind when their use is contemplated during treatment with sulphonamides.

Other substances inhibitory to the action of sulphonamides are known to be present in most body tissues and fluids but the concentration of sulphonamide produced in their therapeutic use can overcome such inhibition. In pus, however, and in necrotic tissues the inhibition of the bacteriostatic action is so marked that it negates any therapeutic usefulness. This restricts very considerably the local use of sulphonamides and their systemic efficacy once suppuration has occurred.

The activity of the different sulphonamide compounds depends on the degree of dissociation of the compounds and thus any apparent differences in activity are quantitative on this basis and not qualitative. Thus the apparent specificity of different compounds in different infections is only related to the fact that the less the susceptibility of the organism the more activity in the compound will be required, though the essential action produced is the same. In addition, other physical attributes may influence the choice of drug. If, for example, a local effect is required in the gut and no systemic action be required it will be advantageous to use a sulphonamide which is not absorbed in any appreciable quantity from the alimentary tract.

With the exception of sulphaguanidine, succinylsulphathiazole and phthalylsulphathiazole absorption from the small intestine is rapid and little of the drug reaches the large intestine. After absorption the sulphonamides are distributed throughout the body uniformly. They enter the body fluids including the cerebrospinal fluid and the secretions in concentrations approximating the blood level. They also pass through the placenta and enter the fetal circulation and are present in the milk of lactating women.

Excretion largely occurs through the kidney. Some of the sulphonamides are excreted to a large extent unchanged, but a proportion, which varies considerably in individual sulphonamides, is acetylated in the liver before excretion. These acetyl compounds are inert therapeutically but assume importance because a number are less soluble than the parent compounds and may crystallise out in their passage through the kidney and produce blockage in the urinary tract. In addition, although possessing no therapeutic action, they retain the toxic properties of the parent compound and in some instances acetylation renders them more toxic. The degree of acetylation of the compound before excretion must also be considered when a local action is required in urinary tract infections for only the proportion of the sulphonamide which is excreted unchanged has therapeutic action locally. Many acetyl compounds are more soluble in an alkaline medium and, in consequence, this mechanism of excretion necessitates an adequate administration of fluids during treatment and also necessitates that the urine be kept alkaline.

The maintenance of constant adequate concentration of sulphonamide completely to prevent the growth of organisms has been shown to be of major importance. If all growth is not prevented early some organisms will continue to multiply and may become resistant even to very high concentrations of the drug. Moreover, such resistance may not be to one compound but may be present to all sulphonamide

compounds. This behaviour can occur in a wide range of organisms which may retain this resistance for a long time.

This phenomenon of resistance is unlikely to occur with short, adequate courses of treatment, but may assume importance during a long course of treatment and especially in relation to efforts at prophylaxis.

## THE THERAPEUTIC USE OF SULPHONAMIDES

It is essential for the optimum effect of the sulphonamides that certain principles in their use, and safeguards against ill-effects, should be carefully observed.

In the treatment of infection the concentration of the sulphonamide must be raised to an effective level at the site of infection at the earliest opportunity. The earlier this can be done the better, since sulphonamides are more effective against small rather than large numbers of organisms, and treatment is ineffective if suppuration has occurred. Having attained an effective level, this must be maintained throughout the whole period of treatment. Regular dosage is therefore essential to ensure that the rate of absorption shall be equal to the rate of excretion.

As the rate of excretion of many sulphonamides is relatively rapid, this will necessitate frequent and regular administration of the drugs. Failure to recognise or to observe this necessity may well negate effective control of the infection. The dosage must be regular throughout the 24 hours, even although it may entail waking the patient, for inadequate dosage or inconstancy of adequate concentration not only fail to control the infection, but may encourage the production of resistance in the bacteria to the action of the sulphonamides.

The sulphonamides are given by oral administration unless there is any special contra-indication. They may be given in tablet form or in powder form in water or suspended in milk or with mucilage. Alkali should be given during treatment in sufficient dosage to render the urine alkaline to litmus. Sodium bicarbonate is the best to use for this purpose. Doses of 1 g. 4-hourly will usually be sufficient, but must be increased if the urine is not rendered alkaline. The sulphonamides can, if desired, be suspended in the alkaline mixture with mucilage.

If swallowing is impossible the mixtures may be given by nasal catheter or by stomach tube. If this method be also impracticable the sulphonamides may be given intravenously or intramuscularly. For this route the soluble sodium compounds are used.

These sodium compounds are strongly alkaline and will cause considerable necrosis. Intramuscular injection should not be used, therefore, if it can possibly be avoided. In the rare instances, when it is essential, the injection site must be chosen with great care and should be remote from important surrounding structures, especially nerve tissue. Should more than one injection be required the injection sites should be as widely spaced as possible.

The intravenous use of these preparations is safe, provided care is taken to prevent any leakage around the vein, and the injection is given slowly. The solutions should never be given with blood or serum transfusion, since they may cause protein precipitation, but may be given in dilute solution by continuous infusion with saline or glucose saline.

The sodium compounds are totally unsuitable for injection into serous cavities, and should never be used in this way. Injection into the spinal theca will result in disastrous necrosis of the central nervous system.

The use of the sodium compounds either intravenously or intramuscularly should only be undertaken when administration by mouth is impossible. Administration by these routes should never be continued longer than is absolutely essential and the oral administration of suitable sulphonamides commenced as soon as possible.

An adequate response to treatment should occur within 4 days of full dosage. But treatment should always be continued for at least 2 days after the temperature has become normal. Under ordinary circumstances the total length of treatment will not, therefore, exceed 7 days.

Failure to respond within 4 days demands an urgent review of the case, for either the infection is resistant to this form of treatment, and perseverance with such treatment is both useless and dangerous, or the dosage is inadequate and must be corrected rapidly. It must also be recalled that even an organism susceptible to sulphonamide action will be protected from this action in the presence of suppuration.

During the whole of the treatment with sulphonamides it is essential to maintain a high fluid intake. The total fluids must be kept up to at least 3 litres in the 24 hours. This will usually ensure a urinary output of 1,500 ml. Sufficient alkali must be given to render the urine alkaline. These precautions must be taken whenever systemic treatment is undertaken. In some circumstances it is difficult to maintain this high fluid intake. When the intake remains low it is necessary to use the more soluble of the sulphonamide preparations such as sulphacetamide, and in less severe circumstances preparations such as sulphadimidine, the acetyl derivative of which is comparatively soluble and less likely than many others to provoke urinary complications.

Infections of the urinary tract need separate consideration. High concentrations of sulphonamide can be maintained in the urinary tract by low oral dosage, but with a fixed dose of sulphonamide the urinary concentration will obviously vary directly with the urinary volume. In order to produce effective bacteriostasis in the urinary tract an adequate level of sulphonamide must be present constantly in the urine. With diuresis a larger amount of sulphonamide will have to be given to maintain the same concentration of sulphonamide. Since with small or large urinary volume the risk of urinary complication will, of necessity, be the same, since the concentration of sulphonamide is the same, there is no advantage in preserving a diuresis.

The smaller the urinary volume, therefore, the smaller the dose of sulphonamide required. The smaller the dose of sulphonamide, the less the risk of systemic toxic effects, and therefore in the treatment of urinary infections it is advantageous to restrict the fluid intake, so that the dose of sulphonamide can be kept as low as possible.

When renal function is impaired, it may be necessary to maintain a high fluid intake to prevent the onset of renal failure. A higher dose of sulphonamide will have to be given in these circumstances and care observed in the choice of preparation. A more soluble preparation will usually be chosen, so as to obviate any risk of added urinary complication, and if treatment has to be prolonged it must be ascertained that the blood level of the sulphonamide has not risen to an unduly high level.

It has previously been mentioned that sulphonamide bacteriostasis is more easily produced when the concentration of bacteria is small rather than large. It is, therefore, sometimes advantageous in gross urinary infection to increase the urinary volume when using sulphonamides for such cases to reduce the volume concentration of organisms by a diuresis to assist the sulphonamide action.

In all circumstances it is advisable that the urine should be made alkaline. Not only does this render many excretion derivatives more soluble but frequently enhances the bacteriostatic action of the sulphonamides. In a few infections of low sensitivity to sulphonamides the alkali may not enhance the bacteriostasis. Such infections should not now be treated with sulphonamides.

Consideration of all these factors is essential in every urinary infection if good results are to be obtained, and a failure to recognise all the factors involved has resulted in a confusion of multiple régimes and dosage schemes.

Lastly, it should be remembered that the prolonged use of succinylsulphathiazole and allied compounds may inhibit the alimentary biosynthesis of components of the

vitamin B complex and an adequate supply of these vitamins should be ensured during the treatment.

## THE TREATMENT OF SPECIFIC INFECTIONS WITH SULPHONAMIDES

### THE TREATMENT OF INFECTIONS NOT LIMITED TO THE INTESTINAL OR URINARY TRACT

The scheme of dosage is essentially the same in the treatment of all infections in this group, and the range of dose is dictated by the severity of the infection and the mode of administration by circumstances.

Sulphanilamide and sulphapyridine are not now used, and have been superseded by the more active compounds such as sulphadimidine and sulphadiazine. Although sulphathiazole can be used with good results, the dangers of urinary complications and sensitisation are certainly much higher with this compound and, unless in individual circumstances a specific reason is present for its use, it is better avoided. The doses suggested are for adults of average weight and major deviations from the average will call for modification of the dosage either way.

In severe infections treatment should begin at once with a dose by mouth of 4 g., followed by 2 g. 4-hourly. This dose should be maintained for at least 3 days; after this, if the response has been good, the dose may be decreased to 1 g. 4-hourly, and should be continued until the patient has been afebrile for at least 48 hours. In many cases it is difficult to decide when the dose may be decreased with safety, and provided no signs of intolerance develop and the usual precautions are observed, it is quite safe to continue with the larger dose until treatment is completed. It should be stressed again that a good response should be obtained within 4 days, and the treatment should be completed in a week in uncomplicated cases. Failure to obtain this effect demands a review of the diagnosis and further investigation, as previously described. Should treatment need to be prolonged, it is often possible to maintain an adequate effect after 5 days by reducing the dose to 1 g. 6-hourly.

In cases of special urgency or acuteness, or when oral administration is difficult or impossible, initial doses may be given intravenously, or, rarely, intramuscularly. Doses of the sodium compounds up to 4 g. may be given as an initial dose intravenously, or the dose may be split, 2 g. being administered intravenously and 2 g. orally. Treatment should be continued orally whenever possible, but if impossible the intravenous route may be used, either by separate injections of 2 g. 4-hourly, or by continuous intravenous infusion in saline or glucose saline, 2 g. being administered during the four hours. For this purpose the sodium compounds of sulphadimidine and allied compounds may be used. The scheme of dosage and management follows the same pattern as with oral therapy.

In less severe infections an initial dose of 2 g., followed by 1 g. 4-hourly, is often adequate. In this case the dose may be reduced after the fifth day to 1 g. 6-hourly, but if in doubt it is better to continue with 4-hourly doses in order to avoid a fall to sub-effective blood levels.

Children show much more tolerance to the sulphonamides than adults per unit weight, and in infancy it is wise to give a dose calculated on body weight, at least until the weight exceeds 7 kg. The dose should be calculated on the basis of 0.1 g. per kg. of body weight 4-hourly, and an initial dose of double this quantity. The doses may be given intravenously when necessary as described for adults. Should vomiting rapidly follow the administration of a dose by mouth, the dose may safely be repeated.

When a child has reached a weight of 7 kg. or more, or approximately from the

ages of 1 to 3 years, it is unwise to persist with these dose calculations, and the dose for this age can be calculated as one-third of the adult dose. From the fourth to the tenth year half the adult dose should be given, and from the tenth to the fourteenth year two-thirds of the adult dose. After this time adult doses may be used.

The foregoing schemes of treatment are suitable for infections with the hæmolytic streptococcus, with the pneumococcus and with the meningococcus. They are also suitable for systemic treatment used to supplement local measures in wounds and in peritonitis.

In some infections with the hæmolytic streptococcus nephritis may complicate treatment. This complication does not prevent the use of sulphonamides, but great caution should be observed with the dosage and a careful watch kept for toxic manifestations, and it is preferable to use other methods. The blood level should be ascertained and should not be allowed to exceed 10 mg. per 100 ml.

Staphylococcal infections, purulent meningitis other than meningococcal, and mixed infections of the lung are unsuitable for treatment with sulphonamides.

Infections with the non-hæmolytic streptococci are rarely susceptible to sulphonamides and treatment with sulphonamides should not be given unless the organism is shown to be sensitive.

Chemotherapy with sulphonamides does not in any way influence the necessity for surgical intervention in the treatment of infection with suppuration, nor should it prevent the administration of antitoxin whenever this is indicated by the variety of infective organism.

#### THE TREATMENT OF INTESTINAL INFECTIONS WITH SULPHONAMIDES

The sulphonamides which are used for this purpose are sulphaguanidine, succinylsulphathiazole and phthalylsulphathiazole. Sulphaguanidine has been used extensively, but owing to its absorption from the gut in appreciable amounts and the danger of toxic reactions it has largely been superseded by the other two compounds, which are also more active against both coliform and dysentery organisms.

These drugs have been of the greatest use in the treatment of dysentery. Sulphaguanidine should be given in doses of from 3 g. to 5 g. by mouth, according to the severity of the infection, 6-hourly for 3 days, followed by 3 g. twice daily for 4 days. When the dose can be calculated on a weight basis an initial dose of 0.1 g. per kg. body weight, followed by 0.05 g. 4-hourly, should be used until the diarrhoea ceases, followed by 0.05 g. 8-hourly until the stools have been normal for 2 days. It is unwise to prolong this treatment for more than 14 days, but the treatment may be repeated after an interval.

Succinylsulphathiazole and phthalylsulphathiazole may be given in similar doses. The dose of the latter compound need not exceed 0.04 g. per kg. body weight, or 0.02 g. when the diarrhoea has ceased. The doses for children can be calculated on the same basis.

Sulphadiazine and allied compounds have also been used for the treatment of dysentery and give good results when used in the dosage recommended for severe infections in the previous chapter. Great caution, however, is necessary in their use to ensure against ill effects after absorption, particularly in relation to renal complications, and the same is true though to a lesser degree in the case of sulphaguanidine. In view of this and the efficacy of succinylsulphathiazole and phthalylsulphathiazole it is recommended that these should be used in preference to other compounds in the treatment of dysentery. When these compounds are used for more than a few days it is wise to ensure an adequate dietary supply of vitamin B. The results of treatment are good and the carrier rate is practically abolished in infections with Shiga and Flexner organisms, but in Sonne infections the results are less satisfactory.

Typhoid and paratyphoid infections and bacterial food poisoning do not respond to this treatment. The results in the treatment of cholera are still inconclusive, and in non-specific gastro-enteritis in children there is little or no benefit. In amoebic dysentery the sulphonamides have been used with benefit, often in association with other forms of therapy, to eliminate secondary infection prior to specific treatment. In non-specific ulcerative colitis the results are disappointing, but sometimes some benefit is produced by their use. When the lesions are in the rectum or lower colon predominantly some benefit may accrue from the use of retention enemata of 7 to 10 g. of succinylsulphathiazole suspended in mucilage, given daily over courses of 10 days. Continuous therapy is inadvisable, but the course may be repeated after an interval.

#### THE USE OF SULPHONAMIDES IN INFECTIONS OF THE URINARY TRACT

The choice of sulphonamide for the treatment of urinary infection should be determined by ascertaining the sensitivity of the organism if suitable facilities are available for this purpose. But in the interpretation of such information for clinical use the rate of excretion and the degree of acetylation of the compound must be taken into account, so that the actual concentration of the active compound that will be produced in the urinary tract can be assessed.

As a rule sulphathiazole is the most active compound. Excretion begins rapidly and will continue to maintain an adequate concentration in the urinary tract for well over 8 hours, so that in ordinary circumstances dosage will not need to be more frequent than 8-hourly, though in exceptional circumstances when an unduly high concentration is required, 6-hourly dosage may be necessary. Sulphathiazole is acetylated to a relatively small degree so that the effective excretion concentration is high. Unfortunately the acetyl derivative is relatively insoluble but the solubility is much increased in an alkaline urine and the bacteriostatic action of the parent compound is enhanced in an alkaline medium also. The quantity of compound, however, required to produce bacteriostasis in the urinary tract does not present any undue hazard under ordinary conditions if the precaution of making the urine alkaline is observed and unnecessarily high dosage is not used. In the usual method of treatment it is wise to use as small a systemic dosage as is compatible with the production of an adequate concentration of the compound in the urine. The total fluid intake should therefore be somewhat restricted and kept to approximately 1500 ml. The urine should be made alkaline to litmus by the administration of sodium bicarbonate. Sulphathiazole should then be given by mouth in doses of 0.5 g. 8-hourly. In severe or urgent cases this can be increased to 0.5 g. 6-hourly. Provided no toxic manifestations ensue this method is suitable for long-term treatment if necessary and also can be used for prophylaxis.

To prevent the relapse of infection, treatment should be continued until the urine is free from pus cells. The use of sulphathiazole is then stopped for 48 hours: a catheter specimen should then be examined. If the urine is sterile no further treatment is given, but it is essential that a further examination of the urine should be carried out 1 week later. Relapse should be treated by a further course on the same lines but frequent relapse should indicate the necessity for a different mode of treatment and, if it has not already been undertaken, full investigation of the urinary tract.

Treatment can be equally efficacious by the use of sulphadimidine and similar compounds, but a larger systemic dose will be necessary for a higher concentration of the sulphonamide is usually required and the degree of acetylation of sulphadimidine before excretion is much greater. The dose must therefore be increased as compared with sulphathiazole and a medium dosage would be 1 g. 6-hourly, and in the absence of precise information as to the sensitivity of the organism usually



it would be given 1.5 or 2 g. at a time. It is usual to make the urine alkaline in any treatment with sulphathiazole but the enhancement of bacteriostasis in an alkaline medium with sulphadimidine is not pronounced as with sulphathiazole and the acetyl derivative is not appreciably more soluble, although fortunately the acetyl derivative in this case is readily soluble over the ordinary range of pH and does not present any undue anxiety. Treatment with mixtures of sulphonamides has been advocated in order to spread the excretion time by using compounds of different excretion rates, and also to reduce the risk of urinary complications by diminishing the individual concentrations in order to prevent crystallisation. Such a method carries advantage in theory and provided the dosage be adequate will produce equally good results, though in practice it does not offer any great therapeutic advantage, as a rule, over the use of a single compound.

In some circumstances, particularly when kidney function is impaired, it may be essential to preserve a high urinary volume in order to maintain an adequate renal function. The fluid intake will have to be high enough to ensure a urinary output of not less than 1500 ml. per day, a larger systemic dose of sulphonamide will obviously be required if a urinary concentration equivalent to the other methods of treatment is to be obtained, and the sulphonamide should be given in doses as previously recommended for systemic infection of moderate degree. In order to avoid any possible additional urinary complication the more soluble sulphonamides should be used. Sulphadimidine is more suitable for this purpose for it is usually quite free from the risk of such complication, but if the renal impairment is considerable it may be necessary to use a freely soluble compound such as sulphacetamide which carries the advantage of great solubility but is unfortunately less efficacious in producing bacteriostasis and will require a higher concentration. The further management of infection should proceed exactly as described in the other method of treatment.

There are many circumstances in which such treatment may be required prophylactically, or merely to control the degree of infection prior to the use of more active measures to sterilise the urinary tract. Sulphadimidine and sulphacetamide in the way previously described, can be used for this purpose. If, however, such a course is prolonged and there is a known impairment of renal function it is wise to ensure by direct examination of the blood that the concentration of the sulphonamide is not reaching a dangerous level. In most circumstances the concentration should not rise above 10 mg. per cent., and above 15 mg. per cent. is dangerous.

## THE COMPLICATIONS OF SULPHONAMIDE THERAPY

During the administration of sulphonamides a number of toxic effects may be encountered. Many of them are of minor importance, and are seen with great frequency and only assume importance if they are unduly distressing to the patient or interfere with adequate dosage. In some cases, however, they may herald some serious manifestation of intolerance or toxicity, and no untoward symptoms or signs should be ignored without due consideration and assessment.

Some clouding or disorientation of mind is frequently encountered, especially with high doses of sulphonamide, and cyanosis with methæmoglobinæmia or sulphæmoglobinæmia is not uncommon. These manifestations are seldom of importance unless extreme in degree, and do not necessitate interference with treatment.

Vomiting and nausea are frequent, more especially with the use of sulphapyridine. They can frequently be overcome by altering the method of administration, and giving a powder suspended in milk or mucilage, or in combination with alkali. If vomiting is difficult to control, it is usually worth trying the use of another sulphonamide compound, but administration by parenteral means may be necessary. It

should always be borne in mind that the vomiting may herald more severe toxic reactions.

#### URINARY COMPLICATIONS

The urinary complications are all related to obstruction in the urinary tract by the deposition of sulphonamides or other derivatives owing to their relative insolubility.

Complete anuria may result if attention is not paid to the fluid intake during treatment, and endeavours are not made to keep the urine alkaline. If these precautions are carefully observed, urinary complications are infrequent. A careful watch should always be kept on the urinary volume and for the appearance of blood, both microscopic and macroscopic, in the urine. Spontaneous complaint of pain in the loins, or even generalised abdominal discomfort, should arouse suspicion.

In the presence of pain, diminished urinary volume or hæmaturia, great caution should be observed, and, unless absolutely essential, the treatment should be stopped. If it is necessary that treatment should continue, generous amounts of fluid must be given, together with alkali, and the urinary volume carefully observed. It is wise, also, if suitable, only to use an easily soluble compound such as sulphacetamide. If, however, oliguria continues, treatment should be stopped. If these measures prove inadequate, and anuria develop, or a marked oliguria persist, ureteral catheterisation should be performed, and irrigation of the ureters and renal pelves be undertaken. This measure should not be unduly delayed, as it has been shown to be a life-saving measure.

With due precaution, or early treatment, this complication is usually overcome, and no permanent ill effects on the kidney result.

#### TOXIC EFFECTS IN THE BLOOD

Many patients receiving treatment with sulphonamides show mild degrees of anæmia, which recover spontaneously or with the administration of iron during convalescence. Occasionally severe anæmia is seen with aplasia of the bone marrow, and in some instances severe purpuric manifestations. A rarer, but more disastrous anæmia occurs in the first few days of treatment in association with a severe degree of hæmolysis. More frequent in younger age groups, it appears to be associated with idiosyncrasy to sulphonamide, and is usually exceedingly sudden in its onset. Within a few hours of premonitory headache, severe hæmolysis, at times accompanied by hæmoglobinuria, may appear, followed by fever, jaundice and anæmia.

The white cells may also be affected. Agranulocytosis is a most dangerous complication. It is usually suggested by the onset of fever, headache and soreness or ulceration of the throat, occurring during treatment with sulphonamides. It seldom occurs early in treatment, and is most likely to be seen when treatment is unduly prolonged, thus differing from the effects on the red cells and suggesting that the disease may be brought about by sensitisation to the sulphonamides.

A minor degree of leucopenia is not infrequently seen, but agranulocytosis is not assumed to be present unless the polymorphonuclear count is below 1000 per c.mm., and this investigation is the only certain method of diagnosis. If, however, the white count falls rapidly, treatment should be stopped when the count has reached 4,000 per c.mm., in order to prevent, if possible, the danger of this complication.

The treatment of these toxic effects in the blood is immediate cessation of treatment with sulphonamides and the administration of fresh blood by transfusion. When hæmolysis has occurred, it is wise to keep the urine alkaline and ensure copious urinary output to prevent, if possible, the development of oliguria or anuria from the deposition of blood pigments in the kidney.

## DRUG FEVER

Fever is frequently produced by sulphonamide compounds. Most commonly it occurs during the course of treatment, but it may appear during the first day after cessation of treatment. It tends to occur earlier when sulphonamides have been given previously, and is unusual before the eighth day with initial courses of treatment.

Fever is the dominant manifestation, often with rigors, but there may be associated vomiting and even delirium, and occasionally pain and swelling in the joints. Exacerbation of fever during the administration of sulphonamide should arouse the suspicion of this complication, and unless an adequate explanation is forthcoming from the clinical condition of the patient the drug should be stopped. A rapid defervescence usually occurs and no further treatment for this condition is required.

More difficulty is encountered when the fever of the infection passes imperceptibly into drug fever. It should be borne in mind that fever present for more than a week indicates either a failure of treatment or the presence of drug fever. In either case, the treatment should be stopped and the diagnosis will then become apparent.

Fever which recurs after the drug has been stopped for more than 24 hours is almost invariably a recrudescence of infection, and not a result of the therapy with sulphonamide.

## CUTANEOUS MANIFESTATIONS

The most common toxic manifestation in the skin is the development of a papular erythematous rash, associated with fever and often vomiting. It most commonly occurs late in a primary treatment, from the seventh to the ninth day, but may occur even within a few hours if sulphonamides have been administered previously. The rash may adopt various patterns, and its distribution is variable, but in all varieties there may be pruritus, often severe. A condition resembling erythema nodosum occurs sometimes from the use of sulphathiazole, and rarely a severe exfoliative dermatitis with any of the sulphonamide drugs. The development of these complications is related to the development of sensitivity to sulphonamides.

Sensitisation can occur both from administration by mouth and by application to the skin, and in both cases seems to be provoked more commonly by sulphathiazole than any other sulphonamide. There appears to be a relationship between the combining of protein and sulphonamide and the development of this phenomenon. The process appears to take about 8 days, and if produced from skin application, induces local eczematous change with a generalised itching eruption, together with fever and malaise. If produced by oral administration, it may be associated with the development of cutaneous lesions, but may not be apparent until sulphonamides are used again.

In either case the condition of sensitivity may last for months or years. It may be specific for an individual compound, but may be a wide group sensitivity. This fact must be borne in mind if administration of sulphonamides is contemplated following their previous use either by mouth or on the skin. It should also limit the use of sulphonamides in treating minor degrees of infection, and application of sulphonamides to the skin should not be undertaken for more than a few days, 5 at the most. Treatment with sulphonamide might be urgently required at a later date, and alarming symptoms may be produced by even a small dose in a sensitive individual, and there is little evidence at present that methods of desensitisation are either safe or successful.

## PREVENTION OF COMPLICATIONS

From the preceding description of these complications of the use of sulphonamides, it is clear that a number of these troublesome and often dangerous manifestations

can be avoided if care is taken both in the choice of compound and the management of the other features of the individual case. Before deciding to use a sulphonamide it is essential to ascertain whenever possible whether sulphonamides have been given previously, and, if so, what compound has been used, how long it has been used, and in what quantity, and whether the patient experienced any untoward symptoms. To avoid as far as possible manifestations of hypersensitivity, a different compound should be prescribed, but as the sensitivity may not be limited to one compound a small dose of sulphonamide should be given first, if circumstances allow, and the full course should be delayed for 8 to 12 hours, to see if any signs of sensitivity occur. Such precautions may prevent severe reactions.

Whatever sulphonamide is being administered, it is important to ensure that the fluid intake is adequate, so that urinary volume will be at least 1,500 ml. in the 24 hours; and in the case of the sulphonamides, the acetyl derivatives of which are more soluble in an alkaline medium, alkali should be administered.

Finally, watch must be kept each day for early manifestations of toxic reaction, and if treatment has to be prolonged for any reason, a white blood cell count with both total and differential count must be done at least twice weekly after the first week of treatment.

## THE USE OF SULPHONAMIDES IN PROPHYLAXIS

In view of the striking results of the use of sulphonamides in the treatment of infection, it is natural that attention should be drawn to the possibility of the prevention of infection by the prophylactic use of such compounds, particularly in a community exposed to infection by an organism known to be sensitive to sulphonamides.

It is clear that the indiscriminate and prolonged administration of these compounds is not without grave risk, but if it should prove possible to overcome an outbreak of infection within a few days, the risks would be no greater than with the therapeutic use of sulphonamides, and such a result would amply justify the risk. For example, the risk would be well justified if infection with the hæmolytic streptococci could be avoided and a relapse of rheumatic fever thus prevented in an individual. To attain this effect, smaller doses of sulphonamide are required than would be necessary to treat an established infection, and there seems little doubt that sensitisation is far more likely with the larger therapeutic doses than the smaller doses required for prophylaxis. It is perhaps in this respect rather easy to over-emphasise the possible dangers of prophylactic doses without due regard to the benefits which may accrue. It must also be remembered that such measures might induce resistance to sulphonamides in various organisms. There is some evidence to suggest that in some epidemics this may have occurred; the risk, however, does not appear at present sufficient to negative further exploration of these prophylactic measures.

The use of sulphonamides in the prophylaxis of gonorrhœa and chancroid has been extensively investigated, and there is no doubt that adequate prophylaxis after exposure to infection will, in the vast majority of cases, prevent the development of the disease; and the result of individual prophylaxis has proved so successful that it has far exceeded the risk entailed, although there is no doubt that in inadequately treated patients the gonococcus may become resistant to sulphonamides.

The results of prophylaxis in rheumatic fever are also encouraging, and there is no doubt that relapses while taking small doses of sulphonamide over a prolonged period are definitely diminished. Although a number of such cases will show some toxic manifestations, the number is surprisingly small, and only in a few cases has it been necessary to discontinue the treatment. The patients, however, must be under careful supervision, especially in the early stages, to watch for the development of

fever or skin rashes, and again during the second to sixth week a careful blood examination will be necessary to avoid the risks of agranulocytosis.

The encouraging results in rheumatic fever led to an investigation of the control of scarlet fever and other infections with the hæmolytic streptococcus. There is a strong suggestion that epidemics of scarlet fever can be brought under control more easily by the widespread prophylactic use of sulphadiazine, particularly in a closed or semi-closed community. The carrier rates, however, for the hæmolytic streptococcus were not diminished, but at the same time there appeared to be a reduction in the number of upper respiratory infections. These experiments have been largely conducted in training camps, and it is not yet certain how valuable such measures will prove for civilian problems.

The development of an outbreak of cerebrospinal fever is always accompanied by a high incidence of carriers of the meningococcus in the naso-pharynx. During the treatment of the established disease it had been noted that the organism disappeared rapidly from this site. The application of this knowledge was exceedingly successful, and by the use of small doses of sulphadiazine for 2 to 3 days an outbreak of cerebrospinal fever abruptly terminated and carriers were virtually eliminated. If, therefore, a case of cerebrospinal fever occurs in a community and the carrier rate is found to be high, the whole community can be treated and the incipient epidemic aborted.

The use of sulphaguanidine and succinylsulphathiazole in the prophylaxis of dysentery, particularly in closed communities, has also been tried. In this disease, as in cerebrospinal fever, the symptomless carrier rate is often high, and this undoubtedly contributes to the spread of infection. Experiments of such prophylaxis have been very encouraging, but knowledge on this point is small at present, and it is unfortunate that the Sonne bacillus is less susceptible to this chemotherapy than other dysentery organisms.

Although the sulphonamides have no effect on virus infections, attempts have been made to prevent secondary bacterial infection occurring during the course of the disease. The results of the prophylactic use of sulphonamides in measles are encouraging, and the incidence of secondary infection is thought to be much diminished.

Prophylaxis with sulphonamides in other diseases is as yet virtually untried, but there is a wide field for possible future use.

E. F. SCOWEN.



## SECTION II

### INFECTIOUS DISEASES

#### A. BACTERIAL DISEASES

THE main results of the invasion and infection of the body by micro-organisms are discussed in the section upon infection and immunity. It is important to distinguish clearly between "invasion", "infection" and "intoxication", and the reader is referred to the section mentioned for the consideration of these several processes.

#### TOXÆMIA

This term is applied to the condition of a patient who is absorbing into the tissues and circulation toxins elaborated at some local site of microbic infection. The diseases caused by the specific microbes of diphtheria and tetanus are examples of toxæmia, the sites of infection being in the former disease the fauces or larynx or skin, and in the latter disease the damaged tissue about a wound or abrasion. The symptoms of toxæmia are variable, and depend upon the special affinity that the toxins concerned have for certain tissues or organs. There are, therefore, general symptoms common to many microbic infections: fever, rigors, malaise, vomiting, pains in the back and limbs, headache, sweating, etc.; and special symptoms, such as are manifested by an affinity of the toxin for nerve structures (paralyses, spasms, delirium, etc.) or for the heart (arrhythmia, tachycardia, circulatory failure, etc.) and others.

The importance of "focal sepsis" as a cause of toxæmia is hard to assess, but is certainly less than was once believed. In some instances, low fever and vague symptoms of general ill-health are associated with chronic infection of the teeth, tonsils, nasal sinuses or urinary tract, and are relieved when this is effectively treated. The attribution to "focal sepsis" of arthritis, various myalgias and other local disorders remote from the site of the infection rests on less secure ground.

#### SEPTICÆMIA

Septicæmia is a condition in which the infecting microbe transgresses the tissue barrier at the site of local infection and invades the blood-stream, multiplying therein, and thus continuing the infection in a general manner. The mere existence of the microbe in the blood-stream is not to be considered as necessarily constituting a true septicæmia. Thus we know that during the first few days of an attack of typhoid fever, of pneumonia and of certain other diseases, the specific microbe can very often be isolated from the circulation by blood culture. The more thoroughly the investigation of microbic infections by blood culture is undertaken, the more patent it becomes that at some stage or other the infecting organism exists in the circulation. *Bacteriæmia* is a convenient term by which to express the (temporary) existence of micro-organisms in the blood-stream in states other than true septicæmia.

There are two main conditions of septicæmia in so far as this is related to the local infection. (1) The local infection may be obvious, the septicæmia clearly resulting from this; or (2) no local infection may be discoverable, or the local infection may be, at best, merely surmised. Even at a careful post-mortem examination the source of local infection may not be manifest in some of the cases illustrating this type of septicæmia.

The microbes chiefly concerned in septicæmia are *Staphylococcus pyogenes*, *Streptococcus pyogenes* and the pneumococcus. Much less commonly *N. gonorrhæa*, *H. influenza*, *N. meningitidis* and *Ps. pyocyanea* perform this rôle.

The local infections tending to lead to septicæmia are chiefly concerned with the throat (streptococcus), the uterus ("puerperal fevers"), the subcutaneous tissues of the hand and foot (infections during operations and post-mortem examinations, septic wounds, etc.), and the site of surgical operations (post-operative septicæmia).

**Symptoms.**—The symptoms in septicæmia vary much; there is also great variation in the intensity and course of the disease. Some of the worst cases from the point of view of prognosis are those in which physical signs are conspicuous by their absence, whether as regards the site of the local infection or as regards the development of secondary lesions (thromboses, visceral inflammations, etc.). Thus, in a case of puerperal septicæmia, if a careful examination of the pelvic organs reveals no defect in the uterus or its adnexa, and if no signs of local concentration of the infecting agent be found elsewhere, the case is likely to be one of great anxiety.

It is to be realised that the description which follows is that of a fully developed case, such as was commonly seen before the introduction of chemotherapeutic and antibiotic agents. It happens but seldom now that such treatment is not established early in the disease, with consequent modification of the clinical picture.

The symptoms include pyrexia, usually considerable in degree, and most often intermittent in character. Rigors are not uncommon, though by no means constant. The patient is generally free from pain and local discomforts, but feels exhausted and very ill. The mental state is usually normal; in some cases the outlook is disproportionately optimistic. Sweats are common, especially if the pyrexia is markedly intermittent. Diarrhœa may occur. Some degree of general abdominal distension is common. The spleen may be sufficiently enlarged, yet sometimes too soft, to be palpable. The pulse is quickened, the pulse tension lowered and there may be subjective cardiac disturbances related to the toxic myocarditis which is an invariable result of the main pathological process. A progressive anæmia is one of the most striking features in most septicæmias, both clinically and upon examination of the blood. The leucocytes vary a good deal, and their number constitutes a helpful point in prognosis: the smaller the count the worse the outlook. Loss of weight is not a noticeable symptom, except in cases which become "chronic", nor must the absence of this feature lead, of itself, to a favourable view as to the outlook. Erythematous patches are often seen, both diffuse and discrete, especially in cases due to streptococcus infection; they are prone to be evanescent. Purpura is not uncommon. Joint pains and swellings are also common, and though such an arthritis may subside a careful watch must be kept for signs of suppuration. Pleurisy and pericarditis are not infrequent in staphylococcus infection.

**Prognosis.**—The prognosis is serious in all cases of septicæmia, though less so now than formerly. This is partly because, as the result of the earlier and more extensive use of blood cultures, more cases are recognised, but chiefly because the exploitation of chemotherapy and antibiotics has completely transformed the outlook in many instances of the disease. Of serious import are the following: rigors, the absence of signs of the local infection, the absence of a leucocytosis, rapid progression in the associated anæmia, early dilatation of the heart, vomiting, pleurisy, insomnia and delirium or stupor.

**Treatment** (see pp. 6 and 15.)

## PYÆMIA

When septicæmia is complicated by the formation of multiple abscesses, or of multiple foci of tissue necrosis, the clinical condition is conveniently spoken of as pyæmia.

All pyæmic patients are septicæmic, but not all septicæmic patients are pyæmic. Some septicæmias tend to be pyæmias from the first, in other cases there is a late development of the pyæmia after a period of simple septicæmia lasting for days or, it may be, weeks. In the great majority of cases of pyæmia the primary infection is obvious.

There are three types of pyæmia according to the anatomical distribution of the primary infection in relation to the circulation.

1. *Systemic venous pyæmia*.—This is the form which is seen in osteomyelitis due to *Staphylococcus pyogenes*, in suppurating wounds (staphylococcus, streptococcus, *Bact. coli*, etc.), in suppurations of the urinary and bronchial tracts, and in suppurating dermatitis and cellulitis. The metastatic abscesses form in the lungs, kidneys, perirenal tissues, joints, bones and, less often, in the heart wall and in the brain. The symptoms are those of a severe septicæmia together with those of the disease-processes set up by the focal events just referred to. Some of the cases are of long duration, and when this is so the patient is apt to become very emaciated.

2. *Portal pyæmia* (suppurating pylephlebitis).—This is the form of pyæmia resulting from certain pyogenic infections in the alimentary tract—rectum, colon, appendix, gall-bladder and elsewhere. The infection follows in ascending fashion the radicles of the portal vein, setting up a septic thrombosis and ultimately causing multiple abscesses in the liver. The symptoms are those of a severe febrile illness with acute or subacute abdominal signs, moderate jaundice and an enlarging liver. The diagnosis is sometimes difficult, but when indubitable the prognosis is extremely grave. The micro-organisms concerned are generally of the coliform group, or streptococcus; mixed infection is not uncommon.

3. *Arterial pyæmia*.—This form of pyæmia is seen in septic endocarditis. The focus of primary infection, so far as the pyæmic process is concerned, is the endocardium, and especially of the valves, where colonisation of microbes takes place, and whence innumerable septic emboli proceed into the arterial system. Seeing that in the great majority of the cases this focus occurs on the left side of the heart the emboli, if they set up metastatic areas of infection, do so in organs and tissues supplied by the systemic vessels: spleen, brain, kidneys, limbs, etc. In the less common instances, where the endocarditic focus is on the right side of the heart, the infection being grafted upon a congenital lesion, the emboli lodge in the pulmonary vessels, producing multiple infarcts in the lung, usually with associated pleurisy.

The microbes most often causing septic endocarditis are organisms of feeble virulence (streptococci of the salivary and faecal groups, or *H. influenzae*); this fact accounts for the infrequency of suppuration in the infarcted areas occurring in this disease. When, however, the endocarditis is due to such virulent microbes as *Staph. pyogenes* and *Str. pyogenes*, abscess formation does occur in the infarcts.

*Treatment* (see pp. 6 and 15).

## TERMINAL INFECTION

Micro-organisms which are found in the tissues in the course of a post-mortem examination are related to them in four different ways: (i) They may be the primary infection leading to the disease-process which causes death. (ii) They may be present as secondary infection, in association with the primary infection, and they may or may not be largely responsible for the death of the patient. (iii) They may be present as a "terminal infection", the disease-process from which the patient suffered being not itself manifestly of microbic origin, but one tending to lower the tissue resistance to infection. The terminal infection in these cases generally, as the name implies, precipitates the lethal event, or actually causes it. (iv) They may be present merely as an agonal or sub-mortem invasion, or even as a post-mortem invasion. It is



necessary carefully to distinguish between the last two of these relations. The mere isolation of organisms from certain tissues (e.g. the mucoid material of the middle ear) in the post-mortem room does not prove that they were present in these situations during life, still less that they were operative by way of actual infection. It is even doubtful if the cultivation of organisms from the blood of the heart, or from the cerebrospinal fluid, after death, gives evidence of infection during life, though some authorities consider that it does. Much depends, of course, upon the conditions at the time of the investigation.

*Terminal infection* does certainly occur, however, in well-recognised form and quite distinct from sub-mortem invasion. The organisms most often responsible for the condition are the less virulent strains of streptococci (*Str. viridans* and *faecalis*), the coliform group, staphylococci and the tubercle bacillus. *Proteus* and *Cl. welchii* are also found to operate in this manner at times.

The disease-processes in which terminal infection frequently occurs are cirrhosis of the liver, chronic nephritis, diabetes, leukæmia and heart disease. There is a latent form of septic endocarditis (most often streptococcal in origin) which is also of the nature of a terminal infection. Serous membrane tuberculosis, and especially peritonitis, is quite common in cirrhosis of the liver. Many of the patients in whom this terminal infection occurs are so ill at the time the event arrives that it frequently goes undiscovered, partly because their responses to infection are feeble and partly because clinical examination is difficult.

## STAPHYLOCOCCAL INFECTION

*Staph. pyogenes* infection may be either local or general. Local infections are usually cutaneous and include boils, carbuncles, pustular acne, onychia, sycosis, eczema (sometimes), ciliary blepharitis, suppurating sebaceous and Meibomian cysts, suppurating burns, cuts and abrasions. Invasion of mucous surfaces does occur and staphylococci may be responsible for infection of the cranial sinuses (including the middle ear), for some cases of broncho-pneumonia and of gastro-enteritis (food poisoning). Staphylococci may also be present in the urinary tract, particularly in association with the tubercle bacillus or a stone. General infection, while usually acute or even fulminant, may run quite a chronic course. Pyæmia is prone to occur and the metastatic foci may be single or innumerable. Perinephric inflammation is an important example of the solitary metastasis; in this condition the initial focus may be a trivial skin lesion, healed perhaps for several weeks; the onset is usually abrupt, often with a rigor and pain in the upper part of the loin; some further weeks may elapse before the peri-renal swelling becomes palpable. Osteomyelitis and some cases of septic arthritis, particularly of the hip and intervertebral joints, have a similar pathogeny but are wont to be the source of further emboli—in kidneys, lungs, myocardium and brain.

## STREPTOCOCCAL INFECTION

The streptococci form a group of micro-organisms in which the different members vary greatly in virulence. They also vary in their morphological and cultural features and in their biochemical reactions. There is, therefore, no little difficulty experienced in any effort at successful classification. Broadly speaking, there are two main groups of the microbe. (1) There is the highly virulent group called *Str. pyogenes*, to which the alternative name *Str. hæmolyticus* is applied, on account of its property of hæmolysing when cultivated on blood-agar. (2) And there are the less virulent groups, *Str. viridans* and *Str. faecalis*. The first type is usually seen in long and curling chains when recently isolated, and the second is usually seen in short chains of two, four or some number of relatively few members.

*Str. pyogenes* is the causative microbe in erysipelas, scarlet fever, in acute streptococcal abscess formation, in acute cellulitis and lymphangitis, in severe operation and post-mortem infections when these are of streptococcus origin, and in the more virulent streptococcus infections complicating the puerperium, influenza and some other specific fevers.

*Str. viridans* is found in association with pyorrhœa alveolaris, with secondary streptococcus infection in rheumatic fever, with arthritis occurring in connection with focal infections and with most chronic and subchronic infections of streptococcal origin. The streptococci found in the heart valves, and in the blood-stream in cases of subacute septic endocarditis, are for the most part of this nature.

*Str. faecalis* occurs in the lower bowel, and is a common cause of urinary tract infections, and an uncommon one of endocarditis.

The clinical results of streptococcus infection vary according as the infection is by the first or by the second of these types of the microbe. In infection by *Str. pyogenes* the disease-process is usually acute and often fulminant. Septicæmia results not infrequently, and pyæmia is not uncommon. If endocarditis results from the infection it is acute, and if embolism occurs the infarcts suppurate. In infection by *S. viridans* the disease-process is prone to be chronic, or at most subacute. Septicæmia is uncommon, except in association with endocarditis, in which condition embolic infarcts proceed to coagulative necrosis, but not to abscess formation.

Treatment (see pp. 6 and 15).

## ERYSIPELAS

**Definition.**—An acute specific disease, due to infection of the skin by *Str. pyogenes*, leading to local dermatitis and constitutional symptoms, of which fever and toxæmia are the most prominent.

**Ætiological Factors.**—Infection by *Str. pyogenes* is certainly the essential factor. The more carefully the cases are examined and the patients questioned the more certain it becomes that in the great majority of them some abrasion, it may be very slight, is present in the skin at the site of infection. This abrasion may be an actual wound, whether of a surgical operation or not. More often it is less apparent—a scratch, an insect bite, the chafing of a foot by a badly fitting shoe, etc. Contact by the human hand during the infliction of these slight injuries is not uncommonly a feature in the case.

Bad hygienic conditions seem to contribute to the incidence of the disease, such as defective sanitation and ventilation in public institutions. Formerly the disease was rife, almost epidemic, in hospitals, and chiefly amongst the surgical patients.

The disease is said to have a seasonal incidence (January to May), and Newsholme showed that the curves of its prevalence conformed somewhat to those of scarlet fever and acute rheumatism.

The disease is more common in women than in men, perhaps because of the puerperal cases.

**Symptoms.**—There is an incubation period of some 2 to 5 days. The onset is usually abrupt, often with a rigor (or a convulsion in little children) and a sharp rise of temperature—102° to 103° F. In severe cases the patient suffers from malaise, aching pains about the body and headache. The headache may be so severe as to mislead the observer into thinking there is some cerebral infection (e.g. meningitis). Delirium may be present, rendering the doubt still greater. If, as is sometimes the case, the local lesion is not apparent to the patient, or is not discovered on examination, the case may be very obscure indeed. But in the majority of instances there is a feeling of heat, tightness, or pain at the site of infection, leading to the recognition of the dermatitis. The inflammation usually appears during the second day—the skin is red, hot to the hand, slightly raised, with a spreading margin upon which

there may be minute vesicles containing clear or turbid fluid. The area spreads rapidly, and becomes œdematous, the degree of this latter effect varying with the situation of the inflammation. If this is the face, the œdema is marked, especially if the eyelids and lips are involved: the whole face may then be greatly swollen and the patient's features scarcely recognisable. On the limbs there is frequently present some degree of lymphangitis—red streaks, more or less continuous, stretching upwards towards the groin or axilla, in which situations the lymph nodes are frequently swollen, painful and tender. When the dermatitis is fully developed the vesicles already referred to may become blebs of considerable size.

In less severe cases the constitutional disturbance may be much milder, but so long as the diagnosis is definite the development of serious symptoms must always be regarded as possible, especially if the patient be elderly, debilitated or alcoholic.

The course of the disease varies considerably. If uninterrupted by specific treatment it lasts from 1 to 3 weeks. There is a rare type of *recurring erysipelas* in which the same area of skin is involved again and again. One or other of the lower extremities, or the face, is the common site. Though the immediate response to chemotherapy may be satisfactory in this type, drugs do not confer immunity.

**Complications.**—Albuminuria is not uncommon in all cases in which the temperature is high. Signs of nephritis supervene in not a few severe cases; when this is so the question should arise as to the previous integrity of the kidney. Œdema of the larynx is a rare complication; spread of the inflammation from the face to the orbit is less uncommon, and in this event meningitis is to be feared. Pneumonia sometimes occurs, again in debilitated, elderly or alcoholic subjects. Septicæmia, it may be with a fulminating form of septic endocarditis, is another serious possibility.

**Diagnosis.**—Reference has already been made to those cases in which the real nature of the disease is masked by the severity of the general invasion symptoms and the non-discovery of the skin lesion. Apart from such instances the diagnosis is rarely difficult if the examination be carefully conducted. The presence of even the smallest vesicle in association with a suspicious red area of skin should be investigated by piercing it with a very fine capillary glass tube and filming and cultivating the contents, even if these seem to the naked eye to be clear fluid. The discovery of a long-chained streptococcus in the films not only establishes the diagnosis, it enables the practitioner to adopt prompt measures of treatment.

**Prognosis.**—As is the case in all pyogenic infections, the introduction of sulphonamides and penicillin has completely altered the course and outlook of erysipelas. The prognosis, however, remains serious in infants and in old people. It is relatively unfavourable in alcoholics and nephritics. In all others the outlook is good. But septicæmia is of grave omen, and if associated with endocarditis it is frequently fatal. Meningitis, following orbital cellulitis and ophthalmia, is scarcely less lethal. The occurrence of acute nephritis, of cellulitis of the neck or of pneumonia, though all of these give rise to anxiety, does not render the case hopeless.

**Treatment.**—**PROPHYLACTIC.**—The patient should be isolated, and the greatest care should be taken in nursing, as well as in all the examinations made by the medical attendant. The sick-room should be large and well ventilated.

**CURATIVE.**—(i) *Local measures.*—Various applications are in use. Perhaps one of the best is ichthammol ointment (25 per cent.), though this has the disadvantage that it somewhat obscures the local signs. A lotion of perchloride of mercury (1 in 4,000), continuously applied on linen strips, is free from this objection. In erysipelas of the face the eyes should be protected by a few drops of mild silver protein (argyrol) (5 per cent.) applied two or three times in the 24 hours.

(ii) *General measures.*—The majority of patients show improvement in both the local and general condition in 24 hours, and there is no need for penicillin. Penicillin is, however, indicated if improvement is not manifest in 24 hours, or if one of the graver complications, e.g. septicæmia or orbital cellulitis is suspect; or if the infection

is complicating chronic nephritis or alcoholism. Full diet is allowed, provided it can be digested.

(iii) *Radiotherapy* has been successfully exploited in the recurrent variety.

## SCARLET FEVER

**Synonym.**—Scarlatina.

**Definition.**—A specific fever of sudden onset and acute course, characterised by faucial or other local infection by *Streptococcus pyogenes*, a diffuse punctate erythema of the skin, and a tongue at first furred but later raw, with prominent red papillae. Desquamation follows, and inflammatory sequelae may occur, involving especially the ears, cervical glands and kidneys.

**Ætiology.**—Scarlet fever is a disease of temperate climes and seldom gains a foothold in tropical or subtropical countries. It is endemic in large cities and populous centres, tending to flare up every few years in local epidemic form owing to the accumulation of susceptible subjects. Its general epidemic prevalence, however, is irregular, and no definite periodicity has been recognised. In the United Kingdom it is prevalent in the latter part of the summer and reaches its maximum at the end of the autumn; the period of least prevalence being the spring. Of late years, although the incidence has not appreciably declined, the mortality has fallen and the type of case become much less severe. Severity, however, has always varied greatly at different periods and in different regions.

The case mortality of scarlet fever is now not more than 0·5 or 2 per cent. It is greatest in the first year of life and diminishes with age.

Of predisposing causes, childhood and the absence of acquired immunity are the most important. Infants under 1 year of age seldom contract the disease, but mother and new-born infant may share the infection together. The maximum incidence occurs during the fifth and sixth years of life, a period slightly later than in such diseases as whooping-cough and measles. Adults are not exempt, but scarlet fever is rare in the aged. There is a tendency in some families to take the disease in a very severe form. As a rule, one attack protects permanently. Multiple recurrences should probably be attributed to some other cause than scarlet fever.

Poverty, by entailing shortage of food, overcrowding and defective isolation facilitates the spread of the disease and augments its death-rate.

The infective agent resides in the mucous secretions of the nose and throat and in the secondary suppurative lesions. The disease is infectious from its commencement, and the exact duration of infectivity cannot be predicted for any given case. Desquamation is not regarded as dangerous unless the scales are contaminated by the patient's discharges, and the infectivity of urine which remains albuminous has never been proved. The infectivity of scarlet fever is not nearly so great as that of measles, varicella or small-pox.

In most cases infection is by droplets derived directly from a person suffering with, or recently recovered from, the disease, but transmission by infected fomites or infected milk may also occur. Aerial infection by dust is possible, and dust from floors and blankets may possibly be a vehicle. It is an important fact that discharges from the nose, throat and ear may remain infectious for many weeks, and pre-existing purulent discharges also become infectious when scarlet fever is contracted. The occurrence of catarrhal infection of the nose or throat in a scarlet fever convalescent may lead to a recrudescence of infectivity.

Carriers have on occasions spread the disease without themselves showing signs of infection. On rare occasions, too, convalescents, although apparently healthy, have for months remained capable of transmitting the fever. The infectivity of carriers appears to be intermittent, and the receptivity of those exposed is increased by close

and prolonged contact, debilitating circumstances or acute disease, of which diphtheria may be cited as an example. Attendants on scarlet fever cases, although long immune, may finally contract the disease.

Infected milk may be responsible for localised and, sometimes, for more widespread outbreaks of the fever. In most instances the milk has been infected from a human source, in kitchen, dairy or farm, but possible derivation of infection from cows with ulcerated udders and teats is suggested by the well-known Hendon outbreak. Scarlet fever is not known to be transmitted by water or by sewage. Cases of wound infection are not numerous, but puerperal scarlet fever is well recognised.

**Pathology.**—Klein, in 1887, isolated a streptococcus from the teats and udders of cows at Hendon, and considered it the causal agent in a milk-borne epidemic of scarlet fever. It became customary, however, to regard the streptococci found in the throats and tissues of scarlatinal cases as secondary invaders, it being impossible to grow these organisms from the blood of patients suffering from the fever in its toxic, and presumably uncomplicated form.

Drs. George and Gladys Dick, of Chicago, however, in 1923 produced evidence that scarlet fever is a local infection of the throat by a hæmolytic streptococcus, and attributed the general symptoms of the disease to erythrogenic toxins absorbed from the local focus. They infected patients with scarlet fever by swabbing the fauces with a pure culture of this organism and elaborated a test analogous to the Schick test in diphtheria. This is the *Dick test*, made by the intradermic injection of 0.2 ml. of a suitable dilution of filtrate of a broth culture in isotonic buffered solution. Boiled filtrate is used as a control. An erythema at the point of injection, maximal in 24 hours, indicates susceptibility to scarlet fever. The same types of reaction occur as in the Schick test (*q.v.*) but in the Dick reaction the erythema is not indurated. During the first days of scarlet fever, unless antitoxin has been administered, a positive result may be expected. A vivid rash may mask a positive test. A few convalescents remain positive to the test, the majority become negative within 2 or 3 weeks. The Dick reaction is almost always negative at birth but the new-born infant of a susceptible mother is usually Dick-positive. It is noteworthy that a large percentage of Dick-positive individuals, although harbouring the bacilli, escape the disease.

In scarlet fever there are, therefore, two components: that resulting from the invasive properties of the hæmolytic streptococcus; and that due to absorption of the erythrogenic or Dick exotoxin elaborated by the invading organism. The same strain of streptococcus may cause scarlet fever in one patient and simple tonsillitis in another, because susceptibility to the infection may be associated with immunity to the exotoxin. It is the presence or absence of immunity to the toxin which is revealed by the Dick test. The causal organisms are usually  $\beta$  hæmolytic streptococci of Lancefield's group A, and Griffiths has shown by agglutination that they are members of a group comprising many different serological types.

Susceptible persons can be immunised by subcutaneous injection of increasing doses of scarlatinal toxin at intervals of 7 days. For adults the Dicks advise four or five injections, commencing with 500 "skin test" units and ending with a dose of 50,000, 80,000 or even 120,000 units. The skin test unit of scarlet fever toxin is the smallest amount which gives a standard positive reaction in persons susceptible, and a negative reaction in those immune. The standard reaction is the appearance within 24 hours of an area of erythema not less than 1 cm. in diameter. If too large an initial dose of immunising toxin is given, a transitory "miniature scarlet fever" may result, and rheumatism may be activated, but this is rare. The simultaneous injection of 2 or 3 minims of 1:1000 adrenaline chloride solution prevents serious reactions. Immunity develops more slowly than in diphtheria, and its duration is indefinite but prolonged. If the Dick test proves positive 6 months after, a further injection is recommended in the case of those nursing scarlet fever.

By immunising horses, an antitoxic serum is produced, which will bring about a

rapid amelioration of the toxic symptoms of scarlet fever, but has little influence in preventing complications.

Schultz and Charlton pointed out that intradermic injection of 1 ml. of the serum from a patient convalescent from scarlet fever will, in a few hours, cause a local blanching of the rash of the fever. This is known as the *blanching test*. W. Mair suggests that the test is due to antitoxic immunity in the donor, which will account for its occasional failure, and also the fact that the serum of some donors not known to have had scarlet fever, will give the reaction. Scarlet fever antitoxin has the same blanching property, and is now used for the test.

The post-mortem appearances in scarlet fever are not distinctive. The rash, unless hæmorrhagic, disappears after death. Such gross changes as are found in the fauces, cervical glands, lungs, heart, kidneys and liver, together with moderate enlargement of the spleen and lymphoid structures, merely indicate an acute infective process. In severely toxic cases, early decomposition with much post-mortem staining of the tissues, fluidity of the blood and subserous ecchymoses, indicate the intensity but not the identity of the infection. In cases surviving longer, inflammations of the lungs, serous sacs, endocardium, pericardium and joints may be present, and desquamation may be recognised. Scarlatinal nephritis is acute (type I) nephritis.

**Symptoms.**—The incubation is short, the period between infection and the first symptoms being from 2 to 4 days, with an average of 72 hours. The rash appears 4 days after injection.

Invasion is abrupt, the cardinal symptoms being vomiting, headache and sore throat. In some severe cases vomiting may be so urgent as to suggest irritant poisoning, especially if accompanied by diarrhœa; in mild cases vomiting may be absent. Rigor is uncommon, convulsions occasionally occur in children. Cough and catarrhal symptoms are decidedly rare, but a mild conjunctival injection is not unknown. The skin is hot and dry, the cheeks are flushed and the eyes bright. The limbs ache, the appetite is in abeyance and the tongue rapidly becomes coated with white fur, through which the papillæ project as red points (*strawberry tongue*). Slight nocturnal delirium is common. The temperature rises rapidly, and even on the first day may reach 103° or 104° F. An undue acceleration of the pulse is usually a marked characteristic of sharp infections, rates of 160 or more being common in young children, and rates of 120 to 140 in adults.

Very mild attacks often occur, and in these the symptoms of invasion may be absent, the rash being the first indication of the disease.

Inflammatory redness of the tonsils, fauces and uvula is present in the early stages of the disease. Later, this becomes more vivid, the tonsils are swollen and a distinct follicular exudate often appears; œdema of the fauces soon makes its appearance in severe cases, and may be accompanied by free mucous secretion. The tonsils may become covered by a thin necrotic film, or a more or less coherent exudate may form which encroaches on the faucial pillars and base of the uvula, and closely simulates the membranous exudate of diphtheria. In the more severe forms of scarlet fever, the tonsillar and faucial inflammation is very intense, and both ulceration and sloughing occasionally occur; thick muco-pus trickles down from the naso-pharynx, the nasal sinuses are invaded and acrid discharge blocks the nostrils and excoriates the upper lip. The respiratory obstruction is especially severe if adenoids are present. In such severe cases, inhalation broncho-pneumonia is a decided danger.

A punctate injection may often be seen on the soft palate and adjacent part of the roof of the mouth even before the appearance of rash on the skin, and is diagnostic. The skin eruption usually appears within 24 hours of the invasion, but may be delayed, sometimes for several days. It appears first on the upper part of the chest, the root of the neck and the upper arms as a finely punctate erythema; sometimes it is first seen in the axillæ. It quickly spreads over the trunk and limbs, reaching the legs last. The cheeks are merely flushed, and the existence of an area of circum-oral pallor is a

well-known and striking feature. The thick skin of the palms and soles is also in most instances free from the distinctive rash. The eruption shows a symmetrical intensification in certain regions, such as the lower abdomen and groins, the inner aspects of the thighs, the axillæ, the back, and the points and flexures of the elbows and knees. Pressure produces a transient blanching.

Of the two elements of the rash, one is minutely punctate, the other erythematous. It is the former which gives it its distinctive character. On coarse skin the puncta are particularly large. When the erythematous element is intense the skin may actually appear œdematous and the puncta be quite obscured. In such cases, on subsidence of the rash, yellow staining may be apparent. In addition to punctuation and erythema, minute petechiæ or small linear hæmorrhages are sometimes seen in the flexures of the elbows (*Pastia's sign*), groins, wrists and knees. By application of a tourniquet to the upper arm, petechiæ may be rapidly produced at the flexure of the elbow. This is the *Rumpel-Leede phenomenon*. It may also be positive in measles, small-pox, typhus, purpuric states and peliosis rheumatica. The linear hæmorrhages in the flexures remain when the rash has faded, and together with coarse injected papules on the outer sides of the arms and legs afford valuable diagnostic evidence. The rash on the buttocks and extremities may assume a slightly blotchy suppurary appearance, and so bear a distant resemblance to that of measles. Minute sudamina sometimes accompany the rash, giving rise to the variety known as *scarlatina miliaris*. Itching is not common, and urticaria is rare, but in some cases accompanies or precedes the outbreak of the rash.

The rash may be quite transitory or may last a week or even longer. Generally speaking, it is more pronounced in severe attacks, but sometimes attacks which are quite mild show rashes of considerable intensity and persistence. A dusky, blotchy, morbilliform eruption, generally limited to the convexity of the knees and elbows, but sometimes more widespread, may supervene in grave cases. It is known as the *septic rash*.

At the time of the initial faucial inflammation the lymph glands at the angles of the lower jaw are swollen and tender. During the eruptive period a moderate enlargement of the axillary and inguinal glands, sometimes of the posterior cervical glands as well, is often to be detected. The spleen is rarely to be felt. At times the glandular swelling leads to confusion with rubella, but the glands do not attain the size or show the marked localisation and tenderness characteristic of this disease.

In an average case a rapid rise of temperature marks the invasion, but the maximum may not be attained until the full development of the rash on the third or fourth evening, when readings of 103°, 104° or even 105° F. may be registered. Slight morning remissions occur. The fall is by lysis, reaching the normal by the fifth or sixth day of the disease. Termination by crisis is unusual. In bad cases of a septic type, the fever is prolonged, with increasing daily oscillations as septicæmic symptoms become prominent. In the malignant or toxæmic type of the disease, the fever is higher from the first and shows less remission, but occasionally is ominously subnormal throughout. A protracted remittent fever may occur in scarlet fever without local symptoms or complications to account for it; this variety is sometimes known as the "typhoid type". It is septicæmic in origin.

Abrupt rises of temperature during the convalescent period may signalise the onset of such complications as adenitis, otitis, nephritis, endocarditis, empyema or a metastatic abscess. Sometimes such pyrexial attacks occur without ascertainable cause, but a thorough examination of the patient is always necessary. Very mild cases of scarlet fever without obvious febrile disturbance certainly exist.

Desquamation is characteristic, but the degree to which it occurs is very variable. The tongue peels in patches or strips, and by the fourth day is raw with prominent papillæ (*raspberry tongue*). The flushed cheeks begin to shed a fine powder during the febrile period. Fine peeling of the lobules of the ears, of the margins of the lips and of the skin at the root of the neck, possibly also above the pubes, next makes its

appearance. By the end of the first week, peeling is generally well marked on the neck, chest, inner sides of the arms and possibly on the trunk. Within a fortnight it may be seen on the hands and possibly on the feet. It may not be complete on the latter until over 6 weeks from the onset of the fever. Partial redesquamation often occurs on the soles and is not infectious. The characteristic of the desquamation is the pinhole or ringed form in which it commences, the horny layers of the skin being shed first over the summits of the papillæ, forming apertures which enlarge centrifugally and fuse with their neighbours. Where the skin is thick, as on the hands, and feet, it tends to separate in larger flakes, or may even be thrown off in the form of incomplete casts. A characteristic form of peeling is sometimes seen on the fingertips when separation begins, as a split parallel to the free edge of the nail.

In severe cases considerable loss of hair may accompany or follow desquamation, but is temporary only, at all events in the younger patients. Furrows may also appear across the nails and take several weeks to reach the free edge.

Although desquamation typically proceeds as described above, there are cases of true scarlet fever where it is insignificant. It is unsafe to pronounce definitely against scarlet fever on this ground until 3 weeks have elapsed. In doubtful cases the hands and feet should be watched with care. A change to negative in the Dick test is confirmatory. A dry powdery appearance of the palms and soles is sometimes the sole indication of peeling. During desquamation the skin may appear harsh, dry, cracked or even eczematous.

A polymorphonuclear leucocytosis makes its appearance shortly after infection and reaches a maximum with the full development of the rash. It persists a variable time. In severely toxic cases it may fail to appear. A unique feature in favourable cases is an increasing eosinophilia during convalescence: this may even reach 10 per cent.

**VARIETIES.**—These are: (a) Simple or Benign; (b) Septic or Anginous; (c) Toxic Malignant and (d) Hæmorrhagic. Surgical or wound scarlet fever and scarlet fever occurring during pregnancy or the puerperium, also have their special features.

*Simple scarlet fever* is characterised by an onset of moderate severity in which the initial vomiting is not repeated and sometimes is absent. The faucial inflammation is slight, and the temperature, which may reach  $102^{\circ}$  F., has almost reached its acme in 24 hours; generally the climax is reached by the third day and amelioration of symptoms is then rapid. The urine may be normal throughout, or a trace of albumin may accompany the febrile disturbance. By the third or fourth day the tongue, at first slightly coated, has peeled, and slight powdering may be evident on the cheeks. Convalescence is rapid.

The *septic or anginous* variety comprises most of the severe and fatal cases. It is characterised by intense faucial inflammation and a tendency to the development of septicæmic manifestations. Repeated vomiting, sharp diarrhoea and prostration may signalise the onset. The faucial inflammation is either severe from the first or unexpectedly becomes so after a lapse of 2 or 3 days. The tonsils are much swollen and a patchy or coherent membranous exudate may form. Rapid and destructive ulceration of the tonsils, soft palate and its pillars sometimes occurs. The mucous membrane of the mouth may be excoriated and bleed at the slightest touch. The pharynx, and even the upper aperture of the larynx, may become involved in the inflammation, although, as a rule, implication of the latter is more suggestive of diphtheria than of scarlet fever. The discharges from the throat excoriate the angles of the mouth and a purulent acrid rhinorrhœa irritates the nares and upper lip. Deglutition is painful, respiration is obstructed, and the patient often sleepless, restless and later delirious. The cervical lymph glands become swollen and tender, and peri-adenitis or extensive sloughy cellulitis of the neck may ensue. This sometimes gives rise to fatal hæmorrhage by eroding large veins or even an artery. Cyanosis and coldness of the extremities and cardiac dilatation are common. The rash is generally intense, dusky and blotchy. The temperature often reaches  $104^{\circ}$  or  $105^{\circ}$  F.



the early stages of the disease, and pyrexia may persist long beyond the ordinary period and, changing its type, assume a remittent or intermittent septicæmic form.

Death may occur in the first week; more often life is prolonged into the second week, by which time circulatory failure becomes pronounced and hypostatic congestion of the lungs or spreading broncho-pneumonia occurs. Otitis, arthritis, purpurations of the serous sacs, endocarditis or nephritis may appear as complications, and a true scarlatinal pyæmia be evident.

Many patients show septic symptoms of a much milder type and make good recoveries. In grave cases which recover, improvement is very gradual and usually lasts in towards the end of the second week, but may be later.

*Toxic or malignant scarlet fever* is characterised by a toxæmic condition out of all proportion to the degree of inflammatory reaction in the throat. Such cases are marked by high fever, cerebral disturbance, profound prostration and grave circulatory failure. The rash is often petechial, but in the most severe attacks the patient may die before it has time to appear, and the real nature of the disease may only be revealed by the supervention of scarlet fever in contacts. The throat may be intensely injected, but the œdema, ulceration and thick, purulent secretion which characterise the septic variety may be absent altogether. Sometimes convulsions precede death, but mostly delirium merges into coma. Rarely, however, the patient dies of circulatory failure with vomiting, prostration and extreme pallor, but with clear intellect, suggestive of the type of death seen in some cases of diphtheria.

Sufferers from the malignant type of scarlet fever mostly succumb within a week of the onset, sometimes within 24 hours. But, as in the septic form, cases of the toxic or malignant type are not now so common or characterised by such extreme malignancy as formerly.

*Hæmorrhagic scarlet fever.*—Rarely scarlet fever assumes a purpuric form, with bleeding into the skin and sometimes from the mucous membranes also. This complication may make its appearance towards the end of the second or during the third week, and often proves fatal. It is possible that some of the cases formerly described as scarlatinal, where hæmorrhages occurred earlier in the eruptive stage of the disease, were really hæmorrhagic small-pox, with prodromal rashes of scarlatiniform character.

*Surgical scarlet fever* may be a sequel of operations, wounds or burns and scalds. It is often seen after operations on the nose and throat. The incubation period is short, often less than 3 days, and the rash may make its first appearance around the site of trauma. Faucial inflammation save in throat infections is often slight, and although the exanthema is present, faucial swabs may be negative. The infected wounds show a great tendency to suppurate. When the infection starts from a wound or abrasion on a limb, injected lymphatic vessels are often evident which show a characteristic punctate rash along their course. The corresponding lymph glands are enlarged and tender. The infected lesion may be small and is often overlooked, but the discovery of lymphangitis in a scarlet-fever patient should always arouse suspicion that the infection is of this type. When the fever follows burns or scalds the incubation period is also short and the accompanying angina may be slight. Cases of surgical and of burn scarlet fever where the throat is not primarily involved are not highly infectious. They are often left in general wards with impunity, but there is no doubt that occasionally they spread the infection.

Scarlet fever may arise in the pregnant woman. In early pregnancy it is rare, and is said not to lead to abortion; but occurring later it is very prone to produce abortion or premature delivery. When the infection occurs either immediately before or immediately after labour, it is apt to assume a grave form with a very high mortality from septicæmia; but mild attacks may occur even at this period.

Anomalous forms of scarlet fever occur in which one or more of the cardinal symptoms are lacking. In some only sore throat is recognised (*Scarlatina sine eruptione*), and yet the patient may transmit the typical disease. The cases of infec-

tious sore throat which often herald outbreaks of scarlet fever belong to this category. In these patients there is immunity to the erythrogenic toxins but antibacterial immunity is lacking. In others the rash is so ephemeral or atypical that its true nature escapes recognition; in yet others, the rash is the most pronounced feature, both fever and sore throat being insignificant. In cases where the rash is very scanty or insignificant and also after antitoxin treatment, desquamation may not be at all marked.

**Complications.**—These fall into two groups: those which arise locally in connection with the faucial and naso-pharyngeal inflammation, and those of a general or more remote character. To the first group, in order of frequency, belong otitis, cervical adenitis rhinitis, secondary tonsillitis and stomatitis, and aspiration bronchopneumonia. The second group includes rheumatism, albuminuria, nephritis, endocarditis, inflammations of the serous sacs and metastatic abscesses. In severe infections complications show a great tendency to occur in combination rather than singly.

**Otitis.**—This is met with in from 10 to 15 per cent. of the cases, and is an inflammation of the whole mucous tract of the middle ear. Its greatest frequency is in childhood, and its incidence is favoured by the presence of adenoids. It is more common in severe attacks, and may show itself by the end of the first week of the fever or later. It is often bilateral. Earache with an injected and bulging tympanic membrane are the signs to be expected, but sometimes a free discharge of muco-pus or pus and blood from the ear is the first indication. Unexplained pyrexia not due to fresh faucial or glandular extensions or to one of the distant complications should always lead to a careful examination of the ears. Perforation generally occurs in the upper part of the tympanic membrane. Deafness may occur, but fortunately is transient in most cases. Pain and tenderness with slight œdema of the mastoid appear in some instances, and may be accompanied by restlessness, vomiting and fluctuating temperature. The intensity of these mastoid symptoms may vary from day to day. In children the mastoid air cells are very superficial, and pus easily makes its way beneath the covering periosteum.

Rarely the labyrinth becomes implicated. In such cases sudden deafness, vomiting, vertigo and nystagmus may occur. Labyrinthine deafness may be permanent.

Such intracranial complications as meningitis, extradural abscess, lateral sinus thrombosis, cerebellar or temporo-sphenoidal abscess, belong to the more chronic forms of ear disease, but occasionally they arise during the acute stage. Persistence of mastoid tenderness with local headache and slight fever may be the only signs of smouldering inflammatory mischief invading the dura in the vicinity of the lateral sinus.

In most instances scarlatinal otitis subsides in a few weeks, the perforation of the membrane closes and hearing returns.

**Secondary adenitis.**—A considerable swelling of the upper cervical lymph glands may suddenly occur during the convalescent stage of the fever. The swollen glands are usually those behind the angle of the mandible or higher up under the insertion of the sterno-mastoid muscle. The adenitis, the basis of which is a congestive œdema with reticulo-endothelial proliferation, generally supervenes during the second, third or fourth week of the disease. It is marked by local tenderness and a sharp accession of fever. In favourable cases the temperature becomes normal in a day or two and the glandular swelling rapidly subsides, but suppuration may ensue.

Secondary tonsillitis should suggest the possibility of diphtheritic infection. Peritonsillar abscess may occur. Ulcerative stomatitis with much fetor of breath and sometimes even sloughing of soft tissues and necrosis of bone are also looked upon as secondary infections. Vincent's organisms, amongst others, should be sought for in such cases.

**Rhinitis.**—Acrid or purulent rhinorrhœa is characteristic of septic attacks. The air sinuses may become infected. A rhinorrhœa which occurs in the later stages of the fever is often responsible for the transmission of scarlatinal or diphtheritic infection. True diphtheria bacilli are more frequently found in the nasal than in the ear discharges.

*Nephritis.*—Slight albuminuria during the eruptive stage of scarlet fever is transitory and of no great importance, but about the third week nephritis may supervene. Its incidence has fallen progressively during the past 50 years in part because of the increasing mildness of scarlet fever and in part, perhaps, on account of the use of antitoxin. Formerly between 4 and 7 per cent., the case incidence is now under 0·5 per cent. It is more common in severe than in mild attacks. Chill, damp and exposure favour its incidence. The onset may be insidious or fulminant. In the insidious cases albuminuria, at first slight, and even intermittent, is the first sign. In the fulminant cases, headache, vomiting, pyrexia and even rigor may mark the onset. The urine becomes heavily loaded with albumin, casts and blood, and there is more or less suppression. The temperature may rise gradually or suddenly and show marked daily remissions. Lumbar pain is uncommon, but abdominal pain and constipation are marked features of some attacks. The amount of dropsy is very variable; it may be considerable in ambulant cases. Anæmia is of rapid onset and very pronounced. The blood pressure is raised. In a favourable case some improvement occurs within a week, the secretion of urine increasing, but the hæmaturia and albuminuria take much longer to clear up. In some cases albuminuria persists and chronic nephritis may ensue. The duration of an average attack may be put at 7 weeks, but is subject to much variation. Broncho-pneumonia, pulmonary œdema, œdema of the glottis and uræmic symptoms occur in severe cases. Convulsions may be recovered from, but coma is of bad augury.

In the septic type of scarlet fever sharp hæmaturia with casts and streptococci may accompany other pyæmic manifestations. This is embolic in origin.

*Rheumatism.*—This is common, and usually makes its appearance towards the end of the first week. The arthritis is fleeting and mostly involves the hands and wrists. Joint effusions are not always present. The temperature is raised. Sometimes the endocardium and pericardium are implicated, as in ordinary rheumatism, but the profuse sweats and creamy tongue are absent. Scarlatinal rheumatism is more common in adolescents and adults than in children. A history of previous rheumatism is often obtained.

A mono-articular or multiple suppurative arthritis with, it may be, other pyæmic manifestations is sometimes seen and is generally of later onset.

*Cardiac complications.*—There are three groups: those due to toxæmia; those secondary to rheumatic or pyæmic complications; and those accompanying nephritis. The toxæmic effects are cardiac dilatation and acceleration of the pulse, which are so characteristic of this fever.

Scarlatinal rheumatism is occasionally the precursor of simple or more rarely of malignant endocarditis. The influence of nephritis in producing hypertension has already been mentioned. Pericarditis may occur quite early in some cases of the septic type. The effusion is generally purulent.

*Pulmonary complications.*—Neither bronchitis nor broncho-pneumonia is common, but aspiration broncho-pneumonia may complicate septic cases. Oedema of lungs may arise during the course of acute nephritis. Lateral sinus thrombosis may give rise to pyæmic infarction of the lungs, empyema and even pneumothorax. A primary empyema, often of insidious onset, occurs in some patients. Pneumonia is rare; occurring early in the disease, it is streptococcal in nature and the prognosis is very grave.

Streptococcal peritonitis is a very rare sequel of scarlet fever.

*Nervous complications.*—If the delirium of onset, the nervous manifestations of nephritis and the cerebral complications of otitis are excluded, it may be said that nervous disturbance during the course of scarlet fever is rare. In those predisposed, epileptic fits may signalise the invasion. Hemiplegia with convulsive onset, incomplete paraplegia and peripheral neuritis have all been described, but hemiplegia is more often secondary to nephritis or to a cardiac lesion than primary. Chorea develops occasionally, usually in association with arthritis and endocarditis. Tetany some-

times occurs. Mental disturbance of a maniacal or melancholic type is an infrequent sequel, or may show itself during the acute stages.

On rare occasions *gangrene* of the extremities has been encountered. It is sometimes embolic in origin and leads to mummification, but gangrene has more frequently been described in association with purpura and sometimes with congenital syphilis.

*Post-scarlatinal diphtheria* was, in pre-antitoxin days, one of the gravest complications. Diphtheria may develop at the onset of the fever, but more often appears during early convalescence, frequently and deceptively as a rhinitis. It occurs more often in hospital-treated cases than in others. Every throat or nose inflammation about the nature of which there is the slightest doubt should be subjected to bacteriological examination at once. This is a more rational procedure than the indiscriminate injection of all scarlatinal patients with diphtheria antitoxin. All ear discharges should also be bacteriologically examined.

*Relapse and reinfection.*—A recurrence of the fever and rash before complete recovery from the initial attack occurs in from 0.5 to 7 per cent. of those treated in hospital. In such cases it is usual for the original infection to be replaced and protracted by one of different serological type.

*Diagnosis.*—Detection of  $\beta$  hemolytic streptococci in the nose or throat suggests scarlet fever and their absence the reverse. A positive Dick test before the third day of the attack is in favour of scarlet fever (it should become negative later) but a negative result does not exclude it. A positive Schultz-Charlton blanching test, made by the intradermic injection of 0.2 ml. of a 1 in 10 dilution of immunised horse serum applied to the newly developed rash, preferably on the lower abdomen, is of more value. The reaction takes 8 hours to develop, and attains a diameter of 3 cm. or more. Its value in the diagnosis of doubtful cases with ill-developed or fading rashes is small.

The chief diagnostic difficulty arises with mild attacks and with patients who come under observation after the initial stage. In the former the rash is evanescent, constitutional disturbance slight and the tongue often atypical. A history of a previous attack is of great weight for exclusion, but diagnosis can only be confirmed by the supervention of desquamation or of some characteristic complication. Sometimes the infection of a contact gives the clue. In days immediately following the rash significant signs are: slight staining of the trunk, faint striae in the flexures of the elbows, knees and groins, or a triangular patch of fading punctate erythema over Scarpa's triangle. The submandibular glands may be enlarged, and coarse papules resembling goose-skin present on the outer aspects of the arms and legs. The tongue has usually peeled by the fourth day and remains raw and papillated for about a week. Slight albuminuria, in the absence of diphtheria, is significant.

Desquamation of the typical pinhole type rarely occurs in other conditions than scarlet fever; the character of the accompanying symptoms and the time of appearance of the peeling must be taken into consideration.

*Simple tonsillitis* is distinguished by the absence of punctate rash, a tongue which does not peel but remains heavily coated and absence of desquamation elsewhere. But a simple erythema may be present, with fleeting muscular pains and sometimes otitis, and even endocarditis or nephritis may occur as complications.

Careful scrutiny of the body for a rash will usually prevent confusion with *diphtheria*. When faucial exudate is present in scarlet fever, it is usually softer and less coherent than in diphtheria, and any subjacent grey ulcerated areas are depressed below the general surface. In scarlet fever, too, the faucial pillars and palate may show the punctate rash, whilst pallor of the throat is more distinctive of diphtheria. In scarlet fever, febrile disturbance is more marked, initial vomiting is common and delirium may occur. The fugitive erythema which sometimes appears on the chest in diphtheria is not punctate. Bacteriological examination is decisive in diphtheria, but the two diseases may coexist.

When *influenza* is rife, cases of scarlet fever are apt to be overlooked; but in *influenza* rashes are exceptional, and careful observation of the progress of the disease will soon lead to a correct diagnosis.

*Lobar pneumonia* may, in children especially, by its abrupt onset, high fever, vomiting and faucial inflammation, give rise to suspicion of scarlet fever, a suspicion favoured by the flushed face and circumoral pallor which may be present. But the throat affection is trivial, the respirations are rapid and accompanied by action of the *alae nasi*, and there is no punctate rash on the chest. Sooner or later consolidation of the lung may be detected, often in such obscure cases at the apex or high in the axilla.

*Food, drug, serum and enema rashes* often cause difficulty. Of drugs the most important rash-producers are *copaiba* and similar oleo-resins, quinine, phenazone, the salicylates, aspirin and belladonna. Arsphenamine compounds, gold salts and sulphonamides may also do so. Anomalous distribution or polymorphic character of the rash should at once arouse suspicion, especially so the discovery of urticarial wheals. Fever, slight generalised adenitis, enlargement of the spleen and leucopenia are recognised accompaniments of some drug rashes.

*Erythema scarlatiniforme* is characterised by a punctate eruption which is sometimes patchy and confined to the trunk. The rash is remarkably persistent, and desquamation may ensue whilst it is still in the florid stage. The peeling is profuse and the subjacent skin often erythematous. The characteristic sequelæ of scarlet fever are wanting. The disease is not known to be infectious and is very apt to recur, which gives a clue to its recognition. *Acute exfoliative dermatitis* is by some regarded as identical.

*German measles* in the scarlatiniform stage closely resembles scarlet fever. The diagnosis turns on the trivial character of the accompanying symptoms, which are chiefly catarrhal, and the tender swelling of the posterior cervical, mastoid and occipital glands. Even when the rash is scarlatiniform on the trunk, distinct morbilliform elements may often be recognised about the wrists and on the lower extremities, and this, with the history of an initial spotty rash on the face and around the mouth, is of great significance. The eyes are suffused and subsequent desquamation is insignificant. Sequelæ are practically unknown.

*Measles* is more easily distinguished. The rash is different and invades the face. Catarrhal symptoms are pronounced and Koplik's spots are present. Difficulty is only likely to arise in those cases of scarlet fever where a blotchy rash is present, or where the appearance of a septic rash may simulate intercurrent measles.

*Prodromal rashes* of a scarlatiniform type may appear in small-pox, chicken-pox and measles. In small-pox, the petechial rash is usually confined to the bathing-drawers area and to the axillæ. Sore throat is in favour of scarlet fever, whilst rigor and severe lumbar pain suggest small-pox. The eruption of the latter disease appears on the third day, and a doubtful case should always be isolated over that period. The initial rashes of small-pox are said to be absent in children under 10 years of age.

The eruption of chicken-pox may be heralded by a rash which is scarlatiniform, but it is more likely to be erythematous. The diagnosis turns on the condition of the fauces and tongue, the absence of other signs of scarlet fever and the speedy appearance of vesicles on the palate and the trunk.

As a prodromal rash in measles, a scarlatiniform eruption is rare. The catarrhal symptoms which accompany it will arouse suspicion, which is confirmed by the discovery of buccal inflammation and Koplik's spots.

**Prognosis.**—The mortality of scarlet fever varies with the type of the prevailing epidemic. Of late years, in Great Britain, a mortality of less than 1 per cent. has been the rule. Of other factors, age is the most important, the mortality being greatest in infancy, diminishing rapidly after the second year, and continuing to fall as puberty is reached, the least fatal period being from puberty to 36, after which age a slight rise occurs. The death-rate is slightly higher in males than in females. Tuberculous

infections are apt to be lighted up, and puerperal patients run a grave risk of septicaemia. Chronic renal disease is likely to be adversely influenced.

Malignant attacks are often fatal, and the septic type of attack is also serious, especially if broncho-pneumonia supervenes. In adults, sleeplessness and delirium are unfavourable signs, and in children, convulsions occurring after the initial stage. Nephritis in many instances clears up, especially if detected early and properly treated. Grave symptoms are coma, repeated vomiting and suppression of urine. Oedema of lungs often precedes the fatal issue. Haemorrhagic scarlet fever, fortunately rare, may be rapidly fatal. Perhaps one case in every three recovers.

Of other complications, pericarditis is the worst. It is often purulent and may be associated with empyema. Early pneumonia is rare but often fatal. Hemiplegia, if of vascular origin, mostly becomes permanent. The danger in otitis media is remote rather than immediate.

**Treatment.**—**PROPHYLACTIC.**—Infectivity ceases mostly within a period of 4 to 6 weeks, but is apt to be prolonged in the presence of complications. A negative throat culture does not always indicate cessation of infectivity, and this test is not employed as a routine measure. Late desquamation of the hands and feet is not a source of infection, but discharges from the nose, throat or ear are dangerous.

Convalescent carriers are responsible for something less than 3 per cent. of the cases treated in fever hospitals. They are often characterised by unhealthy conditions of the nose, throat or ear, discharges from which may have reappeared. Patients with persistent tonsillitis, adenitis, rhinorrhoea or otitis should be isolated for at least 12 weeks from the commencement of the fever.

The discharge of patients direct from wards containing others in the acute stage of the disease should be avoided; isolation for a few days in a separate apartment is advisable. It is safer to remove those who remain Dick-positive during convalescence from all contact with acute cases. In cold weather the practice of bathing on the very day of discharge is not advisable, as a catarrh may be thus induced. Patients should not pass straight from isolation into the company of children and other susceptible persons.

Thorough disinfection of the sickroom and all its contents is essential. In wards special care should be taken to minimise dust from floors and blankets. This can be effected by oiling permeable floors periodically with a crude petroleum known as spindle oil and treating blankets and bedclothes with a 2 to 4 per cent. watery emulsion of purified mineral oil. This will withstand two or three washings.

Individuals in close contact with scarlet fever although themselves immune, have at times been found to convey the infection (*immune carriers*). The infectivity of some carriers has been known to last for weeks and even months.

An isolation period of 2 or 3 weeks is quite sufficient provided convalescence is complete and there is no evidence of inflamed throat or of discharge from the nose or ear, no suppurating or recently enlarged glands, and no eczematous patches about the nostrils, mouth or elsewhere. The quarantine period for contacts is 10 days, but often this is not enforced in the case of healthy adults no longer exposed to infection.

In institutional and ward outbreaks the contacts should be Dick-tested for susceptibility and throat swabs examined for hæmolytic streptococci. Those who harbour streptococci should be isolated. The susceptibles in ward outbreaks usually receive 5 or 10 ml. of antitoxin, but this establishes a temporary passive immunity to the toxin only, not to the infecting organism against which a daily dose of 1 g. of sulphadiazine may be given for 12 days.

**CURATIVE.**—Doubtful cases should be isolated until a definite diagnosis is made. Their premature transfer to a scarlet-fever ward is unjustifiable. Isolation of scarlet fever at home is most successful when a whole floor can be set apart for the patient and attendants, and no children of susceptible age remain in the house. The sick room should be large, light, freely ventilated and adequately warmed, the temperature

being maintained at 55° to 60° F. Overalls should be worn by attendants, and all articles used by the patient sterilised at once.

The action of the skin is promoted by a daily wash and a tepid sponge every evening during the pyrexial stage. This may be replaced by a daily warm bath when defervescence is complete. The bed coverings should be adequate, but not too heavy. During the febrile stage the diet should consist of milk, barley water and weak tea. Water and fruit juices may be given freely, to counteract dehydration. A full diet may be given directly the tonsillitis allows the patient to swallow without discomfort. In the absence of complications there is no need for the patient to be confined to bed for more than a week.

Attention should be paid to the mouth, teeth and gums, since oral sepsis is believed to bring its own train of local complications. The bowels should be regulated with mild aperients.

The sulphonamides and penicillin are of great value in controlling the local lesion; penicillin is to be preferred and should be administered in the doses recommended on page 8. These drugs, however, have no influence upon the rash and do not counteract the effects of circulating toxin. The routine use of antitoxin is no longer advocated and it should be reserved for the now rare severe cases. Reactions are often marked and the intramuscular route is advisable; 20,000 to 40,000 units may be injected depending upon the gravity of the infection. Preliminary desensitisation is essential in sensitised patients (see p. 4). A unit is the amount of antitoxin which neutralises 50 skin-test doses of the standard scarlet fever toxin.

Pyrexia, with restlessness, insomnia and delirium, may be controlled by tepid sponging and acetylsalicylic acid or paraldehyde. A cold pack at 60° or 70° F. for 15 or 20 minutes is beneficial when nervous symptoms are pronounced. After the middle of the second week, if albuminuria is present, cold sponging and cold packing should be avoided.

Persistent vomiting may be controlled by the use of diluted or citrated milk or temporary substitution of albumin water. *Liquor iodi mitis* in doses of 3 or 5 minims in water is often efficacious. When swallowing is painful the feeds should be small and often repeated.

For the local treatment of the throat and nose, gargles are quite ineffective. Ointment should be applied to the nares and upper lip to prevent excoriations.

Local septic complications should be treated with antibiotics or chemotherapy. Cervical adenitis is treated by smearing glycerin on the neck and applying cotton wool. Poulting appears to precipitate suppuration. Inflamed glands should only be incised when the presence of pus is certain. Care should be taken that the ears are clean. The pain of otitis may be mitigated by the application of hot, dry cotton wool, or a rubber hot-water bottle. Incision of the tympanic membrane is rarely necessary when chemotherapy is started early. Discharging ears should be cleansed frequently with hydrogen peroxide and mopped dry with spirit but never plugged. After the fourth week of the fever, removal of adenoids and infected tonsils shortens the duration of discharge. Watch must be kept for mastoid tenderness and œdema. If there is persistent mastoid tenderness or pulsating purulent aural discharge in spite of chemotherapy, mastoidectomy is required.

Scarlatinal rheumatism is usually mild and transitory; salicylates, or acetylsalicylic acid give relief. When joint swellings persist, a mild pyæmic condition is often present, and may be associated with endocarditis. Some advise a cautious trial of intravenous scarlatinal serum in such cases, but the use of sulphonamides or penicillin is more rational. When the presence of pyæmic arthritis is suspected an exploratory aspiration under strict asepsis may be advisable. This may lead to subsidence.

*Scarlatinal nephritis*.—The importance of daily examination of the urine and avoidance of chill must be emphasised. No patient with albuminuria should be allowed up and, if nephritis sets in, prolonged rest in bed is more than ever essential.

The incidence is said to be less in patients treated with penicillin. Treatment is the advocated for acute nephritis, described on p. 1119.

Grave circulatory failure calls for strict recumbency and oxygen inhalations.

The most promising treatment for *hæmorrhagic scarlet fever* is blood transfusion.

## RHEUMATIC FEVER

**Definition.**—An acute disease, characterised by fever, arthritis and a special tendency to carditis.

**Ætiology and Pathology.**—An association of rheumatic fever with hæmolytic streptococci of Lancefield's Group A has long been recognised and is firmly established. The history in many cases is of an upper respiratory infection followed, after a latent period of 2 to 3 weeks, by the onset of rheumatic fever. Years of patient investigation have failed to prove the disease immediately attributable to invasion of the tissues by these streptococci; blood cultures are uniformly negative and in fatal cases no bacteria can be recovered from the diseased organs. The problem of the relation between the hæmolytic streptococcus and the lesions of rheumatic fever remains. The explanation most favoured at the present time is that the disease process is a manifestation of bacterial allergy (see p. 5). The toxic products of streptococcal infection are the allergens in the view of the protagonists of this hypothesis, who cite the resemblances between rheumatic inflammation and the allergic tissue response of animals injected with foreign proteins in their support.

While most workers regard rheumatic fever as a consequence of hæmolytic streptococcal infection and as an example of specific bacterial allergy, this belief has not gone unchallenged. Although serological evidence of infection, such as positive precipitin and complement fixation reactions and raised titres for antistreptolysin-O and antifibrinolysin, is usually to be found, it is not invariable. It has been suggested that the rheumatic process is usually set in motion by a streptococcal infection, but that its effect is not a specific one and that other influences, such as trauma, cold, damp and fatigue may initiate attacks. Those who hold such views regard rheumatic fever as a non-specific allergic reaction or possibly as a response to an increasing titre of auto-antibodies against some constituent of connective tissue.

It is possible that susceptibility is hereditary and claims have been made that it is transmitted as a single autosomal recessive character. There is, however, general agreement that rheumatic fever is more common in the presence of poverty, overcrowding, malnutrition and damp, and it is difficult to separate the effects of these environmental factors from hereditary predisposition.

Rheumatic fever is rare before the age of 4 years or after the age of 30 years; the curve of incidence shows a peak at 7 years. There is a particular tendency to recurrent attacks. Little racial predisposition is to be noted and, although florid rheumatic fever is rare in tropical countries, rheumatic heart disease is common. In Great Britain autumn provides more attacks than any other season of the year.

**MORBID ANATOMY.**—The characteristic pathological lesion of rheumatic fever is the Aschoff node. It is usually fusiform in shape, consisting of a central area of necrosis with a number of epithelioid cells arranged fan-wise and a surrounding halo of lymphocytes. The nodule is later replaced by fibrous tissue.

Rheumatic fever is an affection of connective tissue and its lesions are scattered throughout the body; the most frequent sites are the heart, joints, subcutaneous tissues, arteries and serous membranes. Inflammatory reactions occur in systemic, pulmonary and cerebral arteries; they are marked by lymphocytic infiltrations with proliferative changes in the arterial linings which may obliterate small vessels. Pulmonary consolidation of a curious rubbery consistence is not uncommon in fatal cases, but its specific rheumatic character has been called in question.

The heart bears the brunt of the affection in fatal cases; Aschoff bodies are



always found in the myocardium, disposed around vessels, and often associated with a diffuse myocarditis. Lesions occur along the line of closure of the valves: swelling and necrosis of the fibrillæ are followed by fibrinous depositions which later become organised to form the familiar verrucous vegetations and finally, undergoing thickening and fibrosis, lead to the valvular defects of chronic rheumatic heart disease.

**Symptoms.**—In adults the onset often following 2 or 3 weeks after a streptococcal infection of the naso-pharynx, is usually abrupt, with the sense of chill, accompanied almost at once by pains in a joint, the knees and ankles being the commonest. The characteristic clinical picture is of a fugitive polyarthritides; the acute inflammatory changes in one joint flitting overnight to light upon another, leaving the first apparently normal. Knees, ankles, wrists and shoulders are affected in this order of frequency. The number of joints affected and the severity of the inflammation vary greatly; at its worst there is swelling, redness with intense pain and a rapidly appearing effusion. Less commonly the joint disease affects several joints simultaneously and in children small joints may show changes. It is not rare in the adult for the arthritis to be strictly monarticular, usually limited to one knee, and for the migratory tendency to be lacking. Articular function suffers no permanent impairment and is soon restored to normal.

The temperature may reach, but seldom exceeds, 102° F. unless a complication such as pericarditis be present; the fever remits, or even intermits, so that the chart shows an "irregular" curve. The pyrexia is peculiarly sensitive both to exacerbations in the disease (which are common), to relapses (which are also common) and to complications. Sweating is generally profuse, the sweat being of a peculiar "acid" smell. The urine is scanty and high coloured, and if the fever is marked there is usually a trace of albumin present. As in most acute fevers, the secretions of the mouth and alimentary tract are lessened, leading to a heavily coated tongue, anorexia and constipation.

The heart is affected to a variable degree by rheumatic inflammation in at least 75 per cent. of cases of rheumatic fever. Definite evidence of carditis in the presence of active rheumatism is provided by (1) the development of a blowing pan-systolic murmur at the apex or a short mid-diastolic apical murmur indicating mitral valvulitis, (2) the development of a mid-systolic murmur at the base or an early diastolic murmur in the left parasternal region indicating aortic valvulitis, (3) a rough to-and-fro murmur over the præcordium indicating pericarditis (together with electrocardiographic changes), (4) outward displacement of the apex beat due to cardiac dilatation. Slight shifts in the position of the apex are difficult to evaluate and gross degrees are associated with other signs of carditis, (5) the appearance of signs of heart failure, (6) the development of conduction defects or other arrhythmias confirmed by changes in the electrocardiogram. Gallop rhythm is not reliable and difficult to interpret as most normal children have a third heart sound and tachycardia due to fever often produces a summation gallop.

The blood shows a considerable leucocytosis (15,000 to 30,000) and an anæmia which is a constant feature of the disease and quickly reveals itself in the patient's facies. The erythrocyte sedimentation rate is increased during the active stages of the disease; in the acute phase Westergren's method may give readings of 100 mm. or even higher in the first hour.

Electrocardiograms show pathological alterations in the great majority of cases if tracings are repeated sufficiently frequently. The PR interval will frequently exceed 0.21 seconds; abnormal T waves and evidence of intraventricular block may occur. A prolonged QT interval is common during the active phase.

**ABERRANT TYPES.**—Subacute attacks are common, especially in children (see p. 51) and in old rheumatic subjects. Their importance lies in the fact that all the time the heart may be suffering damage. Although this is less common in adults than in children, arthritic signs may be absent in cases of rheumatic endocarditis, as in rheumatic pericarditis.

**Complications.**—As already stated, at least one-half of all cases develop some heart lesion. We have spoken of *myocarditis* and of *acute endocarditis*, and of the advent of the latter, should it arrive, about the end of the first week. The endocarditis is generally a valvulitis; most often mitral, less often aortic, but in some cases both mitral and aortic. *Pericarditis* is less common, though it may be the only manifestation of rheumatic infection; and pericardial effusion, especially of the massive sort, is nowadays quite uncommon.

Skin eruptions, though a specific feature of the infection, are not very common, except in children. The profuse sweating quite often leads to *sudamina*, and these, becoming inflamed, lead to *miliaria*. True *rheumatic erythemata* are much more common in the subacute cases than in the acute ones. *Purpuric* eruptions, again, are more often seen in aberrant types of the disease.

The only *pulmonary complication* of any consequence is pleurisy, and this is by no means common if we preserve the usual strict criteria of physical signs for its recognition, and omit "pleurodynia", in which condition the pain is more often intercostal than pleural. Indeed it may be said that, in the absence of pericarditis and of severe endocarditis, rheumatic pleurisy is rare. Pneumonia also is unusual, but there is a condition of the lung in severe rheumatic fever, again when complicated by grave endocardial, pericardial and pleural affections, which simulates it somewhat; the lung tissue is in a mixed state of congestion, collapse and œdema. A thin serous pleural exudate often accompanies this condition of the lung, and, no doubt, because of the associated pericarditis, it is more often found on the left than on the right side. Rheumatic *peritonitis* has been described in children.

*Hyperpyrexia* was formerly a much dreaded, and not very uncommon, complication. It is now of extreme rarity. The condition arises suddenly in most cases, though in a few there is a suspicious prodromal amelioration in the pain, sweating and general discomfort. The temperature rises rapidly to 106°, and unless checked by cold applications it may quickly reach 109° or 110° F. Before this stage is reached the patient has become tremulous and excited, then delirious and then semi-comatose, with a dusky lividity of the face and a failing pulse. Most of such cases are fatal. If prompt treatment succeeds in lowering the pyrexia it may need to be resorted to again in a few minutes or hours, since recurrence of the condition is to be expected.

**Course.**—The course of rheumatic fever is variable and unpredictable. Monocyclic, polycyclic and continuous forms have been described, but a more useful classification is into: (a) those in which the active process rapidly subsides and the patient recovers without cardiac damage or with only a minimal valvular defect; (b) cases in which the process remains active for months or years with frequent recrudescences and rapidly advancing disability; (c) rapidly progressive cases terminating fatally in a few weeks or months.

Variations from these three categories are common. Recurrence is frequent, being estimated at 25 per cent. in patients between 4 and 13 years, but only 8.5 per cent. in patients between 14 and 16 years.

Activity of the disease process is judged by the presence of fever, arthritis, rheumatic nodules, tachycardia, leucocytosis, a raised erythrocyte sedimentation rate and transient electrocardiographic changes.

*Convalescence* is often tedious, and the resultant anæmia and heart weakness warn the careful practitioner not to attempt to hurry it. Rheumatic fever patients are as liable to *relapses* as they are to recrudescences, and it is no uncommon thing to see a patient slip again into almost as bad a state as he originally was, including, it may be, painful swelling of the very same joints as were first affected. The great danger of these relapses lies in the risk of heart inflammations arising during the subsequent attacks, when perchance the patient escaped them at the first.

**Prognosis.**—Recovery is the rule in this disease; death during a first attack is very uncommon. When death occurs there is invariably serious carditis, especially

myocarditis, and acute pulmonary complications (pleurisy and "rheumatic pneumonia") are usually present also. In rare cases, death occurs in a state of hyperpyrexia. When the attack supervenes upon old rheumatic carditis, the prognosis is less good, heart failure being more easily induced. But in general it may be said that rheumatic fever is serious, not from its case mortality, but from its crippling effect upon the heart. *Residual conditions* are entirely cardiac injuries and chiefly scarred valves and auricular fibrillation.

**RHEUMATIC FEVER IN CHILDREN.**—The disease is very common in children, in whom, however, the clinical picture as above described is apt to be departed from in several respects. (1) The arthritis is a less marked feature; it may be absent altogether, and even when it is a troublesome element in the case, the degree of pain is prone to be disproportionate to the amount of redness and swelling of the joints, and may be muscular rather than articular. (2) Skin eruptions are relatively more common—various erythemata especially, of which the most characteristic is erythema marginatum, but also purpura. (3) *Rheumatic nodules* are almost confined to children, having the same age-incidence as *chorea* (see p. 1515). These are discrete lumps, varying in size from small peas to horse-beans; symmetrical in distribution, they are found in the scalp, along the margins of the scapulae and bones of the forearm, about the knuckles and elbows, and, less often, in other situations. They are sometimes tender and painful. They come and go. Occasionally they are present in large numbers; the case is then most likely to be subacute in type and very tedious in its course: they are, therefore, of grave prognostic import as to the ultimate state of the heart, being indicative of a "smouldering" endocarditis. They consist of elements approximating to the "essential" lesion of the disease to which reference has been already made. (4) But the most important difference observable between the disease in children and in adults is the fact that in the former the process is not seldom subacute in its onset and course, and for this reason frequently overlooked for a time. Add to this fact that the tendency to heart involvement in these subacute attacks is no less than in the more acute and more highly febrile bouts, and it is obvious that the recognition of this state of things is of the utmost importance. Unfortunately a large number of cases of subacute rheumatic endocarditis must needs arise without the possibility of prevention, but it is probable that a large number might also be prevented, or considerably modified, by prompt treatment of the subacute rheumatism in childhood which causes the injury. These attacks of subacute rheumatism are sometimes characterised by intercostal pain, sometimes by abdominal pain, sometimes by pain in the legs without special reference to the joints. There seems no doubt that so-called "growing pains" are often rheumatic in nature. In any child so affected the heart should be examined critically, and from time to time. The presence of sore throat, of acid sweats, of one of the erythemata, in conjunction with the above-named pains, should determine a decision to treat the child as suffering from the rheumatic process. The presence of nodules is decisive in a doubtful case.

**Diagnosis.**—Cases of the fully developed disease do not often lead to difficulty in diagnosis, given ordinary care on the part of the practitioner. A few diseases, however, require mention. (1) *Pyæmia* due to coccal infection may lead to some confusion, and the following differential points are worthy of notice. In septicæmia, when there is arthritis, the latter is usually constant in one or two joints, not fugitive and involving many as in rheumatic fever. Moreover, the joint changes tend to suppuration and permanent destruction of the joint structures. Blood cultures and joint-puncture fluids are not infrequently positive in pyæmia, whereas they are constantly negative in acute rheumatism. Rigors are common in pyæmia, the heart infection is likely to lead to embolism, a condition not found in rheumatic fever. But between this type of streptococcal septicæmia and rheumatic fever all grades of cases are seen.

(2) In children *acute osteomyelitis* may be mistaken for rheumatism; rarely does

the converse error arise. But the disease-process is nearly always much more severe, the temperature being much higher and showing greater oscillations. The painful part is generally the lower end of the femur or tibia, and careful examination reveals it to be epiphyseal rather than arthritic. As in pyæmia, to which type of infection the disease really belongs, blood cultures are usually positive (*Staphylococcus aureus*).

(3) *Gonorrhæal arthritis* is not usually so acute a disease, nor is the patient often so ill as in rheumatic fever. The affected joints are fewer in number, and, as in pyæmia, the course of the individual involvement is much longer. The inflammation, too, affects periarticular as well as articular structures; not seldom it involves adjacent tendon sheaths also. Gonococci may be isolated from the joint effusions. Although the presence of a urethral or vaginal discharge makes a diagnosis of gonorrhæal arthritis likely it does not prove it; and it must be remembered that the discharge does not infrequently ceases temporarily with the onset of the arthritis.

(4) *Gout*, when present in the acute arthritic form, may be mistaken for rheumatic fever; rarely does the converse happen. The patient is generally a man over 40 years of age; the number of joints involved is rarely more than two; the skin over these is generally dusky red in hue, and shining; there is often definite soft œdema. The presence of severe pain when the affected joints are at rest is much in favour of gout. The degree of fever is usually much less in proportion to the degree of joint inflammation than is the case in rheumatic fever. The presence of tophi may be taken as confirmatory of gout in a doubtful case.

(5) *Reiter's syndrome* is distinguished by the history of conjunctivitis and urethritis; the arthritis is seldom fugitive and frequently affects simultaneously two or more joints. Fever seldom exceeds 100° F. and there is no improvement with administration of salicylates.

**Treatment.**—(1) *General.*—With as much promptness as possible, the patient is put to bed, and is kept there until it is certain that the inflammatory process has ceased to be active. To gauge activity of the rheumatic infection both clinical and pathological observations are needed. If the obvious features of acute rheumatism, such as fever, sweating, arthritis and subcutaneous nodules are absent, if the position of the apex beat remains constant, if the pulse frequency during sleep is normal, and if anæmia, leucocytosis and the raised erythrocyte sedimentation rate have disappeared then the infective process may reasonably be considered at an end.

The bed should be chosen carefully; narrow enough to admit of easy nursing, and having a soft but firm mattress. The patient lies in blankets with a long flannel garment opening down the front, and having sleeves to the wrists; this garment is changed as frequently as need be, according to the degree of sweating. The position of the patient is one of recumbency, with the affected joints supported in a position of maximum comfort. Movements of the limbs are generally best carried out by the patient's own efforts, and in all except severe cases, movements of the body as a whole may also well be left to the patient. During the acute febrile period the diet should be light and an abundance of fluids permitted. Once the fever is under control the quantity may be increased so that a high caloric value is maintained but care should be taken that it remains easily digestible.

Sodium salicylate is generally held to be a specific remedy. It controls the arthritis and causes the fever to decline. The erythrocyte sedimentation rate reaches normal levels more rapidly and there is general belief, but no convincing proof, that recurrences are fewer and health is regained more quickly when patients are treated with this drug. It should be given in sufficient quantities, and the doses should be distributed as evenly throughout the 24 hours as is compatible with securing good sleep for the patient. At the onset of treatment of an acute case in an adult, gr. 20 should be given every 2 hours during the day, and every 4 hours during the night (gr. 200 in the 24 hours). Many authorities advise that twice this amount of sodium bicarbonate be added to the salicylate to prevent acidosis; the effect of the sodium bicar-

bonate is apparently to diminish the quantity of salicylate circulating in the blood and the combination is probably best avoided unless vomiting makes it imperative. As the fever and pain diminish these quantities may be given somewhat less frequently, a note being kept on the temperature chart of the total amount given in the 24 hours. In a child of 12 years or so, half these quantities may be given. If no amelioration follows these doses in 48 hours they should be increased by 50 per cent. (gr. 150 in 24 hours). If an exacerbation occurs, or a relapse threatens, after the dosage has been reduced, it should be at once adjusted to its original level. The drug is not unpleasant to take, and its taste is easily masked by liquorice water as a vehicle. Quite apart from the inestimable value of giving adequate doses so as to gain time, there is an additional value in this procedure from the point of view of diagnosis, for a patient suffering from acute arthritis with fever, who is not considerably better after 48 hours' treatment by full doses of salicylates almost certainly is not suffering from rheumatic fever. The diagnosis in these circumstances should be at once revised. It will be found that the great majority of patients tolerate the above specified doses of salicylates without ill-effects. In the few instances in which it produces vomiting, or intense depression, or delirium, or coma, or hæmaturia—symptoms thought from time to time to be toxic effects of the drug—either aspirin or salicin may be substituted. But care must be taken in deciding that such symptoms are really due to the salicylate and are not manifestations of the rheumatic poison. Modern synthetic preparations of sodium salicylate are fairly free from the contaminations which were formerly rather common. In the early stage of the disease it may be necessary to adopt more rapid palliative measures for the severe pain, especially if this prevents sleep. Nothing is better than opium, either as pulv. ipecac. et opii, gr. 10, or pil. saponis co., gr. 5. It is better to avoid phenazone and phenacetin. The treatment of heart complications is discussed elsewhere. Against the occurrence of these complications, apart from the value of early and liberal use of salicylates, we seem to be powerless.

*Hyperpyrexia* is met by prompt application of the cold pack; the pack may need frequent renewal, and in extreme cases the water used for it must be iced. The most constant vigilance is necessary in such cases, which, as already stated, are happily rare nowadays.

(2) *Local*.—The position of optimum comfort of the affected joints has been already referred to. The use of splints for fixing the joints often gives relief. In the milder cases it suffices to wrap the joints in cotton-wool and bandage them lightly. In the more severe cases a lotion of tinct. opii, 1 fl. oz.; glycerin, 2 fl. oz.; water, 12 fl. oz.; sod. carb. to saturation, used hot, gives as much relief as anything. An alternative is one of the preparations of methyl salicylate, used freely, but without rubbing. Aspiration of the effusion is scarcely ever needed; its indication, indeed, should raise doubts as to the diagnosis.

(3) *During convalescence*.—Convalescence is generally slow, and should not be hurried. If the heart has suffered by direct inflammation, the recumbent position must be prolonged until it is certain that quiescence is established in that respect; this usually means from 4 to 6 weeks after the subsidence of the fever. The transition from strict recumbency to a sitting posture should occupy a whole week, by the gradual addition of pillows, and the further return to ordinary active life should be graduated with care.

(4) *Preventive treatment*.—The prophylactic value of tonsillectomy has been found to be disappointingly slight, but it is justifiable in patients with recurrent tonsillitis or unassailable evidence of chronic tonsillar infection. At least 2 months should elapse between the disappearance of all sign of rheumatic activity and performance of the operation.

It has been demonstrated that recurrence and recrudescence are much less likely to occur in the absence of infection of the upper respiratory tract. To this end 0.5 g.

of a sulphonamide daily has been given by mouth for a prolonged period. Prevention is also possible by means of long-acting penicillin preparations: a dose of 1,200,000 units of benzathine penicillin can be given intramuscularly at intervals of 1 month.

## CEREBROSPINAL FEVER

**Synonyms.**—The name here chosen seems least open to objection. "Cerebrospinal meningitis" is the best alternative, but cerebrospinal meningitis may be caused by micro-organisms other than the meningococcus, and meningitis may not be present at all, or may not constitute the chief lesion, in some cases of meningococcus infection. "Epidemic cerebrospinal meningitis" is much less desirable, because it suggests that there is an essential difference between the epidemic and the sporadic cases of meningococcus infection, which difference does not in fact exist. "Meningococcus infection" brings the various pathogenic possibilities of the micro-organism into line with those of the pneumococcus, with which it has close analogies, but the term does not connote a disease. Meningococcal fever, as suggested by Banks, is an acceptable alternative.

**Definition.**—A specific disease, due to infection of the body by the meningococcus, occurring both in epidemic and in sporadic form, and most often manifesting itself as an acute meningitis tending to involve the whole cerebrospinal axis.

Epidemics of cerebrospinal fever are marked by several features peculiar to the disease, offering a striking contrast with other epidemic diseases. For a long time these features were very difficult of explanation, until the existence of "carriers" became recognised, and supplied the solution to much of the epidemiological problem. Amongst these curious features may be mentioned the erratic nature of the outbreaks, the inability to trace the connection between one epidemic and another, the relative or even total escape of certain localities close to others in which the disease was rife, and the small proportion of persons affected in any one district. In closed communities, such as camps, and especially in times of war, the disease finds a fertile soil. When the "carrier rate" rises above 20 per cent. an epidemic is likely to ensue.

On clinical, bacteriological and epidemiological grounds there is no distinction to be drawn between sporadic and epidemic cases of cerebrospinal fever. But it is not entirely by means of the sporadic cases that the infecting agent persists, but by "carriers" also. There is little doubt, however, that from the sporadic cases, as from a smouldering infection, new epidemics light up. The present conception of the disease, from an epidemiological point of view, is that of a very widespread infection, with a total morbidity that is very low, but with foci of more intense virulence here and there. These foci of more intense virulence appear and disappear, being preceded and followed by a somewhat higher level of permanent incidence in the districts concerned.

**Ætiology.**—The geographical distribution of the disease is very wide—world-wide, in fact.

Cerebrospinal fever is a disease of winter and spring. This seasonal incidence is borne out by all observers, and is a very important feature of the disease. It compares markedly with the seasonal incidence of poliomyelitis epidemics, which are at their height in the summer months.

In civilians about half the cases occur below the age of 5 years and 65 per cent. below 10 years; after the age of 25 years cases are uncommon. During the war-time epidemics a special risk is run by young men in the Armed Forces and the age-incidence is considerably higher.

Direct case-to-case infection is uncommon, and there is seldom more than one case in a household; thus infectivity must be low. Infection is conveyed by droplets, and the conditions which favour its spread are overcrowding and inadequate ventilation; upper respiratory tract infections which cause sneezing and coughing; and an increase in the carrier rate.

**THE MENINGOCOCCUS.**—The meningococcus (*Neisseria meningitidis*) is rather smaller than *N. catarrhalis* and larger than the gonococcus—the other two pathogenic diplococci which are Gram-negative in staining reaction. It is a strict aerobe, and requires the addition of some animal protein or of legumin to ordinary culture media to ensure growth. After cultivation for three or four generations it will grow on ordinary agar, but sub-cultures die rather suddenly. Optimum growth takes place at 36° to 37° C., and growth ceases at 42° C. and at 25° C. Vitality is low, especially to drying; sunlight kills in less than 12 hours.

**Types of the Meningococcus.**—By employing the agglutination test, controlled by the absorption test, M. H. Gordon (1918) differentiated four separate types of meningococci occurring in the cerebrospinal fluid of actual cases. His classification has now been abandoned in favour of two broad serological groups. Group I, containing Gordon's types 1 and 3 is responsible for 95 per cent. of epidemic cases; Group II strains predominate in sporadic cases.

As the result of this research during the War of 1914–1918, specific type immune sera were introduced which markedly lowered the mortality of the disease. They have now been superseded by chemotherapy.

The primary habitat of the meningococcus, both in actual cases of the disease and in "carriers", is the upper part of the naso-pharynx and the posterior nares.

**Symptoms and Course.**—Cerebrospinal fever is protean in its features and especially in its modes of onset. Out of the large number of different manifestations that occur, certain cases repeat themselves with sufficient constancy to constitute clinical "types", capable of description and of recognition. Cerebrospinal fever is a disease the course of which has been changed by the application of chemotherapy. Much of the clinical description which here follows is concerned with the unmodified infection. Chemotherapy has cut short the disease process and has largely abolished the severe complications.

**1. THE ORDINARY OR ACUTE TYPE.**—The incubation period is difficult to estimate with accuracy; there are reasons for considering it to be 4 or 5 days. The illness begins with the usual symptoms of an acute specific fever, and for the first day or two, or for longer than this if the possibility of the disease under consideration is not borne in mind so as to lead to a special examination, there may be nothing to distinguish the illness from one or other of several acute febrile infections.

The onset is usually sudden, with fever, headache, general malaise and vomiting. The temperature usually rises rapidly and attains a fairly high degree on the first day (102° to 104° F.).

The headache is usually intense, is often referred to the occiput, and shows little or no response to the customary palliative drugs given to relieve it.

There is frequently a rigor in the adult, or a convulsion in the infant or child. Vomiting is more often met with in children than in infants, and is quite common in young adults.

In addition to the three cardinal symptoms at the onset—headache, fever and vomiting—the following are quite common, but are not nearly so constant: delirium, pains in the neck and limbs, and some degree of catarrh either of the nose, naso-pharynx, conjunctiva or ear. In some cases there is considerable bronchial catarrh and in others definite enteritis. In addition to the pains referred to the limbs there may be pain and swelling of the joints.

After some 2 to 4 days of these initial symptoms, evidence of meningeal irritation begins to show itself in more or fewer of the following developments. The vomiting is repeated, despite the fact that the invasion symptoms are past. The pulse is irregular in rhythm, and in older children and in adults it is often relatively infrequent when compared with the height of the temperature. The respirations are irregular. The vasomotor system is unstable, leading to periodic flushing of the face and to the

presence of *tâches cérébrales*. The patient lies on his side with legs drawn up and prefers the shelter of the bed-clothes. The pupils are dilated and the light reflex is sluggish. There is photophobia, with intolerance of noise and of all kinds of interference. Examination of the neck reveals a stiffness of the muscles, which cannot be overcome without pain. The hamstrings are found to be taut, so that the knees cannot readily be extended if the hips are flexed (Kernig's sign). The abdomen is retracted and the superficial reflexes are abolished. The mental state is one of restlessness and mild delirium with troublesome insomnia. The headache may become quite intolerable and may require morphine for its reduction. In a considerable number of cases a rash appears during the first week—either a number of large rose spots about the trunk and limbs, or a macular eruption like that of measles or a few small petechiae scattered over the trunk, neck and extremities. Herpes is common, and is generally situated at the usual places—the angle of the mouth, the chin and the nose. There is a leucocytosis of considerable degree (20,000 to 40,000).

Towards the end of the first week the mental state changes to a condition which may perhaps best be described as one of resistant stupor: the patient can be roused by an effort at examination, or by a change of position; but either proceeding is resented, and he quickly resumes his huddled posture. The headache is less constantly severe, but shows sudden and marked exacerbations, often nocturnal, with complete insomnia. The neck rigidity increases, and the head is retracted. The back also becomes stiff. Flesh is lost rapidly. Polyuria is common, with polydipsia. The temperature generally remains fairly high, and, although this is by no means invariable, the fever approximates to the continued type.

Assuming that the course of the disease is not interrupted by lumbar puncture or by specific therapy, the condition of the patient remains much the same during the second, and perhaps during the third, week of the illness. But the wasting continues. The temperature often becomes intermittent in type. One of the three modes of termination will be followed.

(a) *Recovery*.—This is gradual when it occurs, and is often interrupted by sudden recrudescences, throwing the patient back into a state which leads to renewed anxiety. The temperature chart is often interrupted in its deservescence by sudden rises, with or without a corresponding recrudescence of the meningitic symptoms. Ultimately the fever completely subsides, the patient ceases losing flesh, the headache and stupor pass off and the rigidities slowly disappear. The pulse-rate remains high for some time in a good number of cases, and some authors regard this as a sign that the patient is not yet free from the possibility of relapse, and therefore as an indication for caution in treatment. The actual stage of convalescence, once it is established is rarely interrupted. If the temperature and pulse-rate have remained normal for 14 days, the risk of relapse may be considered to be passed. It may be some weeks, however, before the patient is free from stiffness.

(b) *Death*.—The ordinary type of the disease is not often fatal during the first 2 weeks. When it is, the stupor passes into true coma, the pulse and respiration rise in frequency, and the temperature often shows a sudden ante-mortem rise.

(c) *Becoming chronic*.—More often, if the ordinary type terminates fatally, it is after passing through a subacute or chronic stage. If the "crises" already referred to continue, or if, despite the fall of temperature, there is no corresponding improvement in the general condition, a state of progressive emaciation supervenes, with a tendency to chronic hydrocephalus. The wasting is sometimes extreme, so that bedsores are unavoidable. The rigidity becomes marked, and approaches, even in adults, that degree termed cervical opisthotonos in infants. Feeding becomes difficult, and this adds to the wasting due to trophic disturbances. The sphincters usually relax, leading to incontinence. Papillœdema develops. The patient may continue in this unsatisfactory state for several weeks, or even months, and yet may eventually recover, and without any residual defects. More often, however, he gradually



succumbs to the disease, or, if he eventually survives its ravages, it is to be left with mental defect, deafness, blindness, hemiplegia or diplegia.

Opinions differ as to the frequency of true relapses in cerebrospinal fever. This is probably due to the fact that what some authorities term relapses others consider to be merely recrudescences. It is certain that the latter are very common; indeed, they are a characteristic feature of the disease.

2. **THE SUPRACUTE TYPE.**—This form of the disease is common at the height of an epidemic. The invasion symptoms are abrupt, and the patient is from the first very ill. Delirium is marked, with most tiresome insomnia, and the headache may drive the patient to a state of acute mania. The temperature is usually very high ( $104^{\circ}$  to  $106^{\circ}$  F.), and intermits. Skin eruptions are more constantly present than in the ordinary type; but are by no means necessarily petechial in character. Discharges are apt to occur from the nose and conjunctival sac. The tongue is dry and tremulous. The meningococcus can generally be grown from the blood by culture, and has even been demonstrated in cover-slip preparations made from the blood direct. The leucocytosis is high (30,000 to 40,000). After 3 or 4 days the active mental state changes to stupor; if the cerebral pressure is not now relieved by lumbar puncture this stupor passes into coma. Even if the pressure is relieved by this procedure there is a great tendency for the patient to slip back into a comatose state; then, with pulse, respirations and temperature all rising, with insensitive pupils and absence of corneal reflex, the surface of the body becomes livid, the lungs congested and death occurs.

3. **THE FULMINATING OR MALIGNANT TYPE.**—This form is prone to occur during the evolution of an epidemic. But it is by no means rare as a sporadic manifestation of the disease. It is more often seen in older children, adolescents and adults than in infants and younger children. The abrupt appearance of fever, headache and active delirium, rapidly passing into coma, and the whole course of the disease may not exceed 12 hours.

In all fulminating cases of cerebrospinal fever there is a rapid development of septicæmia. In some of them the septicæmia covers the whole of the disease, symptoms of meningitis being absent, and the meninges being free from gross lesions on examination post mortem. The patient is most often a child, exhibiting petechiæ and signs of circulatory failure—a small frequent pulse, extremities cold and livid, respiration rapid and shallow. A hæmorrhagic suprarenal lesion is often present (Friderichsen-Waterhouse syndrome). Even more constantly than in the supracute type is a blood culture positive; but the course of the disease is too rapid to admit of a diagnosis by this method during life.

4. **MILD TYPES.**—These cases are said to be common during the decline of an epidemic. It is at present quite impossible to say with what frequency they occur, because it is certain that many of them are overlooked. They are often treated as cases of "influenza", owing to the resemblance they bear to that disease. Many cases of acute fever with headache and pains in the back and limbs are regarded as "influenza" from a diagnosis by exclusion. They are not subjected to a lumbar puncture because the condition does not seem sufficiently grave. And if they recover from an illness of a few days' duration this is thought to be confirmatory of the diagnosis. In the presence of an epidemic of cerebrospinal fever, however, a very close scrutiny of these cases should be made, and if there is even doubtful neck-rigidity or Kernig's sign, the cerebrospinal fluid should be examined. Even when lumbar puncture is not at first decided upon a swab from the naso-pharynx should be investigated for the meningococcus.

During an epidemic a patient who presents the symptom-complex of headache, malaise, pains in the back and limbs, slight fever, and some stiffness of the neck is probably suffering from a mild grade of meningococcus infection, and should be treated as such, by a lumbar puncture and the administration of sulphonamide. Subsequent measures will be determined by (a) the course of the disease; (b) the

result of the examination of the cerebrospinal fluid; and (c) the result of the examination of the naso-pharyngeal swab. The value of these cautionary measures is sometimes made apparent by the patient becoming rather suddenly worse after a few days, when it may be quite obvious that the nature of the disease is what was originally suspected.

5. **CHRONIC SEPTICÆMIA WITHOUT MENINGEAL SYMPTOMS.**—Attention has been drawn to this group of cases in which there is the association of a general blood infection, with bouts of pyrexia, often arthralgia or arthritis and various lesions in the skin: petechiæ, maculo-papular eruptions or patches resembling the lesions of erythema nodosum.

6. **POST-BASIC MENINGITIS OF INFANTS (CERVICAL OPISTHOTONOS OF INFANTS).**—These cases were first described by Gee and Barlow (1878). It was formerly met with in children between the ages of 6 months and 2½ years, but is now virtually never seen. It is a chronic hydrocephalic form of the disease which occurs only when the diagnosis has not been made in the acute stage and when the child has been deprived of specific treatment.

**Complications.**—It should be stressed that complications are rare now that chemotherapy has provided such an effective means of treating cerebrospinal fever. The following descriptions are applicable largely to the days before sulphonamides were used.

1. *Hydrocephalus* may arise soon after the onset of the disease, or it may develop, and often rather suddenly, during its course, or it may be the final anatomical expression of the infective process, the counterpart of the symptom-complex seen in the chronic state of the disease. Certain symptoms are specially suggestive of the condition: pallor, cyanosis, increased frequency of the pulse with diminution in its tension and volume, shallow respirations and stupor or coma supervening rather suddenly upon a previous state of consciousness.

If hydrocephalus arise at a later period of the disease than the end of the first week it may show itself with surprising suddenness, and sometimes in patients who seem to have been improving satisfactorily. In addition, to the symptoms just enumerated, there is a recrudescence of the headache, vomiting and fever, which may have to a large extent subsided. More often it appears gradually and concomitantly with the progressive cachexia of the chronic type of infection. A valuable sign of its presence in children and adults is the presence of a resonant note to percussion over the anterior horn of the lateral ventricle (Macewen). This sign is best obtained by placing the head in an upright position and inclining it to one side. The sign is not present in infants in whom the fontanelles are still open.

Hydrocephalus of the chronic stage of the disease is seen very constantly in infants suffering from the post-basic type of infection. Emaciation is a constant feature. The child lies for hours without stirring. There may be reiterated automatic acts, such as the biting of nails or the loosening and pulling out of teeth. The patients are rarely comatose. Vomiting and convulsions may occur.

2. *Psychic disturbances.*—These are not very common, if the delirium and stupor are excluded. But the delirium may develop into mania, urged thereto by the violence of the headache. During convalescence it is not very uncommon to observe temperamental changes, such as puerility or emotionalism, which rarely persist for very long. Secondary dementia is, however, not unknown.

3. *Motor defects.*—Cranial nerve palsies are very uncommon. There are three groups of paralytic complications, but none of them is common.

(a) *Hemiplegia* and, less often, *monoplegia* of cortical type. This usually appears at the height of the disease, and is generally of temporary duration.

(b) *Flaccid paralysis* localised to one extremity or to a part of one extremity. The tendon-jerks are lost. Muscular atrophy may ensue, and R.D. may develop. The prognosis for the limb is by no means bad, and complete, or almost complete, recovery is probable.

(c) *Spastic ataxia*.—It is not uncommon to find convalescent patients very unsteady on their legs when they first begin to walk. Little children often refuse to walk at all for a time, even if they had learnt to do so before the illness began. Older children sprawl about the floor. Adults tend to topple over in an indiscriminate manner. In the majority of these cases there are no signs of organic disease, and the return to a normal gait is usually only a matter of time. In a few of the cases, however, the ataxia is accompanied by exaggerated knee-jerks, true ankle-clonus and extensor plantar response: a state of spasticity. The sphincters are intact, and there is no anaesthesia or analgesia. According to Sophian, who drew attention to these cases, the pupils often remain dilated, with a sluggish light reflex. Recovery, though slow, is the rule.

4. *Special senses*.—Complications involving the eye are very variable, and yet, in relation to the essentially nervous character of the main lesions of the disease, they are not very common. Fortunately, with the single exception of that form of blindness so often seen in the recovered cases of the post-basic type of the disease, very few of the eye complications are permanent. Inflammatory lesions include conjunctivitis, keratitis, iridocyclitis and (rarely) cellulitis of the orbit. Nervous lesions include extrinsic ocular defects which are not uncommon, but are generally transitory (i.e. spasmodic). Amaurosis is relatively common in the post-basic infection of infants; it is fortunately unusual in the more acute infection of children and adults. It is in most cases unaccompanied by any changes in the optic disc, and is therefore to be attributed to cortical changes associated with hydrocephalus. In some cases, however, a state of secondary optic atrophy is present. Optic neuritis is not a common complication; but papillitis, or a lesser degree of change even than this, is said by French authors to be extremely common.

The chief complication affecting the ear is meningitic deafness. This is a common and very serious complication, serious because when it occurs it is apt to be permanent. The auditory defect generally begins early in the course of the disease, and usually before the end of the first week. It is usually bilateral, which adds to the seriousness of the trouble in the event of its becoming permanent. Deafness is still an important complication, because its early onset often precedes administration of sulphonamides. Banks records some degree of permanent deafness in 4.67 per cent. of cases; in half of these it was bilateral and complete.

5. *Arthropathies*.—A certain degree of painful stiffness, and even swelling of the joints, is not at all uncommon as a transitory symptom in cerebrospinal fever. Occasionally, however, one joint shows evidence of much more intense infection, becoming red, swollen and very painful with the slightest movement. It may suppurate, and secondary infection may occur.

6. *Other complications* are the broncho-pneumonia already referred to in little children; occasionally pneumonia in adults; and enteritis.

**LUMBAR PUNCTURE**.—In any suspected case of meningitis a lumbar puncture is as clearly indicated as is puncture of the chest in a suspected case of pleuritic effusion, or a blood-count in a suspected case of leukaemia.

**THE CEREBROSPINAL FLUID IN MENINGOCOCCUS MENINGITIS**.—1. *Pressure and the amount*.—The pressure in the early stages is generally more than 200 mm. of cerebrospinal fluid as measured by a manometer fitted to the lumbar puncture needle. The amount of fluid which flows away before the normal pressure is re-established depends upon the pressure and the consistency of the fluid; it averages about 30 ml.

2. *Naked-eye appearance*.—Various grades of turbidity are met with, from very slight opalescence to a highly purulent exudate. The degree of turbidity varies with the stage of the disease at which the lumbar puncture is undertaken. In the invasion stage the fluid may be clear; in the acute meningitic stage the fluid shows marked turbidity; later, again, as the inflammatory phase passes, the fluid becomes clearer. The presence of blood probably always means that a vessel has been punctured by

the needle. Some degree of clotting takes place when the fluid is allowed to stand, flakes of fibrin appearing at the bottom of the tube.

3. *Chemistry*.—The protein is increased in amount, often to 200 to 300 mg. per ml. The globulin moiety of the protein is also increased. Sugar is greatly diminished and often absent. The chloride content also is lowered as in other forms of meningitis: it is seldom less than 700 mg. per cent., whereas in tuberculous meningitis a reading below 680 is the rule.

4. *Cytology*.—In the early or invasion stage of the disease there is a quantitative increase in the lymphocytic content, a fact which often escapes observation if the lumbar puncture be delayed. With the arrival of the acute meningitic inflammation the chief cell present is the polymorphonuclear, usually in large numbers. At the stage, therefore, at which most lumbar punctures are undertaken, the cell content is chiefly polymorphous (70 per cent. to 80 per cent.). Later, when the stage of chronic hydrocephalus ensues, the lymphocyte again becomes the dominant cell, and in much greater numbers than in healthy fluid. Most observers, however, describe cases of undoubted meningococcus meningitis in which the cell content is chiefly lymphocytic throughout. In the post-toxic type of the disease the cells are most often lymphocytes for the greater part, and the same may be said of cases which are in a chronic stage whilst under investigation, whether the chief seat of the effusion be at the root of the bulb or elsewhere.

5. *Bacteriology*.—Films made direct from the cerebrospinal fluid, or, better still, from the centrifugised deposit, show intra- and extracellular meningococci in the great majority of cases at some time or other in their course. If a careful search be made and no cocci are discovered, it must not be assumed that none are present until the device of incubating the fluid as a whole before it has been allowed to cool is undertaken, and until cultures made upon suitable media are found to be sterile. The number of cocci seen, and their disposition with regard to the cells of the exudate, are matters of great variability. These things depend in the main upon (a) the stage of the disease, (b) the intensity of the infection and (c) the influence of treatment.

*Diagnosis*.—The chief difficulty lies in not suspecting the presence of the disease. It is, of course, much more easy to bear in mind the possibility of cerebrospinal fever during the presence of an epidemic than at other times. It is the sporadic case, although it is usually typical, which goes undiagnosed, at least during the early part of its course.

The reason why it may not be possible to decide on clinical grounds whether meningitis is present or not is because several infective processes, other than that due to the meningococcus, are apt to produce symptoms highly suggestive of meningeal irritation. This state of meningeal irritation, when due to toxæmia and not due to actual meningitis, has been termed *meningism* or *meningismus*. The question whether such a state is entirely toxic, or whether it is due to definite though slight changes in the meningeal tissues which just stop short of an inflammatory exudate, is problematical.

The diagnosis of cerebrospinal fever may be conveniently considered under three heads—(1) from various acute infective processes with toxæmia, leading to "cerebral" symptoms; (2) from certain acute cerebral diseases of primary origin; (3) from other forms of meningitis.

1. *THE DIAGNOSIS OF MENINGITIS FROM TOXÆMIA*.—The question is settled partly by the clinical data and partly by an examination of the cerebrospinal fluid. In a case of fever with "head symptoms", the following differential points should be borne in mind:

(1) *If headache and delirium synchronise, meningitis is probably present, and not merely toxæmia*.—Contrast an ordinary case of typhoid fever (toxæmia), in which headache and delirium alternate, the patient being free from pain when he is delirious, with cerebrospinal fever (meningitis), in which the patient's headache and delirium are both present at the same moment.

(2) *Vomiting*.—If this occurs not merely at the onset of the fever, but on subse-

quent days also, at a time when the invasion period of the infection may be said to be passed, it is evidence of meningitis.

(3) *Pulse and respirations*.—Irregularities in rhythm are in favour of meningitis, and so is a relatively low pulse-rate in comparison with the height of the temperature, provided typhoid fever can be eliminated.

(4) *Papillædema*, though its presence is much in favour of meningitis as against toxæmia, is not of much value in this connection, because it is usually absent at the early stage of the disease when the diagnostic problem requires urgent solution.

(5) *Cervical rigidity and tautness of the hamstrings*, though suggestive of meningitis, are often present in meningism.

These five points are worthy of the most critical investigation. All other clinical features that may be present are equivocal—they may be produced by a toxic state of the brain or meninges. This statement refers to the state of the pupils, whether contracted or dilated; the presence of *tâches cérébrales*; the absence of the superficial or of the deep reflexes; the "peevish" state of the patient with a resistant attitude; marked insomnia or persistent stupor.

(a) *Influenza*.—This probably gives most difficulty in actual practice. It should be noted that cerebrospinal fever is very often mistaken for influenza, whereas influenza is rarely mistaken for cerebrospinal fever. The reason for this lies in the fact that the diagnosis of influenza is too often by exclusion. Fever prolonged past the fifth day, in the absence of an inflammatory focus (bronchitis, pneumonia, pleurisy, sinusitis, etc.), is unlikely to be due to influenza, and should therefore lead to a critical revision of the diagnosis. A leucocyte count is often helpful.

(b) *Typhoid fever*.—The onset of the illness is nearly always a gradual one, and the evolution of the toxic symptoms is much more deliberate than in cerebrospinal fever. This is perhaps the most significant differential point clinically. The leucocyte count is very helpful, and may prove of great diagnostic assistance before Widal's test is available: the count is low in typhoid (2000 to 7000), but it is high in cerebrospinal fever (15,000 to 40,000). The rose spots of typhoid do not appear until the eighth or tenth day, whereas the rash of cerebrospinal fever which might be confused with these usually appears much earlier. If the spleen is palpable in cerebrospinal fever this is the case early, whilst the disease is at its "septicæmic" stage; in typhoid the spleen can rarely be felt before the end of the first week. The dissociation of headache and delirium in toxæmia already referred to is strikingly seen in typhoid fever. Moreover, the disappearance of the headache altogether, which occurs so frequently in typhoid fever after the tenth day, is another point of distinction; although its severity may diminish, it is rarely absent so early in the course of untreated cerebrospinal fever. As soon as a positive Widal test is obtained (usually about the seventh to tenth day), this finding, together with a leucopenia, may be relied upon as decisive in favour of typhoid. A positive blood culture may often be obtained before the agglutination test is available.

(c) *Pneumonia*.—Acute pneumococcus infection is the most common cause of a toxæmic state leading to meningism; the patient is usually a child, but not always; the lung consolidation is often apical and therefore the more easily overlooked. The symptoms of meningeal irritation may precede the signs of pulmonary disease, in which case the diagnosis can only be settled by lumbar puncture, or they may concur with such signs, in which case some care must be exercised lest the case be one of cerebrospinal fever ushered in by pneumonia. Here the leucocyte count is of no help, for there is a high leucocytosis in pneumonia as in cerebrospinal fever. A blood culture may reveal pneumococci, or a chest radiogram may yield evidence of the nature of the infection; but if the diagnosis is considered in serious doubt, it will probably be deemed wise to perform lumbar puncture.

(d) *Malignant small-pox*, on the authority of Milligan, simulates cerebrospinal fever very closely, on account of the sudden onset, headache, vomiting and pain in

the back. But as the eruption occurs on the third or fourth day the diagnosis is not left long in doubt.

(e) *Rheumatic fever*.—If cerebrospinal fever begins with arthritis and profuse acid sweats, if the patient is an adolescent, and if the pains are specially referred to the joints, the diagnosis of rheumatic fever is at first pardonable. The addition of an erythema makes the simulation all the closer. The failure of salicylates to relieve the pain, or to reduce the fever, should at once arouse suspicion. The important distinction between early rigidity of the neck in meningitis and rheumatic stiffness—that the former tends to increase with examination, and the latter tends to decrease—should be remembered in this connection.

2. DIFFERENTIAL DIAGNOSIS OF CEREBROSPINAL FEVER FROM CERTAIN DISEASES OF THE CENTRAL NERVOUS SYSTEM.—The most important of these diseases sometimes introducing a difficulty is :

*Poliomyelitis (infantile paralysis)*.—This disease, like cerebrospinal fever, exists in epidemic and in sporadic forms. Of recent years there have been several epidemics in England. Sporadic cases are common. If the type of the disease is the usual one, little or no difficulty is introduced in diagnosis from cerebrospinal fever, because the invasion or febrile stage is short and the degree of illness it involves is not great, and there may be retention of urine; it is quickly followed by the paralytic stage, and the real nature of the malady becomes manifest. In the meningitic form of the disease a real difficulty may present itself. There may be added to the headache and vomiting, pain and stiffness in the neck and spine, and even some degree of opisthotonos. Careful study of the cerebrospinal fluid usually serves to differentiate the two diseases.

3. DIFFERENTIAL DIAGNOSIS OF MENINGOCOCCAL FROM OTHER FORMS OF MENINGITIS.—(1) *Pneumococcal meningitis* is rarely primary; almost always it complicates consolidation of the lung, or pleurisy, or otitis media, or infection of the nasal sinuses. When it occurs it is apt to be extremely acute.

(2) *Streptococcal meningitis* usually complicates some infective process about the skull, and most often this is middle-ear disease or sinusitis. In the majority of cases some surgical procedure has been attempted for the relief of the primary condition.

(3) *Hæmophilus meningitis* is uncommon and diagnosis depends upon the isolation of *H. influenza* from the cerebrospinal fluid.

(4) *Typhoid meningitis*.—A true infection of the meninges may occur in typhoid fever, but it must not be inferred that a patient necessarily has typhoid meningitis because the bacillus is grown from the lumbar puncture fluid. This may occur without clinical evidence of meningitis and without histological and chemical changes in the cerebrospinal fluid characteristic of meningeal inflammation.

(5) *Tuberculous meningitis*.—After cerebrospinal fever this is the next most common form of acute meningitis and therefore deserves fuller mention. The most helpful points in a differential diagnosis from meningococcus meningitis are the following. Tuberculous meningitis is rarely so sudden in its onset, the meningitic symptoms being preceded by a longer period of malaise, which begins less abruptly than the invasion symptoms of cerebrospinal fever. The temperature is seldom high, except as an ante-mortem event, the usual range being 99° to 101° F. Retraction of the head is transient and ill-marked, or is absent. Photophobia is more common than it is in cerebrospinal fever. In adults aphasia is often a common and an early symptom. True (paralytic) squint is common. The "peevis" condition in children is much more marked during the first week. In both children and adults the depth of the stupor after about the tenth day is much greater. The discovery of tubercles in the choroid is pathognomonic, but these lesions rarely appear before the third week of the disease, and are therefore not of much service for diagnosis. Some authors lay stress upon the presence of signs of tuberculous disease elsewhere in the body as assisting in the diagnosis, but this is, of course, not true. Except in the case of adults, and by no means always then, there are rarely any such signs. The leucocyte count affords no

ifferential help as from cerebrospinal fever, a leucocytosis of considerable size (15,000 to 30,000) being present in tuberculous meningitis. The abdominal reflexes are usually retained, whereas in meningococcal meningitis they are prone to be lost early.

However high a degree of probability that a patient is suffering from meningitis may result from a general examination, confirmation of this view rests entirely upon the results of lumbar puncture. For three reasons it should not be deferred: it establishes the diagnosis that meningitis is present; it decides the nature of the infection; it is a valuable aid to treatment in the event of a positive result.

**Prognosis.**—The mortality in cerebrospinal fever is undoubtedly higher in the epidemic than in the sporadic cases, if the post-basis meningitis of infants, in which the mortality is very high, be excluded. There are, however, no good figures upon which to base an estimate of mortality in the sporadic cases. In epidemics the mortality prior to the introduction of serum treatment was about 70 to 80 per cent. After its introduction the mortality fell to half this figure. With sulphonamide treatment the figure is probably below 10 per cent. In Banks's series of 706 consecutive cases, seen between 1939 and 1947, the mortality rate was 7.36 per cent.

The influence of age is noteworthy. The disease has a high fatality in infants; 23.6 per cent. of 76 cases below the age of 1 year (Banks). The mortality is lowest between the ages of 5 and 10 years; it becomes high again in the elderly.

A fulminating form of onset is invariably bad, and the mortality in these cases is very high, if indeed it is not 100 per cent. In the cases with less vicious invasion symptoms, one or more of the following symptoms betokens a grave issue: early loss of consciousness, wild delirium, persistent insomnia, extensive hæmorrhagic eruption, cyanosis. Later in the course of the disease the worst sign is the appearance of hydrocephalus.

The degree of fever, the intensity of the headache, the amount of rigidity, the presence of marked emaciation, frequency and irregularity of the pulse, rhythmical respirations, the presence of herpes—none of these things yields any information of value in predicting the issue of the disease. In few other diseases, if in any, is it possible for the patient to be so ill and yet to recover completely, as in cerebrospinal fever.

The most important fact bearing upon prognosis is the stage in the disease at which treatment is begun.

**Treatment.**—1. **PROPHYLACTIC.**—The principles governing prophylaxis are those applicable to infectious diseases in general. Although it would appear that the healthy carrier is more responsible for the spread of the disease than the patient himself, it is none the less important to isolate every case of the disease and to exercise all precautions against further contact with healthy persons. Whenever possible the patient should be transferred to a hospital, and preferably to an institution where the staff is accustomed to deal with infectious diseases.

All contacts who are found to be carriers should be placed under quarantine, and should be kept there until the naso-pharynx is free from meningococci. This is soon effected by the use of a penicillin-sulphathiazole snuff. If a case occurs in a closed community, e.g. a school, the inmates should be given sulphadimidine 3 g. daily by mouth for 3 days.

2. **CURATIVE.**—(1) **Drug treatment.**—The introduction of the sulphonamides has revolutionised the treatment of this disease. It is of vital importance that the drug should be given at the earliest possible moment after the diagnosis has been made or is strongly suspected. Sulphathiazole and sulphadimidine (Sulphamezathine) are the drugs of choice. It is important in any case of more than slight severity to secure an effective concentration of the drug in the blood as rapidly as possible; the first dose should therefore be given by the intravenous route. In adults the initial intravenous dose should be 2 g., followed by 1.5 g. orally every 4 hours for 2 to 3 days, thereafter 1 g. 4-hourly for 2 days, and finally 1 g. 6-hourly for 2 days. For children up to the age of 3 years, these doses should be 0.5 g. intravenously; 0.5 g. orally

4-hourly for 4 to 5 days; 0.5 g. 6-hourly for 2 days. Between the ages of 3 and 15 years 1 to 2 g. should be given intravenously followed by 0.75 to 1 g., 0.5 to 0.75 g. and 0.5 to 0.75 g. for the periods and at the intervals specified for adults. Throughout the course of treatment an adequate intake of fluid is essential, and it is wise to prescribe enough alkali, in the form of sodium bicarbonate and sodium citrate, to keep the urine alkaline. In no circumstances should a sulphonamide be given by intrathecal injection, as such a solution is strongly alkaline. Penicillin by parenteral injection, 30,000 units 4-hourly or its equivalent, is indicated in all cases of the superacute and fulminating types and where septicæmic symptoms are evident. It should never be given in meningococcal infection by intrathecal injection because no advantage follows its use and it may provoke an aseptic meningitis.

Serum treatment is now obsolete; there is abundant evidence that its use in conjunction with the sulphonamides does not improve the results obtained with the drug alone.

The persistence of an ensuing temperature of 99° to 100° F. does not necessarily imply that the infection is still active.

(2) *General management.*—The diet is to be adjusted to the patient's condition. The disease is an exhausting one, and as full a dietary as is consistent with the state of the digestive secretions is to be allowed. If the fever is a conspicuous feature, and the patient is drowsy or delirious, the mouth is usually dry; the diet is then necessarily restricted to fluids, which should be given in the form of diluted milk, and freshly prepared meat essences, in small quantities at frequent intervals. Water should be given freely. If the patient is in a state of stupor the act of swallowing must not be relied upon; feeding must then be by the passage of a nasal tube three or four times in the 24 hours. According to the age of the patient, from 5 to 10 oz. of citrated milk and water (equal parts), or of peptonised milk, are allowed to run into the stomach from a funnel attached to the tube and held at the necessary height above the bed. If vomiting is troublesome, peptonised milk should only be used, or whey or albumin water. If this symptom is persistent, it may be advisable to put no food at all into the stomach for 24 to 48 hours, relying upon maintaining the supply of fluid by the rectal or intravenous routes.

Urinary difficulties do not usually occur unless the patient is unconscious, in which case it is important to bear in mind the possibility of retention, which may lead to "overflow incontinence". This condition indicates the use of the catheter, with the customary care in the matter of asepsis.

(3) *The treatment of certain symptoms.*—Headache is usually the most distressing symptom calling for special treatment. Phenazone, caffeine and acetylsalicylic acid may all be tried in full doses; morphine may be imperative in some cases, because nothing else may be of any service. If restlessness, delirium and insomnia are troublesome, paraldehyde or one of the barbiturate drugs should be prescribed.

The pains and the stiffness are best treated by warm baths at a temperature of 102° to 104° F.

In arthritis the affected joint is best treated by fixation and the application of hot stupes. If the effusion becomes considerable, or does not quickly yield to these measures, the joint should be aspirated.

(4) *The repetition of the lumbar puncture.*—A lumbar puncture of necessity precedes the diagnosis, but there is seldom need to repeat it. The cerebrospinal fluid is usually sterilised within 48 hours after adequate dosage with sulphonamides and there is no advantage in repeated "drainage".

(5) *Treatment of hydrocephalus.*—If a condition of hydrocephalus has been diagnosed, it is advisable to tap the lateral ventricles. This procedure seldom allows the normal circulation of the cerebrospinal fluid to re-establish itself, but in infants hydrocephalus often resolves after some months. If chronic hydrocephalus becomes established the intervention of a neuro-surgeon will be necessary.

R. BODLEY SCOTT.



## GONORRHŒA

**Definition.**—This is an infectious disease due to *Neisseria gonorrhœe* or the *gonococcus*, sometimes known as the intracellular Gram-negative diplococcus of Neisser. As its name implies, it is a paired organism and microscopically it may be seen that the paired cocci have adjacent surfaces flattened or slightly concave with a narrow but appreciable interval between them. It is a strict parasite and depends for spread upon direct transference from host to host. It is very susceptible to environment and is rapidly killed by drying or by weak antiseptics. It seldom survives for more than a few hours outside the body except under conditions of artificial cultivation.

**Modes of Infection.**—Sexual intercourse is by far the most common and important mode of infection. The organism may also be transmitted to the conjunctival sacs of newly-born infants by contamination with infected genital secretions of the mother. Occasionally, accidental contamination occurs from infected material; female children are particularly susceptible to infection in this way.

**Diagnosis.**—This depends on finding intracellular organisms with the typical morphology and staining reactions within the cytoplasm of polymorphonuclear leucocytes. Extracellular organisms cannot be accepted as gonococci. Legal proof of gonorrhœa rests upon the demonstration of organisms having all the cultural characteristics of gonococci. There are, of course, many other causes of discharge from the urethra and from other sites which the gonococcus may infect. A positive complement fixation test for gonorrhœa in blood serum is in itself only presumptive evidence of gonococcal infection, but it is a finding which should stimulate further search for other evidence of gonorrhœa.

## GONORRHŒA IN THE MALE

This presents as an acute infection of the mucous membrane of the urethra. The disease commonly remains localised to the urethra and its communicating structures, but sometimes it invades the blood-stream and affects distant structures.

**Symptoms and Signs.**—The incubation period is commonly 3 to 10 days. The clinical onset is variable but at first there is usually a slight tingling discomfort in the urethra, followed by a thin discharge which quickly becomes mucopurulent, and then frankly purulent. There is likely to be a variable degree of dysuria and perhaps slight frequency of micturition. The patient usually feels quite well but there may be slight constitutional disturbance. On examination the margins of the external urinary meatus are red, œdematous and pouting. There is a yellow or greenish-yellow purulent discharge. It is important to be sure that the discharge comes from within the urethra and not from under the prepuce. The urine is hazy, due to pus. If the infection has reached the posterior urethra, a development which takes place in about 10 to 14 days in the ordinary untreated case but occasionally much more quickly, the patient may complain of increasing dysuria and of some frequency of micturition. In severe cases a few drops of blood may appear at the end of micturition, but marked hæmaturia is quite rare. Such patients may show evidence of toxic absorption, such as headache, malaise, increased pulse-rate and pyrexia which is usually of low degree but may reach 103° to 104° F.

**Treatment.**—The antibiotics in common use are all effective in the treatment of uncomplicated gonorrhœa. Single intramuscular injections of from 300,000 to 600,000 units of suspension of procaine penicillin in oil or water are commonly given. The smaller dose is usually effective and is preferable because it is less likely to mask the symptoms and signs of a coincident syphilitic infection. The precautions recommended to prevent masking of syphilis are given on p. 220. Some prefer to

use an aqueous suspension of procaine penicillin fortified with crystalline benzyl penicillin, combining the virtues of initial high levels with prolongation of effect. Penicillin given by mouth is an effective method of treating gonococcal infections in spite of variable and uncertain absorption. The effectiveness of the drug by this route is increased by giving it with suitable buffering substances to the patient when fasting. If divided doses are given at intervals of 1 to 3 hours, the dosage required is little more than that which is effective by parenteral injection, provided that the treatment is prolonged for 15 hours. There is probably special scope for this method in the treatment of children, of highly nervous patients, and of seamen and others who have only occasional access to medical attention.

Streptomycin, in a single intramuscular injection of 1 g. in watery solution, produces clinical cure in a large proportion of cases of uncomplicated gonorrhœa. It has the advantage over penicillin that its effect upon the spirochæte of syphilis is slight and with this dosage there is no danger of masking syphilis. Equally good results have been obtained with the same dosage of dihydrostreptomycin. Chlortetracycline (Aureomycin) has proved effective when given by mouth to the amount of 1 g. three times a day for 1 day, and with smaller dosage. Chloramphenicol by mouth is effective, but it may be necessary to give as much as 6 g. in the course of 2 days. Oxytetracycline (Terramycin) has given good results in small dosage, namely, two doses by mouth each of 0.5 g. with an interval of 6 hours between the two.

The effect of successful treatment is diminution and cessation of purulent discharge within a matter of hours. A slight mucoid secretion may persist for a few days and then disappear.

**Local Complications.**—The following are the possible sites of local complications in the male :

- (1) The para-urethral ducts. The preputial sac. Tyson's (para-frenal) ducts.
- (2) Littre's ducts and glands and, in association with these, the lacunæ of Morgagni.
- (3) The subepithelial tissues of the urethra.
- (4) Cowper's ducts and glands.
- (5) The prostatic ducts and the prostate gland.
- (6) The common ejaculatory ducts and the seminal vesicles.
- (7) The vasa deferentia and the epididymes.

Evidence of a local complication may be found during the acute, subacute or chronic stages of the disease, but it is probable that in most cases the actual time of invasion is during the acute stage of the infection.

#### GONORRHOEA IN THE FEMALE

With uncomplicated infections the sites which are likely to be involved are the urethra and cervix uteri and, sometimes, the vaginal fornices. The symptoms are similar to those in the male, but are usually less marked and seem to be entirely absent in about 30 per cent. of the cases. If vaginal discharge is present in considerable amount it is usually due to coexisting infestation with the vaginal parasite, *Trichomonas vaginalis*, which is present in almost 50 per cent. of the cases. The patient should be examined and specimens taken in the lithotomy position with a good light. The cervix uteri is first exposed with a Cusco's bivalve speculum. With recent infection there is likely to be an acute erosion of the cervix. Specimens are taken for smear and culture after careful cleansing with swabs of cotton wool. If there is marked vaginitis it is likely to be due to the trichomonas parasite, but slight vaginitis in the fornices may be due to the gonococcus. On applying pressure from behind forwards to the floor of the urethra a bead of pus may appear at the external urinary meatus and should then be examined for the gonococcus by smear and culture.

The patient should not pass urine during the 3 hours preceding the investigation. If the infection has reached the chronic stage the gonococcus may be hard to find and a series of tests may be required to demonstrate it.

Treatment of uncomplicated infection in the female is the same as that in the male.

**Local Complications.**—The following local complications may occur in the female :

- (1) Skentitis.
- (2) Bartholinitis.
- (3) Metritis and endometritis.
- (4) Salpingitis, oophoritis and pelvic peritonitis.
- (5) Proctitis.

**Metastatic Complications.**—These may occur in males or females but are far more common in males. They are as follows :

(1) *Arthritis*.—More than one joint is usually affected. The knees, ankles and joints of the feet are the commonest sites.

(2) *Rheumatism*.—Involvement of soft tissues may occur with or without arthritis. The commonest site is the plantar fascia, especially its posterior attachment to the os calcis.

(3) *Metastatic conjunctivitis*.—This is sometimes found in association with arthritis. It is bilateral and the gonococcus cannot be isolated.

(4) *Iridocyclitis*.—This may occur in association with arthritis or as a separate manifestation. It is prone to relapse after apparent cure of the disease.

(5) *Gonococcal septicæmia* with endocarditis and pericarditis is a rare complication.

For detailed consideration of the complications of gonorrhœa, local and metastatic, of gonorrhœal ophthalmia in adults and older children, of ophthalmia neonatorum and of gonococcal vulvo-vaginitis and their treatment, and of tests for cure of gonorrhœa, reference should be made to textbooks of the venereal diseases.

AMBROSE KING.

## DIPHTHERIA

**Definition.**—A disease caused by the Klebs-Loeffler bacillus (*Corynebacterium diphtheriæ*), characterised by a membranous exudate at the site of infection and distinctive sequels of toxæmic origin, the chief being acute circulatory failure, paralysis and albuminuria.

**Ætiology.**—Diphtheria is commonest in temperate climes. Human carriers are the cause of its endemic prevalence; local conditions being merely contributory. In its seasonal prevalence diphtheria resembles typhoid and scarlet fever, the maximum incidence being in the autumn and winter months. An epidemic tendency is noticeable in years of deficient rainfall. Formerly a disease of rural districts, diphtheria is now endemic in cities and shows a tendency to local epidemic outbursts. Its heaviest incidence is on children between the ages of 2 and 5 years, at which age period it is the second most fatal disease of childhood, taking first place in the second decade. New-born infants are rarely attacked. Many cases occur in adults, and rather more females than males are affected.

Catarrhal conditions of the throat predispose to the infection; convalescents from measles and scarlet fever, and in less degree those recovering from whooping-cough and influenza, are very liable to contract the disease, which in the case of recent measles or scarlet fever may assume a particularly severe form. A progressive increase in infectivity and severity is often noticed during epidemics, and of late

years outbreaks of unusual severity have been reported. The immunity afforded by diphtheria is short-lived. Actual relapse is rare, but second attacks may occur.

The disease is highly contagious, and infection is by direct or indirect contact. It is seldom air-borne even over a short distance. The organisms reside in the secretions from the nose and throat, in detached shreds of false membrane, and at times in discharges from the ears, the vulva, sore fingers, infected wounds or skin lesions.

Direct infection may result from kissing, or the reception of droplets of fluid ejected by speaking, coughing or sneezing. Indirect infection may be caused by eating or drinking utensils, handkerchiefs, towels, throat spatulas, clinical thermometers, toy trumpets, slate pencils and the like. The diphtheria bacillus readily grows in milk and produces no suspicious changes; milk thus may serve as a vehicle for spread of the disease. There is no evidence that it is conveyed by drinking water. The diphtheria of birds, cats and most other animals has not proved communicable to man and is due to a different organism, but virulent diphtheria bacilli have been found in nasal discharges and open sores of horses.

Diphtheria bacilli retain their virulence for long periods if protected from sunlight and from currents of air; hence the possibility of transmission by fomites. Sterilisation by boiling water or in the steam chamber is quite effectual.

*Carriers.*—Convalescents may harbour virulent bacilli in their throats, as also may others who have been in contact with the infection. Most are free from bacilli 4 or 8 weeks after the commencement of the disease, but in some the carrier state becomes chronic. The dangerous chronic carrier is usually an immune person, as shown by a negative Schick reaction. The presence of bacilli in the throat secretions of carriers is apt to be intermittent. All carriers are not equally effective distributors of the disease; intimate contact and addiction to such habits as kissing, sneezing, spitting and pencil-sucking are important in this respect. The nasal carrier is believed to be an especial source of danger. Among school children 80 per cent. of the carriers are between 5 and 8 years of age, and male carriers are two or three times more common than female. Throat and nose operations on carriers may be followed by clinical diphtheria. In the search for carriers, pallor, unhealthy tonsils and nasal discharge are important indications, as also a history of recent sore throat. Skin carriers are the subjects of eczematous or impetiginous lesions or whitlows. The discovery of bacilli which morphologically resemble diphtheria bacilli does not necessarily prove they are virulent. Bacilli removed from the throat are rarely harmless, but those recovered from the anterior nares, from discharging ears and from the skin often prove to be non-virulent when tested on guinea-pigs.

The Klebs-Loeffler bacillus is a non-motile, Gram-positive, non-sporing organism which shows a great tendency to appear segmented or clubbed. The bacilli are slender rods, straight or slightly curved, and of varying length and thickness. In films they often show a characteristic grouping which recalls the letters of the Chinese alphabet. Both long and short forms occur, the length varying from 2 to 6 $\mu$ . The segmented appearance of the protoplasm is relied upon for morphological identification. A rapid diagnosis may be made from smears prepared direct from the throat, but it should be confirmed by examination of a film made from a young (6 to 18 hours) culture on blood serum or Loeffler's medium. Diphtheria bacilli ferment glucose with formation of acid, but fail to ferment saccharose. The true bacilli have been divided into *gravis*, *intermedius* and *mitis* varieties, according to their virulence. Differences in growth on a special blood-tellurite medium, coupled with starch-fermenting power in the *gravis* type and a hæmolytic tendency in the *mitis* variety, are the chief distinctive features. There is some correlation between the strain of bacillus and the form taken by the infection: the *mitis* variety seldom causes profound toxæmia, but affects the larynx more frequently than the *intermedius* or *gravis*;

these two latter may cause the disease in all grades of severity, but the mortality from *gravis* strains is higher.

Pseudo-diphtheria bacilli, which, although identical in appearance with diphtheria bacilli, are non-virulent, are frequently found in the nose and ear, more rarely in the throat. Another non-virulent organism of the same group is Hofmann's. This appears in smears as a diplo-bacillus, the elements of which are short, squat and wedge-shaped with apposed bases. It stains uniformly throughout, and is shorter than even the shortest varieties of the diphtheria bacillus. These distinctions apply only to young cultures. Hofmann's bacillus does not produce acid in glucose, or in saccharose media, and is thus further distinguished. The xerosis bacillus, obtained from the conjunctiva, also resembles the true diphtheria bacillus, but it produces acid both in glucose and in saccharose media.

The crucial test of the identity of the diphtheria organism is the prevention of the local or general action of an injected broth culture by the previous injection of diphtheria antitoxin into the test animal. Two guinea-pigs are customarily employed, one of which has been protected by the injection of diphtheritic antitoxin. Subcutaneous injection of a culture of virulent diphtheria bacilli kills the unprotected animal in 48 hours and examination will show the characteristic suprarenal hæmorrhage.

In the throat, diphtheria bacilli are often associated with streptococci, staphylococci, or the fusiform bacilli and spirochetes described by Vincent. Of these, streptococci are most important, as cases of septicæmia have been attributed to them. Diphtheria bacilli rarely become disseminated in the blood-stream but have been found in the lungs and the cervical glands.

**Pathology.**—The constitutional disturbance caused by diphtheria is toxæmic, toxins but not bacilli being absorbed from the primary lesion, probably by the lymphatics. The extent, thickness, persistence and situation of the membrane determine the degree of toxæmia produced. In the formation of membrane, epithelial necrosis first occurs and is followed by inflammatory effusion from the subjacent tissues. This gives rise to the membrane in which stratified fibrin entangles epithelial cells, blood-cells and leucocytes. Nearly the whole of the process occurs outside the basement membrane. Bacilli are found in the false membrane and necrotic material, but not in the healthy tissues beneath. Recently formed membrane is firm in texture and has a glistening or somewhat gelatinous appearance. The tonsils are the common sites of the first membrane formation, but the faucial pillars, the soft palate, the pharynx, the epiglottis and the larynx may be implicated. Extension from the larynx along the trachea and main bronchi is not uncommon, but coherent membrane is rarely found in the bronchioles. Diphtheritic membrane is much more firmly adherent to the mucous membrane of the fauces than to the epiglottis, the larynx and lower air passages. Its appearance in the cavity of the mouth, on the tongue or lips is rare, and even more rare is its occurrence in the œsophagus, stomach or small intestine. The conjunctiva and occasionally the vulva, or a cutaneous abrasion or a surgical wound may become infected.

Apart from the membrane the morbid appearances in diphtheria are not distinctive. The condition, however, of the heart muscle is of peculiar interest. Glycogen is depleted and even in cases in which the myocardium appears healthy to the naked eye, special staining will show extensive infiltration of the muscle fibres with minute granules of mobilised fat. In advanced cases, patches of myocardial degeneration and perivascular aggregations of leucocytes become apparent. The valve escapes. The cavities of the heart may be dilated, the muscle flaccid and friable, and intracardiac thrombi, some obviously ante-mortem, may be found in the recesses of the auricles and ventricles, particularly on the right side.

The renal tubules may undergo extensive degeneration and the stomach may be acutely inflamed, with mucosal hæmorrhages and erosions.

Broncho-pneumonia is not uncommon in extensive faucial and in laryngeal infections, it is usually due to secondary invaders. Emphysema or pulmonary collapse may occur where respiratory obstruction is severe, and massive collapse of the lung may result from paralysis of the respiratory muscles.

The essential nervous lesion is a patchy parenchymatous degeneration of the peripheral nerves. Changes are also found in the vagal nuclei and in the anterior cornual cells. The cerebrospinal fluid contains an increased quantity of protein, usually about 100 mg. per 100 ml.

The lymphoid tissues of the body react, Peyer's patches being swollen and the spleen slightly enlarged. The liver, too, may be swollen from venous stasis and toxic degeneration of its cells.

There is evidence that carbohydrate metabolism is seriously deranged by diphtheria toxin, hyper- and even hypo-glycæmic blood curves being obtained.

Petechial hæmorrhages in the skin, serous membranes, heart wall and diaphragm are characteristic of hæmorrhagic diphtheria. Extensive effusions of blood sometimes occur.

**Symptoms.**—The incubation period may not exceed 24 hours, more commonly it is 3 or 4 days, but a carrier may harbour virulent bacilli for a considerable time before showing signs of infection. The fauces are most often the site of the disease, next in frequency come the naso-pharynx, the nasal passages, the larynx and trachea. Infection of the genital mucous membrane and of wounds is exceptional and of the intact skin rare.

*Faucial diphtheria* may occur in any degree of severity, from a mild catarrhal inflammation, the identity of which is only established by bacteriological examination, to a widespread infection in which membrane invades not only the whole throat but also the naso-pharynx, nose, larynx and, rarely, the mouth, either simultaneously or in succession.

Invasion may be characterised by malaise, headache, anorexia and soreness of the throat. Vomiting occurs occasionally and sometimes shivering; rigor is rare. In children, the onset is particularly insidious, discovery of membrane often being the first intimation of the disease. The exudate in mild cases is limited to a patch on one or both tonsils, sometimes on the uvula or pillar of the fauces, sometimes on the soft palate. More rarely the posterior pharyngeal wall is first attacked. Special characteristics of the membrane are its elevation above the general surface, its well-defined edge, its glistening or pearl-grey colour and its tendency to rapid spread. At first it is separable without bleeding, but later free oozing of blood occurs when it is forcibly detached. Multiple patches on the tonsils may, in the early stage, simulate follicular tonsillitis, but the patches tend to spread and fuse; limitation to one tonsil should always arouse suspicion of diphtheria.

Pyrexia is moderate or absent in mild infections, enlargement of the submandibular glands is slight and early albuminuria so characteristic of grave attacks may be wanting.

*Malignant diphtheria.*—When faucial diphtheria is severe it constitutes a very serious form of the disease with a high mortality. Toxæmia and sepsis may be combined in this grave form which is more common in children than in adults and in some epidemics than in others. It may develop very rapidly. The membrane is thick, tough and adherent, sometimes much discoloured. It plasters the œdematous fauces and may extend widely over both aspects of the soft palate and on the pharyngeal wall. When the membrane is spreading rapidly it may appear shiny and gelatinous, often being thin, transparent and filmy particularly at the growing edge. Nasal discharge points to implication of the naso-pharynx and nose. Rarely extension occurs along the hard palate and into the sulci at the sides of the tongue. Secondary invasion of the epiglottis and larynx is not uncommon. The cervical glands become swollen and tender, and paradenitis may extend and involve the neck in a collar of cellulitis (bull neck). The subcutaneous tissues may then undergo widespread necrosis and

the skin become thinned and much discoloured. A brownish or bloody nasal discharge excoriates the nostrils and the upper lip. Nasal respiration is obstructed and deglutition difficult. The breath has a sickening odour, and the face is puffy or becomes ashen in colour. The skin is dry and the extremities cold. Slight general cutaneous oedema may make its appearance. The patient is restless and sleepless but apathetic. Bleeding is easily induced by interference with the edges of the membrane, and epistaxis may occur. Fever is not proportionate to the gravity of the disease; in the worst cases the temperature is subnormal. Albuminuria is usually profuse and the quantity of urine secreted may be very small, but uræmic symptoms are rare. A steady and progressive circulatory failure, characterised by a falling blood pressure and feebleness of the heart's sounds, is an ominous feature. The pulse may become soft, irregular or quite imperceptible. At this stage the urea content of the blood is elevated. Respiration is rapid and shallow. Vomiting often sets in before the end. Broncho-pneumonia can rarely be recognised by physical signs, but is often present. Death may occur within a week of the onset; sometimes however, under the influence of antitoxin the membrane clears and the faucial oedema subsides, but acute circulatory failure may still be imminent; death often occurring during the latter half of the second week. In those who escape, widespread paralysis is a common sequel.

*Laryngeal diphtheria.*—Infection of the larynx may be primary, but is usually a sequel of faucial infection. Essentially occurring in childhood, its frequency increases up to the fourth year of life, after which it progressively declines. The presence of membrane, even in the smallest amount, on the tonsils or fauces will afford a positive indication of the nature of the laryngitis. Failing this a diagnosis is made by swabbing, by preference, the pharynx or larynx; but treatment must not be delayed pending the result. Hoarseness and croupy cough are early symptoms, soon followed by paroxysms of inspiratory dyspnoea due to laryngeal spasm, with characteristic stridor and recession of the chest wall. During the paroxysms the patient is agitated, sweating and perhaps cyanosed. The cough is loud and croupy. With relaxation of the spasm, dyspnoea may cease and the child fall asleep from exhaustion. At first the paroxysms are mainly nocturnal, later they become more frequent and more prolonged, until finally obstruction is continuous and mechanical. Extraordinary recession of the sternum and lower ribs may then accompany the efforts to respire. The body assumes a leaden hue and death occurs from slow asphyxia. In rare instances the paroxysms of dyspnoea and cough culminate in the expulsion of membranous casts of the larynx, trachea or larger bronchi. The absence of toxæmic symptoms when membrane is limited to the larynx and lower air passages is very striking.

Laryngeal diphtheria may run its fatal course in a few days. In infants its duration may be less than 24 hours. In favourable cases the condition subsides under prompt treatment. Should obstruction persist after tracheotomy or intubation, the presence of membrane in the trachea or larger air passages should be suspected; when, however, the bronchioles are blocked, the character of the dyspnoea is quiet rather than violent. Laryngeal diphtheria in a mild chronic form is a rarity.

*Nasal diphtheria.*—A muco-purulent or blood-stained nasal discharge may be the only evidence of diphtheria in infants and fever convalescents. Infection may be naso-pharyngeal or purely nasal. The former is grave, as toxæmic symptoms may be pronounced, whilst localised nasal infection is more often benign and may be unilateral. In such cases a small patch of membrane may, perhaps, be found on the septum. Possible implication of the nasal accessory sinuses should be remembered. As already mentioned, bacilli from the nose may prove to be non-virulent. Foreign bodies in the nose have at times been associated with persistent nasal diphtheria.

*Conjunctival diphtheria* is usually the result of direct inoculation, but may extend from the nose. It may simulate a mild, simple conjunctivitis, or membrane may form on the inner aspect of the lids. There is, however, a grave form with extreme

inflammatory infiltration of the conjunctiva which may lead to sloughing of the cornea and destruction of the eye.

*Vulval, vaginal and preputial diphtheria.*—Vulval infection may be secondary to diphtheria of the fauces, infection being conveyed by the fingers, or it may be primary. Sometimes it is seen in puerperal women. It is of insidious onset, and the membrane looks like a slough on the inner surface of one or both labia. The inguinal glands are enlarged, and confusion with noma, erysipelas, chancre or gonorrhœa is possible. Severe toxæmia may ensue. The vagina may be infected with the vulva. Preputial diphtheria may follow ritual circumcision. Infection of the puerperal uterus and of the male urethra is rare. Infection of the umbilicus may occur in the new-born.

*Diphtheritic infection of wounds* is not common except under conditions of active warfare, and here membrane formation is not invariable. The wound may merely be dry and grey and the adjacent glands swollen. Bacteriological confirmation is necessary. Paralysis may be confined to the region involved.

*Cutaneous diphtheria.*—Slight infection of the macerated skin at the margins of the nostrils and mouth is frequent and diphtheritic whitlow is not rare, the finger possibly being infected by sucking. Sometimes the raw surfaces left by eczema, herpes or impetigo become secondarily infected, and membrane may form, but skin diphtheria may occur without this distinctive sign. Gangrenous varicella and extensive gangrene allied to noma have been attributed to the action of the diphtheria bacillus, as also have some veldt or desert sores (see p. 1330). Here again paralysis may have a strictly local incidence. Before skin cases are accepted as genuine, rigorous bacteriological proof is essential.

*Septic diphtheria.*—The ordinary grave case of diphtheria may be looked upon as toxæmic. The septic type of case is characterised by pulpy discoloured membrane and great inflammatory œdema at the site of infection, accompanied, it may be, by fetor, ulceration, cellulitis or even gangrene. The adjacent lymph glands are much swollen, periadenitis is marked and suppuration may ensue. Erythematous or measly rashes may appear on the extremities. Constitutional symptoms are severe and the prognosis grave; chiefly, it is alleged, because diphtheria antitoxin has no influence on the septic element, which may be a hæmolytic streptococcus.

*Hæmorrhagic diphtheria.*—Hæmorrhagic symptoms supervening during the acute stage indicate an infection of a severe type. Blood may ooze from the edges of the membrane, and epistaxis occur. This in itself is not necessarily serious, but the tendency to bleed may be more widespread, bruises appearing on the body and bleeding occurring around and along the track of the antitoxin needle. The conjunctivæ may become suffused with blood, and hæmorrhage may occur from the stomach or bowel. Hæmaturia is rare. In some cases small cutaneous petechiæ are the only evidence of the hæmorrhagic tendency, but they are of most sinister import.

*Blood changes.*—A polynuclear leucocytosis is common in diphtheria and reaches its acme at the height of the disease. Sometimes the red cells are in excess of normal and the specific gravity of the blood increased, indicating a reduction in plasma volume with hæmoconcentration. Leucocytosis may be absent in very mild and also in very grave infections. The presence of myelocytes is also characteristic, and their appearance in large numbers indicates a severe toxæmia and a bad prognosis.

*Complications.*—The chief are circulatory failure, paralysis, albuminuria and pulmonary inflammations. Relapse sometimes occurs.

*Acute circulatory failure* is a justly dreaded occurrence. Apart from asphyxia and from respiratory paralysis it is responsible for all the deaths. In diphtheria, excluding the mildest cases and those in which respiratory obstruction exerts its modifying influence, there is from the first a progressive fall of blood pressure, the systolic readings being affected earlier than the diastolic. Recovery is very rare when the systolic reading falls below 65 mm. The fall in pressure is said to be accompanied by a fall in volume and increased concentration of the blood. Vascular



relaxation is believed to account for the early fall in pressure, the effect of myocardial weakness appearing later. The condition culminates in attacks of acute circulatory failure. Where systematic pressure readings have not been taken, vomiting and minor irregularities or intermissions of the heart's action often afford the first warning. True respiratory or sinus arrhythmia, which is so common in childhood and often is exaggerated in diphtheria, should not be confounded with the condition now under consideration. Tachycardia and bradycardia are both disquieting signs. The heart sounds become modified, the first becoming short and soft and the second somewhat accentuated. Reduplication and gallop-rhythm may occur. Vomiting without obvious cause is always a danger signal. The characteristics of the acute attack are great irregularity and feebleness of the pulse, præcordial or epigastric pain, restlessness, rapid shallow respiration, slight cyanosis and a sub-normal temperature. The mind remains clear. Dilatation of the heart and increase in the size of the liver may be evident. Actual dropsy is rare, but sometimes slight œdema of the face, chest and feet appears. Albuminuria may supervene or, if already present, be much increased; partial suppression of urine occurs. Death often results with great suddenness, and should the first attack be survived, which is unlikely, a second or even a third may prove fatal. Rarely recovery ensues.

Death from circulatory failure is an early sequel of severe faucial infections occurring at the end of the first or in the course of the second week. Cardiac failure occurring at a later stage of the disease is often associated with severe paralytic phenomena, and in some cases, at all events, is believed to be of nervous rather than myogenic origin. The absence of residual valvular or myocardial lesions after diphtheria is remarkable. Electrocardiographic evidence of myocardial disease is frequently present. This may consist of changes indicating diffuse damage to the myocardium, low voltage curves, flattened T-waves and depression of ST segments; or signs of injury to conducting tissues, such as all grades of auriculo-ventricular block, bundle branch or intraventricular block. Auricular flutter and fibrillation may occur, but are uncommon. Paroxysmal ventricular tachycardia may be a closing event. It is rare for electrocardiographic abnormalities to appear before the sixth day, or, for the first time, after the twenty-first day of the disease.

*Diphtheritic paralysis* occurs in from 15 to 20 per cent. of cases. It is more often localised than general, and rarely complete in degree. Palatine and ciliary, but not pupillary, paralysis are characteristic. Children suffer more frequently and more severely than adults. As a general rule, the extent and severity of the palsy are proportional to the amount of membrane which was present, but exceptionally, paralysis of diphtheritic type occurs in the absence of recognised infection. The usual time of onset is the end of the third or beginning of the fourth week of the disease, but in grave infections it may even set in before the fauces are clear of membrane. Widespread paralysis, including a dangerous bulbar variety, rarely declares itself before the end of the fourth week, and paralysis of the ataxic type, which is rare, often does not appear until the second or even third month. For a detailed description, see p. 1590.

The limited form of diphtheritic paralysis is transitory, its duration being measured by days or weeks, but the more widespread paralysis may last for months or the best part of a year before recovery is complete.

Hemiplegia sometimes occurs in diphtheria and is due to occlusion of the middle cerebral artery, usually by an embolus. In most cases this paralysis is more or less permanent. Much more rarely an embolus from the heart lodges in a main artery of a limb, producing gangrene.

*Albuminuria* is of common occurrence, but in mild or doubtful cases its absence is not sufficient to negative the diagnosis. It is most likely to be found about the tenth day, but appears earlier and in greater quantity in grave cases. In those who recover, it is transitory and no evident damage to the kidneys results. At times

casts and a little blood may be found in the urine, particularly in toxic or asphyxial cases. Acute circulatory failure greatly increases the albuminuria and may lead to suppression of urine. Acetone often appears in the urine during severe attacks of diphtheria.

*Pulmonary complications.*—Bronchitis and broncho-pneumonia may accompany severe faucial diphtheria, but are more common when the larynx is implicated. The cause is often a secondary infection. Febrile disturbance, increasing dyspnoea, cough and lividity are the signs which should suggest implication of the lung. Auscultatory signs are often equivocal, owing to laryngeal obstruction or the presence of a tracheotomy tube. Massive collapse of the lungs, which may occur in paralytic patients, is often mistaken for acute circulatory failure, pneumonic consolidation or pleural effusion. Some degree of acute emphysema is usually present when the larynx is obstructed, and surgical emphysema of the mediastinal and subcutaneous tissues may follow a difficult tracheotomy and simulate pericardial friction. As sequels of diphtheria, lobar pneumonia, pleural effusion and empyema are rare.

*Otitis media* is exceptional and seldom serious. In this respect it stands in sharp contrast to the otitis of scarlet fever and of measles. Diphtheria bacilli recovered from the ear discharge are often non-virulent, perhaps in 50 per cent. of the cases. Diphtheritic membrane is sometimes formed in the auditory meatus.

*Relapse* of diphtheria is rare. It occurs in little over 1 per cent. of the cases and usually is mild, the membrane being limited to the tonsils and rarely spreading to other parts.

*Diagnosis.*—Every inflamed throat, or nasal discharge, particularly in a child or fever patient, should be regarded with suspicion, and clinical diagnosis supplemented by bacteriological examination before antiseptics are applied. Definite membrane on one or both tonsils or adjacent parts of the throat is characteristic of diphtheria. Tonsillar inflammation, if accompanied by hoarseness or rhinorrhœa or albuminuria, is highly suggestive. Some diphtheritic throats are very œdematous and painful, but, as a rule, pallor of the mucous membrane and absence of pronounced fever and pain are striking features of the disease.

The differential diagnosis between scarlet fever and diphtheria is discussed on p. 44. Simple tonsillitis is usually bilateral, and the exudate, which is soft and crumbling rather than membranous, is follicular and limited to the surface of the tonsils. Pain, pyrexia and constitutional disturbance are more pronounced than in diphtheria, and the tongue remains heavily coated.

Peritonsillar abscess is more characteristic of simple tonsillitis and the secondary tonsillitis of scarlet fever. It seldom occurs in diphtheria.

Vincent's angina may produce a greyish film of exudate on one or both tonsils, and even invade the adjacent parts of the faucial pillars and the soft palate, but the process is rather a shallow necrosis than a true membrane formation. Ulceration may be evident at the centre of the deposit; sometimes it is widespread and destructive. The mucous membrane of the gums and cheeks may also be attacked. The breath has a peculiar and offensive odour, but diagnosis should never be based on this alone. The fusiform bacilli and spirochætes described by Vincent can be demonstrated.

Double infections with diphtheria and Vincent's organisms are not at all rare. Thrush, which produces an exudate like milk curd, is recognised by detection of the characteristic mycelium. It is a disease of infants and greatly enfeebled adults.

Membranous angina may occur in glandular fever, leucæmia and agranulocytosis, or be coupled with severe stomatitis in hæmorrhagic small-pox, acute attacks of erythema multiforme, the Stevens-Johnson syndrome and sporotrichosis.

*Syphilis.*—Both in adults with the acquired and children with the inherited disease the inflamed throat of secondary syphilis is a cause of confusion. The throat is painful and full of mucous secretion. Filmy patches (*snail tracks*) appear on the tonsils

and pillars of the fauces. The tonsillar glands are swollen, well defined and indolent, and there is little or no fever. The rapidity with which ulceration and perforation of the palate occur in some cases is striking. The diagnosis is made from the history, the presence of other signs of syphilis, failure to find diphtheria bacilli, a positive Wassermann reaction and prompt response to vigorous anti-syphilitic treatment.

Other conditions which simulate faucial diphtheria are erysipelatous inflammation, herpes of the soft palate, lesions due to steam, boiling fluids, caustics and the trauma of tonsillectomy.

*Laryngeal diphtheria.*—Croupy cough, hoarseness and stridor in a child will always suggest diphtheritic infection. Examination may show membrane on the fauces. By forcible depression of the base of the tongue with a spatula, the epiglottis may often be seen and membrane possibly recognised on its edge or surface. Rarely fragments of membrane are ejected on coughing, or there may be a history of contact with the disease. All doubtful cases should be treated freely with antitoxin, pending confirmation by examination of a swab taken from the pharynx as near the glottic aperture as possible.

Other forms of laryngitis have to be differentiated. They are (1) the laryngitis of early measles, distinguished by history, catarrhal symptoms, and Koplik's spots. (2) Simple catarrhal laryngitis; in this bacteriological examination is most essential. The voice may be hoarse, and the cough croupy; nocturnal spasms of dyspnoea may occur. Enlarged tonsils and adenoids are often present, and sometimes the history of previous attacks is obtained. (3) The glottic spasm of laryngismus stridulus is also definitely paroxysmal, but although the child crows the voice is not hoarse nor is the stridor persistent. Rickets, tetany and convulsions are the accompaniments in many cases.

Retro-pharyngeal abscess, when low down, produces considerable laryngeal obstruction. Digital examination of the back of the pharynx reveals its presence; sometimes the bulging may be seen on inspecting the fauces.

Rare causes of laryngeal obstruction are congenital laryngeal stridor, congenital syphilis, œdema of the glottis in renal disease, or resulting from inhalation of steam or other irritants, foreign bodies in the larynx and papillomatous growths. These forms of obstruction are differentiated from diphtheria by the history, by careful inspection of the fauces, followed by digital examination, by general examination of the patient and by the negative results of bacteriological examination. In adults the laryngoscope will give useful information. Direct laryngoscopy is also of great value.

*Prognosis.*—The important indications yielded by determination of the extent and position of the membrane have already been mentioned: the more extensive and more persistent this is, the greater is the risk of severe toxæmia. Cases where the membrane is limited to one, or to parts of both tonsils are likely to be mild; when both tonsils are completely covered the attack is more grave, but recovery is still probable; when the fauces and naso-pharynx are extensively involved, the outlook is very serious. The mortality in malignant diphtheria may, despite antitoxin, even reach 60 per cent. The great mortality of laryngeal diphtheria is due to asphyxia and broncho-pneumonia, absorption of toxin from this region being small. Diphtheria limited to the nose and not involving the naso-pharynx has a low mortality.

Enlargement of the cervical glands is more or less proportional to the extent and virulence of the lesion in the fauces and naso-pharynx, and has the same prognostic importance. The efficiency of antitoxin treatment and the day of its first administration have a most important influence. The mortality is almost negligible when antitoxin is administered on the first day of the disease, but it increases progressively to 18 or 20 per cent. if administration is delayed to the fifth or subsequent days.

Age also has a great effect, the disease being very fatal to children in the first year of life, and much more serious in children under 5 than in those over that age.

Malignant and septic attacks with much pallor, copious nasal discharge, considerable glandular enlargement and profuse albuminuria have a very bad prognosis.

Hæmorrhagic symptoms, other than slight bleeding from the edge of the membrane and possibly epistaxis, are grave; particularly so, minute cutaneous petechiæ. Cases such as these hardly ever survive. Repeated vomiting after the initial stage, and signs of acute circulatory failure are most ominous. The chief danger of paralysis, when this ensues early, is its association with acute circulatory failure, but paralysis of the bulbar type is in itself very fatal. Failure of the muscles of respiration and deglutition with liability to broncho-pneumonia and pulmonary collapse constitute the chief dangers of generalised paralysis. If the patient survives, paralysis terminates in complete recovery, but hemiplegia, which is of vascular origin, may be permanent.

**Treatment.**—**PROPHYLACTIC.**—Convalescents should be isolated for not less than 4 weeks from the commencement of the disease, or until three negative bacteriological examinations at intervals of a week have been obtained. The presence of inflammatory conditions or discharges from the throat, nose, eyes or ears is an indication for further detention. Skin eruptions and whitlows should not be overlooked.

The period of quarantine advised is 12 days. This is now generally replaced by supervision with bacteriological examinations. Children from an infected house should not be allowed to attend school until proved free from infection. Contacts in the home or school often become carriers, and should also be bacteriologically examined. Clothing and utensils which have been in contact with the sick should, of course, be disinfected.

When diphtheria breaks out in ward or institution the procedure is as detailed on p. 77. Opinion with regard to the desirability of prophylactic injections of antitoxin is not unanimous. The symptoms of diphtheria may be prevented in contacts by the injection of 500 units of antitoxin, but this method fails if the subject is already incubating the disease, and only affords protection to others for some 3 or 4 weeks. It should be realised that antitoxin does not prevent infection, but only the toxic results of infection. It militates against active immunisation and may produce a condition of hypersensitiveness to the serum, which may have to be used subsequently.

For these reasons, the best authorities are against prophylactic injections of antitoxin in contacts and in favour of repeated examinations for signs of development of the disease, when antitoxin can be administered at once. Meantime, immunisation of susceptible contacts (*vide infra*) can be initiated, since there appears to be no negative phase induced.

In the Schick test we have a means of determining whether an individual is susceptible to diphtheria. If a local inflammatory induration from 1 to 2 cm. in diameter follows the injection of 0.2 ml. of diphtheria test-toxin into the skin (or 0.1 ml. of the U.S.A. reagent), susceptibility to the infection is indicated. The average Schick-test antitoxin equivalent is  $\frac{1}{1000}$  unit. This measure of combining power is preferable to the original standard of one-fiftieth of the minimum lethal dose (M.L.D.) of toxin for a guinea-pig. At the same time, but at another spot, an intradermic injection of heated, and therefore inactive, toxin is made, to discount a "pseudo" reaction due to the foreign protein in the solution of toxin. The absence of a reaction to the active toxin generally indicates the presence of more than one two-hundredth of a unit of antitoxin per c.cm. in the blood, and is a sign of immunity. The injections are usually made into the skin of the forearms. The reaction takes 24 to 36 hours to develop, and another week to subside. Four types of reaction are possible: (1) Negative, (2) Positive, (3) Negative and Pseudo and (4) Combined Positive and Pseudo. These must be discriminated with care. The best time for reading the test is 36 hours after injection, and again at the end of a week when false reactions will have faded and late positive reactions will be detected.

For immunisation, diphtheria toxin, guarded by antitoxin, was originally used. Later, toxin, converted to toxoid by incubation with formalin (*anatoxine*), replaced

this. Toxoid-antitoxin floccules, precipitated by interaction of toxoid and antitoxin produce little or no reaction and are effective. For the immunisation of children, alum-precipitated toxoid (A.P.T.) is now recommended. Two doses (of 0.5 ml.) are given intramuscularly, with an interval of 4 weeks between them. Some prefer an initial dose of 0.2 ml. For adults, who are more liable than children to reactions, toxoid-antitoxin floccules (T.A.F.) are preferable, three injections (1 ml., 1 ml. and 1.5 ml.) being administered, with intervals between them of 3 or 4 weeks. Susceptibility to reaction may be detected by intradermal injection of 0.2 ml. of diluted toxoid (*Moloney test*) or of the particular antigen it is proposed to use. The development of active immunity takes about 6 weeks. This immunity is protracted, but its exact duration cannot yet be specified. Most children over 6 months are susceptible and the ideal time for immunisation is in the eighth month or soon after. At the beginning of school life a supplementary dose of 0.5 ml. is recommended. When the proportion of vaccinated children in a community reaches 70 to 80 per cent. a great reduction of incidence of diphtheria, and of carriers, perhaps to zero, may be expected.

When dealing with outbreaks of diphtheria in wards or institutions, swabs should be taken from the throats and noses of the inmates, and Schick tests performed. The negative reactors are then isolated. They will probably include a dangerous chronic carrier as proved by the virulence test. The positive reactors may be immunised with A.P.T. or combined active and passive immunisation undertaken, injections of 500 units of antitoxin being injected into one arm and the first dose of A.P.T. injected into the other arm at the same sitting. Virulent bacilli in the Schick positive group indicate precocious carriers who will soon sicken with the disease. Measures to prevent dissemination by dust are the same as those recommended in scarlet fever (p. 46).

Chronic carriers are a great source of difficulty. The bacilli cannot be eradicated by local application to the throat or by the administration of antitoxin or vaccines. If the tonsils are unhealthy, they should be enucleated and adenoids removed; this is often successful. In nasal carriers when streptococci coexist the insufflation of sulphonamide powder twice daily for 8 days has seemed effective. Penicillin, too, may possibly be of use. Carriers should spend as much time in the fresh air and sunlight as possible. Before condemning a carrier to isolation, the virulence of the organisms should be tested and confirmed.

**CURATIVE.**—The patient should be isolated and strict recumbency maintained. Diphtheria antitoxin must be injected intramuscularly without delay, the result of bacteriological examination not being awaited in any case in which the diagnosis is reasonably certain. Although antitoxin can neutralise circulating toxin, it is much less effective against toxin which has become fixed in the cells of the body. It is therefore very important that the patient should receive the first dose of serum not later than the third day of the disease; the earlier it is given the better the result, but at whatever stage the presence of membrane indicates prompt dosage. The amount required depends, not on the age, but on the duration of the disease, the extent of the membrane and the degree of toxæmia. For mild cases on the first or second day 8000 to 20,000 units are sufficient; in more severe cases the dose should be 20,000 to 100,000 units, repeated in 12 hours if the membrane still shows a disposition to extend, or laryngeal symptoms are not relieved. Cases coming under observation after the third day of illness require larger doses than those seen earlier.

In malignant, advanced and hæmorrhagic infections, the antitoxin should be given intravenously, undiluted and at blood heat. Injection should be very slow, through a fine needle. The patient is then wrapped in warm blankets, hot water bottles applied and the foot of the bed raised, since rigor and collapse may follow; 100,000 to 200,000 units may be given in this way, followed by intravenous injection of 20 g. of anhydrous dextrose in the form of a 50 per cent. solution in normal saline.

supplemented by 20,000 units of antitoxin intramuscularly into the buttock or outer side of the thigh. In cases which do not respond the intravenous injection is repeated after 12 hours. Intraperitoneal or longitudinal sinus injections may be adopted in some circumstances.

Antitoxin treatment may be followed by certain sequels due to horse serum. These are less frequent when concentrated or protein-digest antitoxins are used. They usually occur a week or more after injection and take the form of erythematous, morbilliform or urticarial eruptions, appearing first in the vicinity of the puncture. Fever, vomiting, arthritic pains or slight joint effusions may accompany the rash. The tonsils may again become inflamed (*angina redux*) and albuminuria may occur. The rashes and other symptoms are transient but may recur. Aspirin often affords much relief, and the cutaneous irritation may be allayed by weak carbolic lotions. On rare occasions rigor, dyspnoea and collapse follow the injection immediately, and death has been known to occur. These symptoms are anaphylactic in nature and may occur if the patient has been sensitised by injection of serum a few weeks previously, or even apart from this. Asthmatics are known to be particularly liable to them. When it is necessary to administer antitoxin in such circumstances, a preliminary injection of 5 minims should be given subcutaneously and the effect watched, or an intradermic test made. If no symptoms occur within an hour the full injection may be employed, otherwise desensitisation is necessary (see p. 4).

Penicillin cannot replace antitoxin in the treatment of diphtheria. There is, however, evidence that in malignant and in septic infections with much oedema and bull neck (possibly due to hæmolytic streptococci) intramuscular penicillin in adequate dosage, even up to one million units a day, causes rapid disappearance of membrane and subsidence of toxæmia. The diphtheria bacilli may disappear within 24 hours.

Absolute recumbency is essential in the treatment of diphtheria. For the mildest case a fortnight is not too long, in the average case at least a month, and for severe infections longer. When the patient is first allowed to sit up in bed the effect on the pulse should be carefully noted. No patient should be allowed to sit up whose pulse is irregular or who has recently vomited. The detection of paralytic symptoms is also an indication for rest.

Local applications to the fauces and nose are of minor importance.

In laryngeal diphtheria prompt administration of antitoxin and the use of a steam tent will generally obviate the necessity of operative interference; but tracheotomy, intubation or laryngeal aspiration should not be postponed, if restlessness, dyspnoea and recession of the chest wall are present, or paroxysmal dyspnoea has supervened.

Intubation is suitable for the milder type of case, but constant skilled supervision is necessary, as the tube may be ejected. As a rule, tracheotomy is preferable, especially if the fauces and naso-pharynx are much involved. Tracheotomy as a sequel to intubation has a very high mortality on account of the class of case in which it becomes necessary. After tracheotomy or intubation the patient is usually placed in a steam tent and the arms secured by light splints or other means. Cough on swallowing is obviated by using thickened foods or by nasal feeding. A method of feeding with the head lying lower than the body is often successful in intubated patients. If all goes well an attempt should be made to dispense with the tracheotomy or intubation tube on the third day, sometimes even sooner. Patients must be watched constantly when the tube is first removed. In cases where the tracheotomy is dry and no secretion occurs, an alkaline spray is useful.

Circulatory failure is treated by removing all pillows, raising the foot of the bed on blocks and applying a binder to the abdomen. The most absolute rest and perfect quietude are essential. Intramuscular injections of suprarenal cortical extract and oxygen inhalation have some value.

Paralysis calls for careful nursing and feeding, with avoidance of muscular exertion, but patients with transient precocious palatine paralysis may be allowed up

after 10 days if the condition is stationary. Massage and electricity may be useful during convalescence, but should be avoided in the early stages. The administration of vitamin B<sub>1</sub> (aneurine hydrochloride; thiamine hydrochloride, U.S.P.) is of very doubtful utility. Extensive respiratory paralysis necessitates artificial respiration with a Drinker or Bragg-Paul apparatus. Active collapse of the lung in diphtheria may be mistaken for acute circulatory failure if its special diagnostic signs are not borne in mind.

During the acute stage of diphtheria and also when albuminuria is present, milk, glucose mixtures and fruit juices are the best food. Solids may be allowed quite early in convalescence. When swallowing provokes coughing, the milk should be thickened with isinglass or cornflour. When pharyngeal paralysis is present, the patient should be fed through a large soft œsophageal tube or by nasal catheter.

The occurrence of anaphylaxis after injection of antitoxin is treated by injection of adrenaline, and by artificial respiration; by some adrenaline is given before injection of serum, as a prophylactic.

## ANTHRAX

**Synonyms.**—Wool-sorter's Disease; Splenic Fever of Animals.

**Definition.**—An acute infective disease caused by the *Bacillus anthracis*. There are three clinical forms of the disease, according as the lesion is in the skin (malignant pustule), in the lung (pulmonary anthrax) or in the intestine.

**Ætiology.**—*B. anthracis* is a large Gram-positive bacillus possessing a capsule. On artificial media it grows in long filaments which, owing to the fact that the filaments do not readily break up into individual bacilli, tend to bend upon themselves and thus cause the outlines of the colony to assume a whorled appearance that is characteristic. Spores always develop in cultures in the presence of free oxygen.

In the tissues, however, the bacilli occur in straight rods measuring from 5 to 10 $\mu$  by 1 to 1.5 $\mu$ , the longer forms generally being found in attenuated cultures, and the bacilli found in the gelatinous œdema are usually longer than those found in blood. Spores never develop within the infected animal, since free oxygen is necessary. The micro-organism is non-motile.

In the herbivora, especially sheep and cattle, the disease occurs epidemically and the infection assumes a septicæmic type. The spleen may be two or three times its normal size, and on section may be diffuent. An impression preparation from the cut surface shows enormous numbers of bacilli together with blood cells and mononuclear leucocytes. The liver and kidneys are in similar condition, and the lymphatic system is extensively involved.

The bacilli in the blood are invariably in the vegetative form, and it is only after being voided from the body that they produce spores, these being extremely resistant to adverse influences. It is claimed that spores may remain on the ground in a state of latent activity for as long as 12 years. They are destroyed by sunlight in 24 hours, but resist the usual concentrations of chemical disinfectants; they are killed by dry heat at 160 to 180° C. and moist steam above 120° C. for 1 hour. It is suggested that soil infection counts for little in this country, most cases being traceable to imported foodstuffs, hides and brushes.

The carnivora are relatively immune, especially the dog.

Man occupies an intermediate position, and the disease is always communicated to him directly or indirectly from animals. Two principal forms occur, malignant pustule, a local infection through a cut or abrasion of the skin or a hair follicle, and wool-sorter's disease, an infection starting in the trachea and bronchi from the inhalation of dust containing spores.

Infections of the intestinal tract may occur but are rare. Such infections must originate from spores, as the bacilli do not withstand the action of gastric juice.

**Bacteriological Diagnosis.**—In a case of suspected malignant pustule direct microscopic examination will usually show the bacilli in the fluid in the surrounding vesicles. Sometimes examination of the sections of the excised malignant pustule is necessary. Cultures on agar will show in 24 hours the characteristic wavy-outlined colonies. Blood cultures in man never show the bacilli until just before death. Putrefaction rapidly destroys anthrax bacilli, hence the recognition of the bacillus in putrefying tissues entails careful bacteriological examination and animal experiments.

A guinea-pig may be inoculated with suspected material, and if anthrax be present will usually die within 2 days, and the bacilli may be demonstrated in the spleen.

**Immunity.**—Pasteur, noting that one attack of anthrax immunised an animal, elaborated a method of artificial immunity. He attenuated cultures by growth at 42.5° C. Sheep survived when inoculated with such cultures, and proved immune to a subsequent injection of a highly virulent living culture. By carrying out this process of active immunity the mortality among animals was greatly lessened. Marchoux showed that the serum of such animals conferred a certain degree of passive immunity; and Sclavo, by using a mixture of such immune serum and progressively attenuated cultures and virulent cultures, obtained very high degrees of immunity in the ass. Sclavo's serum is stable, and if given in quantities of 40 to 100 ml. at an early enough stage in the disease is almost always successful.

**Symptoms.**—There are three clinical forms of the disease. I. **MALIGNANT PUSTULE.**—The site of infection is nearly always upon an exposed part of the body—face, neck, hands or forearms. The incubation period appears to be very short, perhaps not longer than a few hours. A small red papule forms, which rapidly becomes vesicular and then incompletely pustular. By the time vesication occurs there is a surrounding zone of intensely red œdema, becoming a brawny induration by the end of the second day. By this time a ring of secondary vesicles often surrounds the initial lesion, which has now formed a dry and almost black scab, generally raised above the surface of the affected skin. A frequent associated lesion in the case of the arm is lymphangitis, spreading upwards to the axillary nodes, which become enlarged and painful. There is rarely much pain at the site of the initial lesion, though there is usually a good deal of itching and tenderness. Fever is almost constant, and in severe cases may be quite high. The patient is then very ill, with intense toxic symptoms. Mild cases occur, however, and in them both the local and the general symptoms are much less marked.

The prognosis turns upon the severity of the symptoms, especially of the toxic state. Death is sometimes very rapid—it may occur within the first week.

In some cases the initial papule and vesicle are ill-marked, but the attendant œdema is excessive (*malignant œdema*). The mortality in this type of the disease is a good deal higher than in the type in which the pustule is well formed.

II. **PULMONARY ANTHRAX.**—In this variety of the infection the bacilli are inhaled with dust from infected hair or wool. The result is the rapid development of fever, generally ushered in by a rigor, with very intense toxic symptoms and the signs of bronchitis. Cerebral symptoms develop, with great weakness. The whole course of the disease may be very short, even as brief as 24 hours.

III. **INTESTINAL ANTHRAX.**—This is probably the least common form of the disease. The infection is due to eating meat or drinking milk from animals suffering from splenic fever. The symptoms are those of a severe gastro-enteritis—fever, vomiting, diarrhœa and intense weakness. The spleen is enlarged. This form of the disease has been found to occur in small epidemics. The mortality is high, though not so high as in II.

**Treatment.**—(1) **PROPHYLACTIC.**—This consists in the specific immunisation of animals subject to the disease, the complete destruction of dead bodies and in the



careful disinfection of all skins, hair and wool, before these are handled in any industrial occupation.

(2) CURATIVE.—General measures are taken towards the prevention of a general infection. The pustule is kept clean, but is neither cauterised nor incised. The treatment of choice is penicillin (see p. 6), which has now superseded Sclavo's anthrax anti-serum. The sulphonamides have also been employed successfully, and before their introduction neocarsphenamine had a vogue.

## TETANUS

**Synonym.**—Lockjaw.

**Definitions.**—An infective disease, due to the toxins of the *Clostridium tetani*, and showing itself by tonic spasm of the masseter and other muscles with paroxysmal exacerbations.

**Ætiology.**—The bacillus of tetanus is a slender rod 4 to 5 $\mu$  in length and from 0.3 to 0.8 $\mu$  broad. It is a spore-bearing anaerobe. The vegetative forms are slightly motile, and when stained by special methods show numerous fine flagella arranged all round the bacillus. In material from infected wounds, and usually in cultures after 24 hours' incubation at 37.5° C., spores occur. These are terminal, giving rise to the characteristic drumstick appearance. As cultures grow older the numerical proportion of spore-bearing forms increases, and in very old cultures only spore-bearing forms or spores are found.

**Distribution.**—In nature the tetanus bacillus is found in the soil of highly manured districts, and in the dejecta of various animals, especially the herbivora, in the intestines of which it exists without causing pathogenic effects. By comparison with the widespread distribution of the bacillus and its spores the disease is rare. In infected wounds the bacillus occurs with other spore-bearing anaerobes associated with pyogenic cocci, and saprophytic organisms of various kinds. In consequence of its association, in nature and infected wounds, with other organisms, the bacillus is difficult of isolation, as a large proportion of the associated organisms grow with much greater rapidity. Use is made of the fact that the spores will resist a temperature of 80° C. for an hour. Suspected material is inoculated into agar or serum-agar slopes or deep tubes of glucose-agar, and incubated for 48 hours. The culture is then subjected to a temperature of 80° C. for three-quarters of an hour, and subcultures are made on agar plates which are incubated anaerobically. By this means all non-sporing bacteria, and the vegetative forms of the spore-bearers, are killed, and only spore-bearing organisms remain to be dealt with.

The disease follows injury to the tissues in most cases, and even when no injury is known to have occurred, it is highly probable that some slight abrasion has been present. The term "idiopathic tetanus" has been given to those cases in which no discoverable injury is present. Those wounds, usually of the hands, in which the tissues have been badly damaged rather than cleanly cut, are specially liable to be followed by tetanus infection. Cases have occurred from the use of contaminated gelatin used in subcutaneous injections, grey wool employed as padding for splints, from catgut sutures similarly infected and from wounds from blank cartridges and fireworks.

Tetanus is more common in tropical than in temperate zones. A special form of the disease, *tetanus neonatorum*, is peculiar to the tropics, and results from sepsis in attending to the child's navel.

**Pathology.**—In nature the disease is produced by the introduction of infected material through an abrasion or wound, which may be so minute as to escape detection. Probably there is no such thing as idiopathic tetanus, but infection is possible through the bronchial or even intestinal mucosa.

If the bacilli or spores, free from toxin or from pyogenic cocci, be introduced into an animal, infection may fail to occur, the protection afforded being probably accounted for by phagocytosis, for if spores enclosed in a paper sac be introduced into a susceptible animal infection occurs, as the sac protects the spores from phagocytosis. The presence of pyogenic cocci, other micro-organisms, and the fragments of bone and foreign material incidental to compound fractures and gun-shot wounds, all conduce to the conditions favourable to growth of the tetanus bacillus.

The *period of incubation*, following infection with tetanus bacilli, varies with different animals. In man, a period of from 2 to 14 days occurs, but it may be as long as 100 days, and, as a rule, a long incubation means a more favourable prognosis.

*Tetanus toxin.*—The tetanus bacillus, like the diphtheria bacillus, produces its pathogenic effects by reason of the soluble toxin it elaborates. Bacterium-free filtrates of cultures, as shown by Kitasato, when injected subcutaneously into mice, cause tetanic spasms, at first in the neighbouring muscles and later more generally, and death has resulted.

Tetanus toxin is one of the most powerful poisons known, the fatal dose of a probably impure preparation for a mouse being found by Brieger to be 0.0005 mg.

Different degrees of resistance to the toxin are shown by different animals. The horse and man are the most susceptible. On a basis of weight the horse is twelve times and the guinea-pig six times as susceptible as the mouse, while the hen is two hundred thousand times as resistant. The incubation period is shorter when toxin is intravenously injected than when introduced subcutaneously, and is shorter in smaller than in larger animals.

It was formerly believed that tetanus toxin ascended the peripheral nerves, and this view, although contested by Abel, has now been confirmed by the recent work of Payling Wright and his colleagues. There is some evidence that the toxin is altered in the cells of the nervous system to a form in which it cannot be neutralised by antitoxin.

*Symptoms.*—The incubation period has already been referred to. The earliest symptom is, in the great majority of cases, the so-called *trismus* or painless tonic spasm of the masseter muscles. Beginning as a slight stiffness, this increases until the jaws are firmly clenched, the patient being unable to open the mouth. The stiffness may involve the muscles of the neck at the same time as the jaws, or a little later. The facial muscles are affected next, and the facies presents the *risus sardonicus* due to the tension in the frontalis and in the muscles at the angles of the mouth. The muscles of deglutition are another group early affected. There is, from these parts, a steady spread of the spasm to the trunk and then to the limbs. Rigidity tends to appear early in the rectus abdominis and in the adductors of the thighs. The tendon jerks are exaggerated and attempts to elicit them produce spasms, local or general; attempts to elicit the plantar reflex may cause extension of the knee (Gordon Holmes). The tonic spasm in the muscles of the trunk, which may develop in from 12 hours to a week after the appearance of trismus, usually shows exacerbation in paroxysms, with resulting postures termed respectively opisthotonos, emprosthotonos and pleurothotonos, according as the muscles of the back, abdomen or one side of the body are in a state of spasm. These paroxysms may be induced by divers irritants, and are agonisingly painful; the earlier they occur the more grave is the prognosis. Retention of urine is common.

Less common manifestations include a local contracture of muscles in the neighbourhood of the wound, which may precede trismus or more general spasm by several days; the localisation of stiffness and spasm in tetanus may be a result of immunisation. Thus, in a wound of the forehead there may be a facial palsy or an ophthalmoplegia on the same side or, with a wound of the hand or foot, painful spasm of the muscles of the limb may develop before spasm appears elsewhere. In some of these local forms general spasms may be absent throughout or, if trismus

is present, this may be transient. In "*local tetanus*" the incubation period is sometimes as long as 30 days.

The disease is often apyrexial, but in some cases the temperature rises with the development of the general symptoms, which include headache, pains in the back, anorexia, constipation, insomnia, yawning, sweating and a facies of great anxiety. Hyperpyrexia may precede death. Consciousness remains clear. The cerebrospinal fluid is unaffected.

**Course.**—The course of the disease is variable. Sometimes it is as short as 4 or 5 days, the patient dying of spasm of the glottis, asphyxiation, broncho-pneumonia, heart failure or exhaustion. Other cases, less fulminant, last from 7 to 14 days. A few seem to deserve the term "*chronic*".

**Diagnosis.**—A relatively trivial disease which may, however, cause some anxiety from its resemblance to the trismus of tetanus, is the fixation of the jaw seen in certain cases of *septic throat* and *septic*, especially impacted, *teeth*, with phlegmonous involvement of the floor of the mouth, periosteum, etc. Careful examination of the mouth nearly always suffices to determine the real nature of these cases, and the presence of enlarged and tender cervical glands assists the diagnosis.

*Strychnine poisoning* presents features resembling tetanus in that the spasms are very similar in both diseases. But between the spasms in strychnine poisoning the muscles are relaxed, a condition never seen in tetanus. Another point of distinction is the fact that trismus and cervical rigidity never exist alone in strychnine poisoning, whereas they frequently do in tetanus.

In any doubtful case of injury, in which there are damaged tissues, bacteriological investigation of the exudate and of material from the depths of the wound should at once be made.

**Prognosis.**—This is always grave. The mortality in a large series of cases was 45 per cent. (Vinnard). Infants and children rarely recover. The absence of fever, a more or less normal pulse-rate, a long incubation period, and a slow development of the symptoms are favourable points. If the patient reaches the tenth day of the disease, his chance of recovery is considerably increased.

**Treatment.**—1. **PROPHYLACTIC.**—All wounds of a suspicious character should be excised under a general anæsthetic, the raw surface thoroughly treated and antitoxin administered.

Antitoxin has for some time been administered as a routine, when wounds are infected with road sweepings or garden soil and in America often in trauma sustained during Independence Day celebrations, with a consequent fall in the death rate from tetanus.

During the War of 1914-1918 antitoxin was used on an extensive scale. During the early period, with no special arrangements for prophylaxis, the incidence was about 8 per 1000. Later, with the use of 500, and then 3000 international units (I.U.), of antitoxin, the incidence fell to 1 in 1000. Following passive immunisation induced by prophylactic antitoxin, cases which do develop tetanus tend to have a longer incubation period and the disease may remain "*local*". But such passive immunity does not persist for more than 3 weeks; hence to ensure protection the dose of antitoxin must be repeated at fortnightly intervals where wounds do not heal.

Tetanus toxin treated with formaldehyde or alum loses its toxicity but retains its antigenic power. The material, called "*toxoid*", has been proved of great service as a preventive agent. At the R.A.M. College it has been proved that two doses of 1 ml. each of toxoid, given at intervals of 6 weeks, confer immunity lasting at least 2 years. This is now the practice in the British Army before a man goes on active service. The second injection is most essential in the production of active immunity for, following it, the rise in antitoxin content of the patient's serum is far greater than that consequent upon the first.

2. **CURATIVE.**—Keep the patient as quiet as possible in a dark and noiseless room.

Feeding may be impossible by mouth, in which event nasal feeding may be attempted, and if this, too, is impossible because of spasm, recourse must be had to glucose-saline rectal drip.

A complete excision of the primary site or sites of infection is wise wherever this is possible.

It is profoundly important that no delay whatever should occur in the use of antitoxin. Injection may be made intravenously or intramuscularly. Provided there be no contra-indication to the administration of horse serum—freedom from previous serum therapy, freedom from allergic manifestations which might necessitate rapid desensitisation (see p. 4), antitoxin may be injected undiluted into the vein, although it is wiser to dilute it with 200 to 300 ml. of sterile normal saline and allow half an hour for its administration. As soon as the diagnosis is suspected, 50,000 to 60,000 units are given intravenously. Antitoxin is excreted slowly and its presence in the circulation has been demonstrated at least 10 days after a large single dose given by the intravenous route (Cole). Probably nothing is gained by infiltration of the area surrounding the infective focus with antitoxin. Subsequent daily intramuscular doses of 10,000 to 40,000 units are advisable to neutralise any possible continued production of toxin.

Debate still continues over the advisability of intrathecal injections of antitoxin. The balance of opinion is opposed to it and this view is reinforced by the frequency of severe reactions and by the evidence that tetanus toxin, once fixed in the cells of the nervous system, is no longer neutralised by antitoxin. A similar dose should be administered at least an hour before any further surgical treatment or manipulation is undertaken.

Before the onset of tetanic convulsions, a mixture of chloral gr. 15 and bromide gr. 20 given by mouth 2- or 4-hourly, or phenobarbitone gr. 3 by mouth or intramuscularly as often as required, is indicated to lessen excitability and procure sleep. Avertin or paraldehyde administered per rectum are the best remedies by which to control severe spasms. For a man weighing 10 stones (63 kg.), 6 ml. of Avertin or 20 ml. (5 dr.) of paraldehyde shaken up in 200 ml. of normal saline, should suffice to hold them in check for 4 to 6 hours, after which the dose may require to be repeated. While the patient is under the influence of Avertin trismus may be relaxed and attempts at feeding are most likely to be successful 2 or 3 hours after its administration. Chloroform vapour is also of value, but when spasms are severe it cannot be inhaled. A more or less continuous use of morphine or hyoscine is an alternative measure. Some success has been claimed for the use of muscle relaxants, in particular the short-acting succinylcholine, as a means of controlling the spasms. These drugs are given continuously, anoxia and pulmonary infection being prevented by tracheotomy with assisted respiration, frequent suction through the tracheotomy tube and postural drainage.

The sulphonamides and the antibiotics have little effect on tetanus itself, but may be required to deal with the secondary pneumonia which is common in the more protracted cases.

Less success has attended the therapeutic use of tetanus antitoxin than is the case with diphtheria antitoxin. This result is largely, if not entirely, accounted for by the relative slowness in the onset of symptoms in tetanus as opposed to diphtheria. The argument for the prophylactic use of antitoxin in every case of a wound contaminated with road material or soil contaminated with animal excreta becomes correspondingly strengthened.

## TUBERCULOSIS

**Definition.**—Tuberculosis is an infection of the tissues by *Mycobacterium tuberculosis*, leading to lesions which are characterised by tubercles, microscopic or macro-

scopic, themselves undergoing changes leading to caseation, necrosis, ulceration and calcification, and having in close association with them varying degrees of fibrosis. The lesions of tuberculosis form the histological and anatomical basis of a large number of diseases which differ according to the organs affected, the extent of the lesions and the degree of resistance to infection shown by the tissues.

**Etiology.**—**MYCOBACTERIUM TUBERCULOSIS.**—The mammalian tubercle bacillus was first identified by Koch in 1882. Within a few years, two varieties, the human and the bovine, had been distinguished, and other forms, not pathogenic to man, but capable of causing disease in birds, cold-blooded animals and voles, have since been added to the list.

In the tissues and secretions, the bacilli, which tend to occur in small groups, are rod-shaped, straight or slightly curved, with parallel sides and rounded ends. They vary in length from 1 to  $4\mu$  and in breadth from 0.3 to  $0.6\mu$ . They stain with carbolfuchsin, retaining the dye after treatment with acid and alcohol, but are not coloured by Gram's method. In culture the bacillus grows slowly, requiring special media for its cultivation; the cultural characteristics of the various types show well-defined differences. *Myc. tuberculosis* is capable of survival for many months in dried sputa and secretions and is much less easily destroyed by bactericidal agents than other micro-organisms.

Only the human and bovine types of tubercle bacilli are of importance in human pathology; the first, in addition to causing disease in man, is responsible for cases of naturally occurring tuberculosis in monkeys, pigs and occasionally in dogs and parrots; the second occurs as a natural infection in cattle, pigs, horses, man and occasionally in dogs, cats and sheep.

The bovine bacillus is responsible particularly for infections of the cervical and abdominal lymph-nodes; in England and Wales this strain causes 64.7 per cent. of mesenteric and 57.5 per cent. of cervical adenitis; for Scotland the figures are 78 per cent. and 72 per cent. The human bacillus is found in 99 per cent. of cases of pulmonary tuberculosis in England and Wales, but the proportion of bovine infections is greater in Scotland, and still higher in the North of England. Osseous and genito-urinary infections are due to the bovine strain in 10 to 20 per cent. of instances.

**SOURCES OF INFECTION.**—There are two sources of infection in tuberculosis: tuberculous sputa and tuberculous milk. In 90 per cent. of cases the source of the infecting bacilli is dried human sputa. Nuttall found that from 2 to 4 billion bacilli were expectorated in 24 hours by a patient whose phthisis was only moderately advanced. These bacilli are scattered freely in dust when the sputa become dried, and they lie about the surface of the patient's body, or they are projected directly into the air along with particles of moisture when patients cough or sneeze or even speak loudly.

It is difficult to give an exact estimate of the incidence of tuberculosis in cattle; it is probable that about 40 per cent. of all dairy cows of 5 years and over in England and some 17 per cent. of all cattle were infected in 1952. The disease has been virtually eradicated from cattle in the United States, Finland, Norway and Denmark.

**MODES OF ENTRANCE OF THE BACILLUS INTO THE BODY.**—In approximately 99 per cent. of cases of human tuberculosis the bacilli have entered the body by one of two channels—in 90 per cent. this is by inhalation and aspiration into the lungs, and in 9 per cent. by the intestinal route, conveyed by infected milk or swallowed material in some way contaminated with tubercle bacilli. Although 99 per cent. of respiratory infections are due to the human type of bacillus, only 50 to 80 per cent. of tuberculosis, thought to have been acquired by the alimentary route, is caused by bovine strains. Cutaneous, subcutaneous, mucosal and placental infections account for the remaining 1 per cent.; they have no interest beyond that accorded to curiosities.

There has been much debate in the past over the frequency of primary intestinal, as compared with primary respiratory, tuberculosis in children. Ghon (1912) first

showed that primary pulmonary infection was of common occurrence at this age, and later observations have confirmed his views. The relative frequency with which one or other of these routes is followed clearly depends upon the opportunities for infection which confront the child; in countries where the milk supply is "safe", the incidence of abdominal tuberculosis has declined and the proportion of respiratory primary infections has risen *pari passu*. Blacklock's (1932) figures for Glasgow children illustrated this point. In his patients the primary focus was pulmonary in 173 and intestinal in 101; 82 per cent. of bacilli from the primary intestinal lesions were of bovine type compared with 2.7 from the primary pulmonary lesions.

**SECONDARY FACTORS.**—The frequency, amounting to 70 to 80 per cent. of all adults, with which healed primary tuberculosis is found at post-mortem examination and the ubiquity of the tubercle bacillus prove the importance of secondary factors in the cause of this disease. These factors fall into two categories: those which decrease the body's resistance and those which increase the frequency or intensity of exposure to infection.

Man has a relative natural immunity to tuberculosis, but there appear to be racial, familial and individual variations. It is well known that many primitive races are unusually prone to the disease and this has been attributed by Rich to a "native deficiency in the power to develop or maintain acquired resistance". Familial and individual variations are more difficult to assess, because of the varying opportunities for infection within different families, but there is good reason to suppose that they exist.

Malnutrition is generally admitted to decrease resistance to tuberculosis and it is true to say that there is a lower incidence of the disease in countries where the standard of living is high. Nevertheless malnutrition is usually a symptom of poverty and is found in association with overcrowding, inadequate hygiene and poor working conditions; it thus becomes difficult to apportion the blame between these several causes. There is, however, some evidence that a diet deficient in protein is accompanied by a higher incidence of tuberculosis.

Arduous physical labour *per se* probably has little effect on resistance; the low rate of infection in agricultural labourers bears out this view. Early and frequent child-bearing has an adverse influence; the first 3 months of pregnancy and the 2 immediately following parturition are recognised danger periods. Trauma appears capable of reactivating latent disease and local tissue damage may determine the site of a tuberculous lesion. Climate has no demonstrable constant effect on incidence or resistance.

The importance of the patient's attitude to his disease has long been recognised as having an important influence on prognosis; of recent years the view has gained ground that emotional disturbance often precedes, and may precipitate, its onset. It has been suggested that victims of this disease often have in common a defect of personality which makes them unable to deal adequately with their aggressive impulses (Wittkower).

Finally, certain other illnesses lower resistance to tuberculosis: amongst acute infections, measles and whooping-cough are of importance, while it may be a closing event in cirrhosis of the liver, chronic leukaemia, chronic alcoholism, schizophrenia and other chronic mental disorders. The incidence of tuberculosis in diabetes mellitus, although still higher than in the general community, has decreased greatly since the introduction of insulin.

The factors which influence exposure to infection are mainly environmental, and of these the most important is overcrowding. This applies not only to dwelling-houses, but to places of work and recreation. The spread of infection may be favoured in lesser degree by unclean methods of preparing and serving food, by inadequate hygiene and by various trade customs.

The drinking of raw infected milk is the common cause of tuberculosis due to the bovine bacillus.

**INCIDENCE AND MORTALITY.**—Heaf has estimated that in 1948 there were some 180,000 patients with pulmonary tuberculosis on the registers of the dispensaries in England and Wales; from a consideration of the results of mass radiographic surveys, he concluded that there were probably about 57,000 additional cases which had eluded diagnosis. Of recent years the morbidity rate or incidence appears to have risen largely on account of the improvement in diagnostic methods and the use of mass radiography. The mortality rate, however, has declined steadily in England since about 1830 when more than one-sixth of all deaths in London were due to pulmonary tuberculosis. In England and Wales the annual mortality from tuberculosis per 100,000 was 332 for the period 1861–70, 201 for 1891–1900, 87 for the year 1930 and 36 for 1950.

*The results of infection* are of great variety and of all grades of intensity. The variety depends upon the tissues affected, and the route of spread of the infection. The intensity depends upon the degree of relative virulence shown by the bacillus, and the amount of resistance shown by the patient. Tuberculosis may exist without appreciable disturbance to health, and the lesions produced may be commensurate almost with the whole length of a patient's life. On the other hand, the infection may cause an illness of the most severe character, killing the patient in a few weeks. The results of infection are described elsewhere in this book under appropriate headings, but *general infection* leading to the condition termed general tuberculosis is included in this article.

**Diagnosis.**—**THE ISOLATION AND RECOGNITION OF THE BACILLUS.**—In all doubtful cases of tuberculosis this is a point of vital importance. Clinical evidence of the existence of the disease, however complete it may seem to be, must never lack the confirmation of bacteriological proof, whenever this is possible. Seeing that the only proof of the existence of the disease is the demonstration of the bacillus in material derived from the patient, attention must first of all be directed to this investigation. It behoves the practitioner, therefore, to watch jealously for any material that may be available for bacteriological use, and to be quite certain that such material is not obtainable before falling back upon indirect clinico-pathological evidence (see below) to support the diagnosis.

In cases of suspected phthisis, every effort must be made to secure sputa, and it may be necessary to check a habit of swallowing expectorated material. The single, isolated plug of mucus, which is often expectorated in the early morning, should not escape attention. In little children, sputa, as such, are usually absent, but if vomiting occurs in association with lung disease the vomit should be searched for fragments of sputa. In suspected disease of the kidney or urinary tract, the urine must be collected for 24 hours and the deposit submitted to examination. Cases of *albuminuria* or of *hematuria*, in which there is not clear evidence of diffuse nephritis, should raise the question of tuberculous disease of the kidney. Stomach washings, withdrawn first thing in the morning, and the faeces should be scrutinised in doubtful cases of tuberculosis of the lung, peritoneum or bowel. If any *puncture-fluid* is obtainable—as from the pleura, the spinal theca or a joint—this is valuable for investigation in any patient suspected of tuberculosis.

The methods of dealing with these materials are not difficult, though they require thoroughness and patience when the bacilli are present in scanty numbers. The very different significance to be attached to a positive as against a negative result must never be lost sight of; the former affords proof of the existence of a tuberculous lesion, the latter gives at most a presumptive evidence against it.

In dealing with *sputa*, the original carbol-fuchsin method of Ziehl-Neelsen should first be tried. If the results, after carefully searching three or four films for half an hour, are negative, various methods of concentrating the bacilli are available, but culture of the sputa is the most satisfactory procedure.

*Sediment from urine* is best dealt with by the carboic acid method, subsequent

centrifugalisation and staining of the deposit. The smegma bacillus (also acid-fast), which may be present if the specimen has not been obtained by catheter, is differentiated by allowing the stained films to remain in alcohol for 10 minutes; the tubercle bacillus is not decolorised. In *pus*, the search is much facilitated by the use of "anti-formin", and this is a useful adjunct in the examination of faeces also.

*Puncture-fluids* very frequently give negative results to ordinary microscopic examination, on account of the scantiness of the bacilli in them. However, the clot (if such occur), or the centrifugalised deposit, should always be searched thoroughly, as the demonstration of even a few bacilli of undoubted morphological characters is decisive. Cerebrospinal fluid should be incubated, without shaking, for 24 hours, and the "spider-web" clot stained for bacilli. Failing this demonstration, the fluid should be used for culture on Lowenstein's medium (growth takes 3 weeks), and for inoculation purposes, a guinea-pig receiving a liberal amount (not less than 10 ml. if possible).

**Indirect Methods of Diagnosis.**—These depend upon the presence in the tissues of certain sensitising and immunising substances. They are indicated in doubtful cases of tuberculosis in which no material is available for investigation by direct methods (see above). The relative values of these methods are still under assessment; at present their values are probably in the order of their description here.

1. **THE TUBERCULIN TEST.**—The test depends upon the fact that infection by the tubercle bacillus renders the tissues supersensitive to the toxins of the bacillus, if these be introduced into it artificially. This supersensitiveness is shown by the production of certain "reactions" which are recognisable and are regarded as more or less "specific" in their nature. Only three types of test are now employed in man.

(a) *The skin test* (Pirquet's test).—This is best employed quantitatively. Three or more strengths (e.g. 25, 50 and 100 per cent.) of a solution of old tuberculin are rubbed lightly into the skin of the arm, which has been previously scarified. The appearance of papules and erythema at the site of vaccination constitutes a positive reaction.

(b) A modification is the *Vollmer patch test* introduced in 1937; or a jelly containing old tuberculin 95 per cent. may be applied, as recommended by Paterson, to a small area of skin between the shoulder blades previously cleansed with acetone. The area is covered immediately with a piece of Elastoplast, which is left *in situ* for 48 hours. A positive reaction is shown by erythema or slight vesiculation.

(c) *The intradermal test* (Mantoux).—0.1 ml. of 1 in 10,000 old tuberculin are injected into the cutis. The test should be read after not less than 48 and not more than 96 hours. An oedematous swelling not less than 5 mm. in diameter and surrounded by a zone of erythema constitutes a positive reaction.

A negative tuberculin reaction is presumptive evidence that the patient is not suffering from tuberculosis, although loss of reactivity is sometimes noted in pregnancy, acute intercurrent disease and those who are moribund. A positive test indicates only that a tuberculous infection has at some time occurred in the patient under observation; except in small children, it provides no evidence that the infection is active at the time the test is made.

2. **CYTOLOGICAL EVIDENCE OF TUBERCULOSIS.**—Another, and very useful, evidence of tuberculous infection is to be obtained in cases of pleural, peritoneal and meningeal exudates, by estimating the relative numbers of polymorphonuclear cells and of lymphocytes. It is found that, in pure tuberculous infections, the cell exudate is largely, and often almost entirely, lymphocytic in character. In pyogenic infections it is very largely polymorphonuclear; in mixed infections (tubercle with pyogenic infection) the cell-exudate is also of a mixed character.

**Treatment.**—In tuberculosis the preventive and curative aspects of treatment



are closely interwoven. Prevention is one of the major problems of public health and detailed discussion would be out of place, but the principles upon which it is founded are: first, control of infection; secondly, prevention of "clinical" disease; and thirdly, treatment, supervision and rehabilitation of those with active tuberculous infection.

The first includes the segregation of those with the disease in infectious form; the protection of such susceptible classes as infants and school children; and the supervision of groups especially exposed to infection, of which hospital staffs, sailors and workers in certain industries are examples. The provision of "safe" milk would alone eradicate infection due to the bovine type of bacillus.

The development of "clinical" disease can be greatly reduced by the detection of symptomless primary and post-primary infections and careful supervision of this stage. Mass radiography and tuberculin testing have greatly increased the efficiency of case-finding. Under this head, too, come measures which raise resistance to infection by improving general health and nutrition and methods of increasing specific resistance by vaccination against tuberculosis.

This last requires further discussion. Two strains of tubercle bacillus have been used for the preparation of "live" vaccines. The first, known as *Bacille Calmette-Guérin* (B.C.G.), is an attenuated bovine strain, incapable of causing progressive disease in man and originally prepared at the Pasteur Institute in Paris. B.C.G. was first employed in France to protect infants; more recently its use has been extended in an attempt to protect persons, such as nurses and medical students, who are exposed to infection and in whom a negative Mantoux reaction has provided evidence of special susceptibility. It is established that B.C.G. reduces the morbidity from the early sequels of primary infection such as pleural effusion, meningitis and military tuberculosis; there is as yet less convincing evidence that the incidence of phthisis is much diminished. The second strain from which vaccines have been prepared is the murine type of bacillus isolated from voles by Wells in 1937. This vaccine has been shown to raise human resistance to tuberculosis, but it has not yet been widely used, and comparison with B.C.G. is not possible.

Treatment, supervision and rehabilitation of those with active tuberculosis includes the organisation of chest clinics and sanatoria together with the curative measures employed in them. These last are divided into non-specific and specific.

Non-specific measures consist in efforts at improving the patient's nutrition so as to increase the tissue-resistance to the infection—ample fresh air, plenty of good food, bodily and mental rest, and exercise undertaken in graduated fashion under expert supervision. Details of all these measures are given in the article dealing with pulmonary tuberculosis (p. 1031).

Specific methods of treatment of tuberculosis have come to occupy a place of great importance during the past few years and have completely changed the outlook in the military and meningeal forms of the disease. The chief of these is streptomycin, an antibiotic, usually given in conjunction with one of the chemotherapeutic agents, isoniazid or sodium aminosalicylate (see p. 1033).

#### GENERAL TUBERCULOSIS

**Synonym.**—Acute Military Tuberculosis.

**Definition.**—A disseminate form of tuberculosis, giving rise to a severe disease analogous to the septicæmias in pyogenic infection.

There are two clinical forms of the disease, according as the symptoms are chiefly referable to the lungs (the *pulmonary form*), or are those of a general infection without focal signs. This latter form is often termed the *typhoid form*. The pulmonary form is described in the section dealing with pulmonary tuberculosis. In tuberculous meningitis, a common accompaniment of the military form, the infection is probably

not blood-borne, but disseminated through the subarachnoid space. It is described in the section on meningitis.

**Symptoms.**—The *general or typhoid form* resembles typhoid fever very closely. There is usually a period of vague ill-health—as there is in typhoid fever—preceding the more severe illness. When the latter develops there is headache, insomnia, a soft but frequent pulse, rapid respirations, a dry tongue, slight cyanotic flush and pyrexia, which is usually less continued in character than in typhoid fever. Not infrequently the temperature curve is that of a quotidian intermittent fever. In a few cases the rise of temperature takes place in the morning instead of in the evening, a feature not infrequently seen in other pyrexias of tuberculous origin, though not confined to these. Progressive loss of flesh takes place, and also anæmia, but this latter condition may only be found by blood examination, the dusky flush of the face often masking the blood state on mere clinical examination. As the illness progresses, suspicious signs of one or other of the more focal manifestations of the infection often arise: copious fine râles over the lungs, tumidity of the abdomen with palpable enlargement of the spleen and liver, or cerebral symptoms suggestive of meningitic involvement. In a suspected case the chest should be examined radiologically, since the suggestive “snow-storm” appearance may be present if general tuberculosis has existed for more than 10 days or so.

**Diagnosis.**—As the term “typhoid form” suggests, the disease resembling general tuberculosis most closely is typhoid fever. During the first week, or even during the first 2 weeks, diagnosis may be very difficult. In favour of typhoid fever are the persistence of headache, the presence of epistaxis, relative infrequency of the pulse-rate, diarrhoea and early tumidity of the abdomen. In favour of tuberculosis are a frequent pulse-rate, early cyanosis and intermission in the temperature curve. There is leucopenia in both diseases. A positive blood culture occurs during the first week in most typhoid cases, and agglutination with the patient's serum may reasonably be expected after the end of the first week.

**Course and Prognosis.**—The introduction of streptomycin has altered the prognosis in miliary tuberculosis from certain death to a recovery rate of about 60 per cent. The sooner treatment is started the more favourable the outlook; early diagnosis has thus become of great importance.

**Treatment.**—This is the same as for the pulmonary form of miliary tuberculosis (see p. 1033).

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## LEPROSY

**Definition.**—Leprosy is a chronic bacillary disease of low infectivity, peculiar to man, caused by the *Mycobacterium lepræ*, and associated with characteristic lesions involving the skin and mucous membranes (nodular type), and the nerves (anæsthetic type). Infection, however, may remain latent and clinical manifestations never be noted.

**Ætiology.**—The disease has a widespread geographical distribution, occurring in Egypt, Asia, Africa, West Indies and the Pacific Islands, etc. It is not hereditary, and individuals of any age, sex and race may be attacked. Children are more susceptible than adults. *Myco. lepræ* was discovered by Hansen in 1874; it is a non-motile, acid-fast bacillus occurring in large clumps in skin lepromata, septal ulcers and nasal mucus, and has never been cultivated with certainty. The mode of spread is unknown, but intimate contact with lepers is essential; a history of attendance on lepers, of living in the same house, sleeping in the same bed, or sexual connection is frequently obtained. Only 3 per cent. of people, however, living with lepers develop the disease.

**Pathology.**—Leprosy bacilli spread through the lymphatics of the corium and subcutaneous tissues, producing granulomata of the skin and infection of lymph

glands; the nasal and buccal mucous membrane, the eye, larynx and internal organs, such as the liver, lungs and testicles, may be similarly involved and bacilli found. The nerves may swell, turn a reddish-grey colour and undergo an axonal degeneration; scanty bacilli may be demonstrated in the endo- and perineurium. Paralysis, muscular atrophy and deformity follow.

**Symptoms.**—There are three main types of the disease—(1) nodular or cutaneous leprosy; (2) anæsthetic, neural or nerve leprosy; (3) mixed leprosy. The incubation period is uncertain, being 1 to 5 years in most cases, though occasionally persons develop it a few months after coming into an infected area. Often bacilli remain latent for years, and intercurrent disease may be necessary to precipitate clinical leprosy.

**1. NODULAR, CUTANEOUS OR LEPROMATOUS LEPROSY.**—This is the low resistant type, in which there is gross infection of both skin and nerves; the neural signs are mild, since the invading organisms fail to elicit any marked response from nerve tissue (Muir). Prodromata, which are marked, include leprotic fever, rigors, sweating, progressive weakness, diarrhœa, alternating dryness and hypersecretion of the nasal mucosa and epistaxis. The first positive evidence is the primary exanthem, involving especially the face, buttocks, legs or arms, commencing as a slightly raised erythematous macule which later shows dissociation of sensation and absence of sweating; it may disappear, leaving some brownish discoloration, but soon fever recurs with a fresh eruption, and bacilli may be found in the blood. After one or two recurrences reddish-brown elastic nodules appear, often at the site of the old macular rash, and these may become more generalised. Only the dorsal surfaces of the hands and feet are affected. The face acquires a leonine aspect from the enlarged nose, lobes of the ear and pendulous cheeks. The hair is often lost, especially on the outer third of the eyebrows, the nipples become prominent, the breasts may hypertrophy and the mucous membrane of the nose, pharynx and larynx may be affected. Leprotic nodules often involve the cornea and iris. The further history varies; the nodules may remain stationary, disappear or break down and suppurate. Ulcers may form on the eye, causing blindness, and the larynx and pharynx may be destroyed.

**2. ANÆSTHETIC LEPROSY.**—This is a highly resistant type, in which the infection of skin and nerves is less, yet the neural signs are more prominent since the reaction in nerve tissue is more marked. Prodromata consist of mental depression, chilliness and malaise with neuralgic pains and paræsthesias, involving the ulnar, peroneal and facial nerves. Numbness of the hands and feet, anæsthesia of ulnar distribution, and maculæ, giving rise to flat, anæsthetic patches resembling ringworm may be the first indications. These anæsthetic patches may commence as erythematous or pigmented or depigmented areas and ultimately become dry and hairless. A quiescent stage may now set in until definite nerve lesions appear. Demonstrable fusiform enlargement, especially of the ulnar and great auricular nerves may develop, and wasting of the hypothenar eminence associated with contraction of the third and fourth fingers is often seen. Muscular palsies and trophic lesions of the skin, nails and bones, including perforating ulcers, are common, and atrophies and contractures like claw hand may ensue. Necrosis or interstitial absorption of the small bones occur, and fingers and toes may disappear. The fifth and seventh cranial nerves are sometimes attacked, and ectropion of the lower lid, followed by corneal ulceration, is common.

**3. MIXED LEPROSY.**—Many cases ultimately become mixed in type, the nodular and nervous features either developing together or following one another. Tuberculoïd leprosy—so called owing to its histological resemblance to tuberculosis—is encountered in patients with a high resistance. The lesions consist of raised plaques or of macules with raised margins: anæsthesia is well marked, and the nerve branch supplying the area is often thickened.

**Diagnosis.**—Clumps of lepra bacilli which have to be distinguished from tubercle

bacilli can often be demonstrated in nasal mucus, in scrapings obtained from nasal ulcers using a speculum, and in the serous exudate from granulomata of the skin. The "snip method" of removing a small piece of skin with curved scissors, especially from the lobe of the ear, and making smears from its under-surface, is valuable. Gland puncture may also reveal bacilli. In pure nerve cases they can rarely be found unless portions of the nerves be examined. The differential diagnosis includes in nodular leprosy, lupus vulgaris, skin tuberculosis, syphilis and yaws; and in the anæsthetic type, syringomyelia, Morvan's disease, progressive muscular atrophy, peripheral neuritis, cervical rib, ainhum, scleroderma and Raynaud's disease.

The *lepromin* test is useful for determining the degree of sensitisation of the skin to *Myc. lepræ* or its products. The test consists of the intradermal injection of about 0.1 ml. of an antigen prepared from heavily infected tissue from a case of lepromatous leprosy. The site of injection is examined daily. Two reactions occur, the early and the late. The early reaction appears within 48 hours as a small erythematous slightly indurated area, which fades by the fourth day. The late reaction is the significant one. It appears after 1 week and progresses to the third or fourth week. It is characterised by the appearance of a visible and palpable nodule at the site of the injection which may undergo some central necrosis. The lepromin test is positive in many apparently normal adults and in patients with tuberculoid leprosy, negative in lepromatous leprosy and negative or weakly positive in atypical or intermediate forms. It is thus of some value in determining the type of infection in a given patient.

**Prognosis.**—This is by no means good in more advanced cases, though with earlier diagnosis and modern treatment the disease may be arrested, the expectancy of life increased and cases sometimes cured. If the patient can tolerate maximal treatment and maintain a sedimentation rate below ten a good prognosis can generally be given. Nodular leprosy is particularly prone to such complications as tuberculosis, renal disease and pneumonia, and laryngeal and visceral involvement are serious.

**Treatment.**—**PROPHYLACTIC.**—Lepers must be excluded from acting as cooks, waiters, etc., and segregation properly and humanely carried out is best for all parties concerned. Contacts who have lived in the same houses as lepers should be bacteriologically examined every few months for at least 5 years.

**CURATIVE.**—As in tuberculosis, the first essential is to increase the general resistance of the patient by good food, fresh air, regulated exercise, and to eradicate intercurrent diseases such as ankylostomiasis, malaria, etc. The confidence and active co-operation of the patient are essential. According to Muir the erythrocyte-sedimentation test affords a valuable index to the patient's resistance, slow sedimentation being favourable. Only when the resistance is high, and the general state of health satisfactory, should special drugs be used with the object of clearing up lepromata, otherwise lepra reactions, with increase in the local lesions, fever and bacillæmia in nodular leprosy and agonising pain in nerve cases, may develop. Too large and too frequent treatments with special drugs are dangerous, the aim being to avoid lepra reactions and to keep the health of the patient at the highest level. Special drugs: the oils of the *hydnocarpus* and *chaulmoogra* group have been in use for centuries.

*Chaulmoogra* oil and its ethyl ester administered by the oral route often upset the stomach and should not be given intravenously: they may be injected into the muscles, the subcutaneous tissues or the dermis. A 3 per cent. solution of *chaulmoogra* oil is generally injected twice weekly commencing with 0.5 ml. and increasing to 5 ml. Similarly, ethyl ester preparations may be given twice weekly commencing with 1 ml. and increasing to 5 ml.

The sulphones, including the parent substance diamino-diphenyl sulphone (D.D.S.) have recently been found of definite benefit in the severe lepromatous type of lesions which are least responsive to treatment with *chaulmoogra* preparation. Several different sulphone derivatives have been tried including Promin (Promanide), Diazone, promizole and Sulphetrone. All sulphones must at first be given in small

doses. The dose is gradually built up over the course of 2 or 3 months to the maximum recommended. Toxic effects are likely if the dose is too large to begin with or built up too quickly. Gastro-intestinal symptoms including vomiting may occur; jaundice and agranulocytosis have been reported. Leprosy reactions and sometimes a condition resembling *erythema nodosum* usually accompanied by fever may also result from over-active treatment. One of the most serious side-effects is the development of severe anaemia. Any substantial fall of hæmoglobin concentration calls for immediate reduction or cessation of treatment. When patients are anæmic, with a hæmoglobin value below 70 per cent., they should receive treatment with ferrous sulphate and, if indicated, with liver preparations before sulphone treatment is started.

Patients on sulphone treatment thus need to be carefully watched, especially in the early months of treatment. Periodic examination of the red cell count and hæmoglobin concentration should always be carried out.

Treatment should be temporarily suspended or considerably curtailed if toxic side-effects develop. After these have subsided, treatment must be re-established cautiously and slowly.

The effect of sulphone treatment on the clinical course of leprosy is best seen in lepromatous cases, in which the physical signs steadily regress. The first effects noted include the healing of ulcers, clearing the nose and the arrest of eye complications with improved vision. Next the tendency to chronic and subacute allergic reaction lessens, and nodules become flattened and absorbed. Finally, the number of bacilli in sections of the skin and in smears from the nose decreases in number. Bacilli may apparently disappear from lesions after long continued treatment.

Sulphone treatment must be continued for months, if possible for some years. Some authorities believe it should go on at intervals for life. It is not yet possible to say whether cure results from sulphone therapy. Many cases respond remarkably but others apparently equally successfully treated may relapse if the treatment régime is relaxed or stopped. Any erythematous or raised appearances of the skin, or thickened and tender nerves may indicate activity of the disease.

Patients must be free from *Myco. lepræ* for at least 2 years before discharge; even then it is not possible to say whether the condition is really cured or merely arrested, for leprosy is notoriously a disease of remissions.

Desirable maximal adult dosages of some sulphones are given below. Children usually take these drugs well and are dosed according to age and weight. For example, Adams states that a child of 12 years should be given half the adult dose. As stated above, small doses should be given at first and the maximal dosage reached only after 2 or 3 months.

Dosage of sulphones is often restricted to 6 days in the week. Some authorities recommend that treatment should be given for 3 weeks out of every 4. Others give treatment daily and continue for long periods without intermission.

**DIAMINO-DIPHENYL SULPHONE (D.D.S.).**—It is generally agreed that sulphones act by virtue of the liberation of the parent substance diamino-diphenyl sulphone (D.D.S.), which is now coming into wider use.

**Dosage of D.D.S.**—As with other sulphones, the dosage must be small to begin with. Full dosage is reached in about 2 months, at which stage a maximum of 600 mg. is given weekly in the form of tablets taken after meals. Doses of 50 to 100 mg. are given daily for 6 days each week; alternatively 300 mg. may be given twice weekly.

**SULPHETRONE.**—Oral doses up to a total of 18 to 21 gr. weekly may be given in divided doses thrice daily after food. Aqueous 50 per cent. solution is equally effective and cheaper, given in doses of 300 mg. thrice daily.

**DIASONE.**—Muir recommends doses of 900 mg. thrice daily after food for 6 days in the week, treatment being given for 3 out of every 4 weeks. Doses of up to a total of 21 g. per week have also been successfully given.

**THIOSEMICARBAZONE (THIACETAZONE).**—Given orally up to a maximum dose of

150 mg. daily, this drug has been used successfully as an alternative in individuals who are intolerant to sulphones.

Lepra reaction should be treated with diaphoretics such as aspirin, phenacetin, hot drinks and calcium and alkalis in large doses. In nerve leprosy the agonising pain may be relieved by adrenaline intramuscularly or ephedrine given orally or by infiltration of the nerve. Vitamin B<sub>1</sub>, given by intramuscular injection and by the mouth, in large doses, may lead to disappearance of neuritic pain, and a diminution in the tenderness and swelling of the nerves.

Potassium iodide is a dangerous drug, but Muir uses it in the late stages of treatment when the resistance is high and the case has become bacteria-free. Diathermy is of value in subacute and chronic nerve lesions. If the ulnar nerve is bound down to bone—especially at the elbow—freeing adhesions and linear incision of the sheath with or without removal of fibrous tissue may bring relief. Abscesses occurring in the ulnar or other nerves should be incised; drainage is rarely needed.

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## COLIFORM BACILLUS INFECTIONS

The coliform group has been expanded to include, in addition to the original *Bacterium coli* and *Salmonella typhi*, the organisms of bacillary dysentery (*Shigella dysenteriae*), of the paratyphoid fevers (*Salm. paratyphi*) and those responsible for some cases of food poisoning, such as *Salm. enteritidis*, *typhi-murium*, *cholera-suis* and others. Here, infections for which *Bact. coli* is responsible are alone considered, but there are many strains of the organism which differ among themselves in pathogenicity, virulence and cultural behaviour.

**MODES OF INFECTION.**—In health, coliform bacilli are confined to the intestine. The modes of infection of parts of the body other than the bowel are at times very apparent, at others obscure. Of any particular tissue there are three possible routes of infection: (1) The *direct* route, that is, by the immediate transference from the bowel to the infected area; (2) by the *lymphatics* and (3) by the *blood-stream*. In some infections, e.g. of the gall-bladder, pericolic tissues, pelvic cellular tissue, etc., the direct route is no doubt the one generally followed. Of the two indirect routes, however, some doubt exists as to the more likely one in certain cases, such as infection of the urinary tract especially; in some instances of this latter important condition it is clear that invasion takes place again, directly, through the urethra. The cystitis which still occasionally follows the use of the catheter illustrates this; and the greater frequency of cystitis in girls than in boys at the napkin age has been adduced in favour of this route. In the acute pyelitis complicating or following typhoid fever, it is highly probable, though not certain, that infection proceeds via the blood-stream to the kidney, and thus to the pelvis. But in those acute primary infections of the urinary tract, which are so common in both sexes, the mode of entry of the bacillus of the kidney pelvis is problematical.

**SITES OF INFECTION.**—The sites of infection by coliform bacilli are very numerous. Mention will only be made here of those which form the basis of important disease-processes which demand recognition and treatment in practice.

1. The *bowel* itself may be the site of infection. This may take place (a) because the infecting strain of coliform bacillus has absolute pathogenic qualities; or (b) because the virulence of one or more of the usually saprophytic strains is increased; or (c) because the resistance of the mucosa is lowered by chemical or physical changes or by infection by another pathogenic microbe. From one or more of these factors acute gastro-enteritis, enteritis or entero-colitis may ensue. Poisoning by *Salm. enteritidis*, the result of eating contaminated food, is an important instance of (a), and perhaps also of (a) combined with (c). Atypical coliform bacilli are often isolated from the stools of patients with acute gastro-enteritis, but their importance as a cause

of this disease remains problematical, except in certain cases in infants where their ætiological rôle has been established.

2. *Gall-bladder sepsis* is closely associated with coliform bacillus infection. It is commonly held that infection of the gall-bladder by this microbe is one of the important factors in the evolution of cholelithiasis. However this may be, it is certain that coliform bacilli are frequent infecting agents in *cholecystitis*, both acute and chronic. The fact harmonises with the known frequency of gall-bladder infection during typhoid fever.

3. *Appendix inflammations, diverticulitis, pericolic suppuration* and local peritonitis complicating intestinal conditions, are all of them associated with coliform bacillus infection, and in many instances with this alone.

4. The *urinary tract* is infected with great frequency, with how great frequency we are only now realising, as the result of systematic cultivation of the urine in doubtful cases of the condition, and in obscure cases of illness in which no such condition is at first suspected. The presence of coliform bacilli in the urine may derive from the discharge of an infective focus adjacent to the urinary tract, in the prostate, urethra or pericolic tissues, or may be due to true infection of the urinary tract itself, pyelitis, pyelonephritis or cystitis. Concerning the former, no more need be said in this place.

**COLIFORM BACILLUS INFECTION OF THE URINARY TRACT.**—The cases met with may be conveniently described as falling into three groups.

(i) *Acute cases.*—In the majority of these cases the infection appears to arise in the pelvis of the kidney; some are undoubtedly vesical in origin; in not a few it is uncertain where the infection begins. The disease is at times fulminating in its acuteness, being ushered in by rigors, high fever ( $103^{\circ}$  to  $105^{\circ}$  F.), delirium and great drowsiness. More often the symptoms are abrupt and severe, but not alarming. There may be pain and tenderness in the loin, though both may be absent, and one or other kidney may be tender under bimanual examination. But in more cases than not there is a striking absence of both physical signs and focal symptoms, so that, unless the existence of the disease is borne in mind, and the urine is examined carefully, the patient is thought to be suffering from "influenza".

In those cases in which the bladder is, from the first, markedly affected, symptoms of *dysuria* are present—frequency, pain and strangury. Such symptoms draw attention, of course, to the nature of the process.

The *urine* shows a great range of variations in its features. There may be a frank *hæmaturia*, a fact which is not so widely known as it should be: coliform bacillus infection is the explanation of a large number of obscure cases of hæmaturia. The amount of pus is very variable—it may be very considerable, or it may be represented only by leucocytes seen on microscopic examination. In very severe cases portions of the bladder mucosa may be shed in the form of sloughs, but this is uncommon. The number of bacilli present in the urine varies greatly; in some cases they are so abundant as to constitute by far the greater part of the total sediment. The colour and amount of the urine depend upon the degree of pyrexia and the amount of fluid ingested. Constipation is the rule, the tongue is generally covered by a creamy fur and anorexia is common. As in so many acute coliform bacillus infections, the mental state tends to depression.

The disease is often a strikingly dramatic one in children; it is one of the few conditions which may be associated with a rigor, and there is a maximum of febrile reaction with lassitude and even stupor, and a minimum of serious effect upon the vital organs. It is not very uncommon to see a temperature of  $105^{\circ}$  or  $106^{\circ}$  F., with big intermissions; the child is very ill during the pyrexial stage and comparatively well when the temperature falls. Marked drowsiness, even stupor, may occur; such a condition, indeed, should raise a suspicion of this infection in the absence of signs of meningitis. The disease is not very uncommon even in babies.

The course of the disease varies much. Prompt recognition of its nature, leading

to appropriate treatment, usually results in defervescence and the disappearance of pus and bacilli from the urine in 7 to 14 days. But some of the cases last many weeks; it is fair to say that this is not seldom due to failure to diagnose the condition, or to employ efficient measures of treatment.

*Relapses* are very common even when, with chemotherapy, the urine is rendered sterile and the symptoms are relieved. Of complications, *prostatitis* and *epididymitis* are those most often seen; *urethritis* may occur; *pyelonephritis*, especially in young children, may be the precursor of renal failure in later life. It is interesting to record that *epididymitis* may be the first symptom of the disease. This has, in the past, been frequently mistaken for tuberculosis.

(ii) *Recurrent cases*.—A not uncommon type of case is that in which symptoms of acute or of subacute infection occur at intervals over a number of years, the condition of the patient and of the urine being natural between the attacks. Recurring hæmaturia, thought to be due to acute nephritis, to tuberculosis or to calculus, is sometimes due to this condition. The probable source of these re-infections in any individual case is the colon.

(iii) *Chronic cases*.—These are either (a) the sequelæ to acute attacks that have never completely resolved; or (b) they arise insidiously; or (c) they follow instrumental procedures or operations upon the urinary tract; or (d) they complicate mechanical defects, acquired or congenital, such as stricture, enlarged prostate and hydronephrosis; or (e) they occur as secondary infections in cases of renal or vesical calculus or of tuberculosis.

The symptoms in these chronic cases vary greatly. In one group it is the general toxic state that is the main feature—a sallow complexion, loss of tone, a low blood pressure, colon dyspepsia, anæmia, headache and backache. In another group the local symptoms predominate—increased frequency of micturition, which may be extremely trying, pain during or after the act, and referred pain and discomfort in the vesical zone. In a third group there is little or no interference with health, general or local. The importance of chronic polynephritis as a cause of hypertension has only recently become apparent.

*The urine in chronic infections* shows as much variety as do the symptoms. The characteristic "fishy" odour is rarely absent; the reaction is generally acid, but infection by *Proteus* renders the urine strongly alkaline; the amount of pus present may be very little or may be considerable, but the degree to which the patient is troubled by no means corresponds to the degree of pyuria; mucus is in excess; bacilli are constant and, like the pus, are very variable in quantity. Hæmaturia is uncommon in chronic infections, but it is easily induced by instrumental investigation, as are also "flares-up", of the chronic state, with the production of rigors, high fever, severe malaise and oliguria. For this reason, methods of differential diagnosis which do not involve instrumentation should be employed before the patient is subjected to cystoscopy or ureteric catheterisation. Diagnosis rests upon the isolation of the organism from a clean specimen of urine. Of particular importance is the differentiation of the condition known as abacterial pyuria—a subacute illness characterised by pyuria, frequency of micturition and strangury, which yields rapidly to intravenous injection of neo-arsphenamine.

**BACILLURIA.**—This term is properly applied to a urine which is loaded with bacilli, but in which there is no pus, or, at most, a few leucocytes seen on microscopic examination. It is usually of short duration. The appearance of the urine is characteristic: shimmering when agitated and viewed by transmitted light. The smell already referred to as so typical of colon bacillus urinary infections is usually present here also.

#### OTHER SITES OF COLIFORM BACILLUS INFECTION.

(i) *The uterus and Fallopian tubes* are sometimes the site of infection, as in puerperal sepsis; but the infection is then usually a mixed one, with streptococci.



(ii) Some situations quite remote from the bowel are now and again infected by coliform bacilli—the *middle ear*, the *pleura*, the *bronchial tract*, *bones* and *joints*. Infection of the middle ear occurs as the result of impure water in swimming-baths.

*Bact. coli* septicæmia, unless it occurs as a terminal event, in which form it is not at all uncommon, is rare. When it does occur, however, it is by no means always fatal. Septic endocarditis, due to coliform bacilli, is rarer still.

**Treatment.**—Only the treatment of coliform bacillus infection of the urinary tract is of present relevance; the therapeutic problem with infection in other sites is commonly surgical.

The principles of treatment are simple: to determine the sensitivity of the infecting organism to the various chemotherapeutic and antibiotic agents, and to administer, in an attempt to sterilise the urine, the drug thus shown to be most suitable; to correct, where necessary, any mechanical defects in the urinary tract or other abnormalities which may have led to infection.

General measures depend upon the severity of constitutional symptoms. In acute infections the patient is confined to bed and encouraged to drink 4 to 5 pints of fluid in the 24 hours. Sufficient sodium bicarbonate and potassium citrate to make the urine alkaline will relieve strangury.

A catheter or "mid-stream" specimen of urine should be sent to the laboratory for isolation of the infecting organism and tests of its sensitivity. Treatment with sulphonamide (see p. 24) should be started immediately this has been done, without awaiting the pathologist's report. The great majority of these infections respond rapidly to sulphonamide; if the report later shows it to be unsuitable, a change should then be made to the drug to which the organism is most sensitive. Treatment should continue until the urine has been sterile for 4 days.

In more chronic cases it is justifiable to await the result of sensitivity tests, although time may be saved by administering sulphonamide immediately the specimen has been taken.

Particularly in chronic or recurrent cases, the possibility of some mechanical defect in the urinary tract must be considered. These include enlargement of the prostate, calculus, hydronephrosis, cystocele, stricture and various congenital anomalies. Intravenous pyelography, cystoscopy and ureteric catheterisation may be required for their demonstration and treatment will include their correction where possible.

Chemotherapy and the antibiotics have proved so effective in treatment, that the various adjuvant measures, previously deemed necessary, have faded into unimportance. It is true that the bowel must be the source of all coliform bacillus infection, but the path followed by the organism is uncertain and the association with colonic disease uncommon. If such an association is noted, the disease or disorder of the colon must be treated on its merits.

## TYPHOID FEVER

**Synonyms.**—Enteric Fever; Gastric Fever; Typhus Abdominalis.

**Definition.**—An infectious fever characterised by pyrexia of continued type, an eruption, in crops, of rose spots, enlargement of the spleen, abdominal tumidity and bowel disturbance. Ulceration of the small intestine and enlargement of the mesenteric lymph glands and spleen are distinctive lesions.

Typhoid is a septicæmia caused by ingestion of the *Salmonella typhi* of Eberth, which is absorbed by the lymphatics of the small intestine and carried to all parts of the body; it settles in the agminate glands (Peyer's patches) of the intestine, the mesenteric lymph glands, spleen, liver, gall-bladder and bone-marrow. Those organs which have excretory ducts, e.g. the liver and gall-bladder and the kidneys, as well as the intestinal tract, form the chief channels of elimination.

**Ætiology.**—*Salm. typhi* is a flagellated rod-shaped, Gram-negative organism, about  $3\mu$  in length and  $0.6\mu$  in thickness. It is actively motile and easily grown on artificial media. It belongs to the enteric group of organisms, a group which includes also the paratyphoid bacilli (*Salm. paratyphi*). It grows best at blood heat and is quickly killed by boiling water, and within 15 minutes by exposure to a temperature of  $60^{\circ}\text{C}$ . ( $140^{\circ}\text{F}$ ). It may survive for a considerable time in ice, and also for some days in fresh or salt water. It resists drying, so that typhoid may also be propagated by dust or by articles soiled by typhoid excreta. It has been found alive in the mantle-cavity and intestines of oysters, mussels and other shell-fish which have lived in sewage-contaminated water. It multiplies freely in butter and in milk, and may survive in unripened cheese.

The toxins are mainly intracellular. Inoculation of animals produces a septicæmia without the intestinal lesions seen in man. Even in the latter the disease at times occurs without producing intestinal ulcers. The serum of those infected has a specific agglutinative influence on cultures of the organism, a fact which is made use of in diagnosis, and at certain stages the bacillus can be cultivated from the blood, bone-marrow and bile. In man, infection is introduced by the alimentary tract, and is derived, directly or indirectly, from a human source, man being the only reservoir of the disease. Typhoid bacilli can be differentiated into types by the use of specific Vi bacteriophages, a useful measure in tracing sources of infection.

Typhoid occurs in all parts of the world, but is most rife in tropical and sub-tropical countries. In Great Britain it is most prevalent in the months of September, October and November; in other countries the maximum incidence corresponds to the warm season. A hot, dry summer increases the prevalence in the autumn. An epidemic recrudescence is believed to occur every 5 or 7 years. Rather more males than females are attacked, and the greatest susceptibility is between the twentieth and twenty-fourth years. Infants are rarely infected. After the thirtieth year there is a progressive fall in its incidence. It is rare but not unknown in old age.

One attack confers immunity, which usually lasts for life, but second and third attacks have been reported. Where typhoid is endemic a proportion of the community acquires immunity without having passed through a recognisable attack. The supposed racial immunity of certain peoples may in reality be acquired through infection contracted in childhood. Fatigue and overwork are favouring factors, and no condition predisposes so much as does war to typhoid and paratyphoid infections, owing to the aggregation of susceptible subjects under conditions of defective sanitation, fatigue and exhaustion. Prophylactic vaccination has found its greatest triumphs under these conditions.

Propagation is from the human source and may be indirect or direct. Of indirect causes aerial infection, apart from the influence of wind-borne dust and of flies, is very doubtful. Drinking water supplies contaminated by sewage or by the excretions of a carrier are the most common cause of widespread outbreaks. Milk, ice-cream, unripened cheese, butter and other articles of food may also act as local diffusers of infection. Celery, watercress and other green vegetables, eaten uncooked, also spread the disease. Of shell-fish, oysters, mussels, cockles and periwinkles are dangerous. Fomites, enema syringes, bedpans, etc., which have been soiled by typhoid excreta undoubtedly act as infective agents. Laboratory workers have been infected by their cultures.

Direct contagion plays but a small part in the production of epidemics, but assumes importance in causing localised outbreaks, infection being conveyed by the feces, the urine, the vomit, discharges from abscesses and possibly by the sputa. The chief danger arises with mild and unrecognised cases and precocious carriers (*i.e.* by infected susceptibles who have not yet succumbed to the disease). Strict attention to personal cleanliness and proper disinfection of excreta, soiled linen, feeding utensils, etc., go far to eliminate infection, and prophylactic inoculation is a great safeguard.

Of convalescents from typhoid, a small proportion, about 5 per cent., continue to pass bacilli, often intermittently, in the stools for months or years. These are known as intestinal carriers. They may appear to be quite healthy, or may suffer from periodic intestinal disturbance or from symptoms referable to the gall-bladder. Typhoid bacilluria occurs in perhaps 25 per cent. of the cases of typhoid, but is, as a rule, quite transitory, urinary carriers being much less common but possibly more dangerous than intestinal carriers. Carriers are particularly dangerous when they happen to be engaged in handling food, milk or water supplies.

The endemic occurrence of typhoid in certain localities is now attributed to the influence of human carriers rather than to the persistence of infection in the soil, although it is an undoubted fact that the typhoid bacillus may persist for a time and even multiply in sewage-infected earth.

**Pathology.**—The portal of infection is the intestinal lymphatic system. The bacilli multiply in the liver, spleen and mesenteric lymph glands during the incubation period. A bacteræmia initiates the clinical onset and excretion in the bile soon follows. It is now, contrary to former conceptions, held that the Peyer's patches are not involved until the septicæmic stage.

The characteristic lesions are in the small intestine. Proliferation of the large mononuclear phagocytes of the reticulo-endothelial system is the distinctive reaction. In the early stages the Peyer's patches are swollen, the swelling attaining its height about the tenth day of the disease. The solitary follicles of the intestine are similarly affected and a diffuse catarrh of the whole intestinal tract, including the stomach, may be present. Necrosis ensues in the lymphoid masses, and sloughs are formed, the separation of which occurs during the third and part of the fourth weeks. In some cases, resolution may take place without necrosis. The ulcers are ovoid and lie along the long axis of the bowels. Those which arise in the solitary follicles are more circular. The edges of a recent ulcer are undermined, and the floor shows smooth muscular fibres, or the peritoneal coat. Perforation or hæmorrhage may ensue. Immediately above the ileo-cæcal valve sinuous tracts of ulceration may be evident. Ulceration of the large intestine is rare. The ulcers heal without contraction in a week or 10 days. Their inflamed bases very rarely give rise to peritoneal adhesions or bands. When perforation occurs it is usually in the lower ileum, where ulceration is most intense. It may, however, happen in other situations.

The mesenteric lymph-glands are inflamed, but rarely suppurate. The spleen is swollen, soft and cherry red, an acute reticulo-endothelial hyperplasia being present. Splenic infarction may occur, but rupture is rare. The liver presents a parenchymatous degeneration with minute areas of focal necrosis which originate in clumps of macrophages lying in the blood sinuses. Similar foci (*typhoid nodules*) may be found in the spleen and in the bone-marrow. Infection of the gall-bladder may occur with subsequent formation of gall-stones. *Pylephlebitis* is a rare complication. Cloudy swelling of the kidneys is the rule. In chronic urinary carriers inflammation of the renal pelvis or urinary bladder may be found.

The myocardium undergoes fatty and granular degeneration. Hypostatic congestion of the lung bases is the rule with, it may be, distinct broncho-pneumonic consolidation. Gangrene, abscess or infarction of the lungs is rare. Ulceration of the larynx may occur, the ulcers being found in the neighbourhood of the arytenoid cartilages, or at the base of the epiglottis. Necrosis of the cartilages sometimes ensues. Zenker's vitreous degeneration of muscle is particularly marked. It affects the straight muscles of the abdomen, the adductors of the thigh and the diaphragm; rupture of muscle and hæmorrhage may result. Osteo-periostitis of the tibia, vertebrae and other bones may be due to infection with the typhoid bacillus or to secondary invaders. Superficial abscesses, degenerative changes in the central nervous system or peripheral nerves, and venous thrombosis are also possible sequels of typhoid infection.

**Symptoms and Course.**—The period of *incubation* averages from 10 to 14 days, but may be as short as 3 days or as long as 3 weeks. During this period symptoms are generally absent, but ill-defined malaise or, more rarely, gastro-intestinal disturbance may occur.

The *onset* is generally insidious with chilliness, lassitude, loss of appetite and muscular pains. Symptoms which are particularly suggestive are frontal headache, oozing epistaxis, slight bronchitis and disturbing dreams. The tongue becomes furred, and the mouth dry. The hearing often becomes less acute and a brightness of eye may be noticeable. The bowels are loose or constipated. The patient may not take to bed for a day or two. The temperature mounts gradually, being a degree or more higher each succeeding night with morning remissions. By the end of the first week the clinical condition is characteristic. The aspect is heavy and the cheeks are flushed. The lips and mouth are dry, and the dorsum of the tongue covered with a dirty white fur, the tip and edges being raw. The abdomen is slightly tumid, with gurgling in the right iliac fossa. The bowels are perhaps loose, several liquid motions like pea soup being passed in the 24 hours; sometimes, however, there is constipation. The spleen may already be palpable. A characteristic feature is a moderately full but easily compressible pulse, the frequency of which is not increased in proportion to the temperature. The respiration is accelerated. The temperature will by now have attained a maximum of 103° to 105° F., still showing morning remissions of about 1°, and is unstable, reacting quickly to minor disturbances. The urine is high coloured and concentrated, and the skin usually dry. Thirst and headache are the chief complaints.

The rose spots usually make their appearance towards the end of the first week, sometimes on the fifth day, more often between the seventh and twelfth. Each spot is a circular, slightly elevated papule of a pale pink colour from 2 to 4 mm. in diameter, disappearing on pressure. The rash should be sought for on the abdomen, the flanks, the sides of the chest and the back. The spots appear in successive crops, each one fading in 3 or 4 days, and leaving a transitory brownish stain. Often the eruption is scanty, a few spots only being seen; occasionally it is very profuse, and involves the limbs as well as the trunk. The face usually escapes. Minute sudaminal vesicles occasionally cap some of the spots. The eruptive period lasts from 10 days to 3 weeks. A profuse rash does not necessarily indicate a severe attack. The spots are due to bacterial embolisms.

By the second week the fever has reached its fastigium. The temperature maintains its level with slight morning remissions, the headache may abate, but prostration increases and the other symptoms are more severe. The lips become cracked, sordes accumulate on the teeth, the abdomen becomes more distended and diarrhoea is often a marked feature, the stools being liquid, yellow in colour, alkaline and foul. They may be chocolate-coloured or red from admixed blood and small shreds of tissue, or actual sloughs may already be present. The evacuations are not accompanied by colic or tenesmus. The spleen is now larger. The pulse-rate will have quickened to a frequency of 112 to 140. It is often dicrotic, and the heart sounds enfeebled. The bases of the lungs may now show signs of hypostatic congestion, and the respiration be more accelerated with slight lividity of the lips and face. The initial headache is replaced by delirium of a muttering character, and muscular wasting is rapid. The urine may be albuminous and scanty. Patients may succumb during this period from toxæmia, or towards the end of the second week from perforation of the bowel or intestinal hæmorrhage.

During the third week improvement should occur, the temperature becoming more remittent in type, the morning reading falling more rapidly than that of the evening. The tongue cleans and appetite begins to return. During the fourth week desferescence may be completed, the temperature usually remaining at a subnormal level for some time. In severe infections, however, the third week is a period of

increasing anxiety. The symptoms increase in severity and the patient may pass into the "typhoid state", lying on the back in a semi-stuporous condition. The pulse and heart sounds become more and more enfeebled, the pulmonary congestion increases, the extremities become blue and cold, subsultus tendinum appears, and the evacuations are passed unconsciously. Sometimes there is retention of urine. Extreme abdominal distension may supervene, and the occurrence of perforative peritonitis or of hæmorrhage from the bowel is more than ever to be dreaded. In such severe cases the fever may be prolonged through the fourth and fifth weeks before any signs of deservescence appear. They are not necessarily fatal.

*Convalescence* after a severe attack is always protracted. The temperature is at first subnormal, and remains in a very unstable state. The heart sounds remain enfeebled, and the pulse is often rather fast or easily quickened by exertion or excitement. The effort of standing and walking is difficult and painful. The appetite, however, is good, and the weight rapidly increases. The aspect gradually becomes less anæmic. Slight peeling of the skin, loss of hair and ridging or furrowing of the nails is often noticeable. During this period the feet and ankles may show slight œdema, and cutaneous abscesses or localised bone abscesses may occur. Thrombosis may appear in the veins of the calf or thigh; it is the chief complication of early convalescence.

*Relapse*.—Tendency to relapse is a marked feature of typhoid fever, and shows itself in from 5 to 15 per cent. of the cases. The relapse may occur during actual deservescence, but more commonly develops after an afebrile period of a week or a little longer. The symptoms are a repetition of those of the original attack, but in a mitigated form, the fever reaching its acme in a shorter time, and the whole duration being 10 days or a fortnight. The spleen enlarges again, a new crop of rose spots usually appears, fresh ulceration of the bowel occurs and blood culture may again prove positive. On occasions, the relapse equals or exceeds the original attack in severity, and may even prove fatal. Second and third relapses are not unknown. Spurious relapses are recrudescences of fever during convalescence, of short duration and unaccompanied by definite symptoms. Their explanation is often obscure.

*VARIETIES*.—The fact that typhoid fever may show great variations in its clinical characters, and in the severity and prominence of different symptoms, has led to the description of many special types. Different epidemics may differ much in their salient features.

*Variations in onset*.—The onset of symptoms is sometimes sudden, it may be with rigors and vomiting. The temperature rises quickly, and delirium may supervene early. In such cases, death may occur during the second week, or the disease may gradually assume the ordinary type. In exceptional cases, severe bronchitis or pneumonia may mark and mask the onset, and the true nature of the infection may be overlooked. The *prominence of meningeal symptoms may lead to confusion with cerebrospinal fever*, and the differential diagnosis only be possible by examination of the cerebrospinal fluid. If typhoid meningitis is present, lymphocytes or polymorphs predominate, according to the severity of the infection, and the typhoid bacillus grows on culture. More commonly the condition is better described as meningismus; the fluid is under tension but clear; it is sterile and the symptoms quickly subside after lumbar puncture, to be succeeded by the more typical signs of typhoid fever (see also p. 61). Yet another occasional mode of onset is with a primary acute hæmorrhagic nephritis. When acute gastro-intestinal symptoms signalise the invasion, appendicitis or irritant poisoning may be simulated. An onset with faucial angina sometimes occurs.

The terms *pneumo-typhoid*, *meningo-typhoid* and *nephro-typhoid* have been used to designate some of the above-mentioned types.

*Variations in course*.—There is an ambulatory form in which febrile disturbance is generally slight, and the patient continues about during the whole or the greater

part of the illness. Some such cases end in recovery; but others run a very severe course, the patient taking to bed about the end of the second week with aggravated symptoms, or succumbing to hæmorrhage from the bowel, perforation, acute delirium or circulatory failure. Mild and abortive forms of typhoid also occur in which the fever is insignificant, or, after a well-marked onset, ends in a rapid defervescence between the eighth and fourteenth day. An afebrile form is known to occur in the enfeebled or those exposed to great hardships.

*Variations due to age, pregnancy and other causes.*—Typhoid fever is rare in infancy but becomes more frequent in childhood, and then, generally, the symptoms are mild, the pyrexia of short duration and sometimes of a markedly intermittent or remittent type. A primary bronchitis or gastro-enteritis may be simulated. Such complications as perforation or hæmorrhages are rare.

In the aged, particularly in those over 60, typhoid tends to run an unfavourable course, hypostatic pneumonia and circulatory failure being common.

Abortion or premature delivery takes place in from 50 to 70 per cent. of pregnant women who contract typhoid. The fœtus is dead or, if born alive, usually succumbs to an acute typhoid septicæmia. The prognosis as regards the mother is not especially influenced.

In malarial patients the onset of typhoid may be sudden, with a typical rigor; but the severe symptoms proper to typhoid develop later. On the other hand, subtertian malaria may closely simulate typhoid in its commencement.

Chronic alcoholism exerts a very unfavourable influence. Pre-existing pulmonary tuberculosis is apt to advance rapidly during convalescence from the fever. In diabetics typhoid often runs a mild course.

*Special Symptoms and Complications.*—*Digestive system.*—Suppurative parotitis is attributed to duct infection, and occasionally leads to cellulitis. Attention to the cleansing of the mouth goes far to prevent it. Ulcers sometimes appear on the pillars of the fauces and the pharyngeal wall (*Duguet's ulcerations*). Diarrhœa is not a constant feature, some patients being constipated throughout the disease. The diarrhœa often disappears after a few days' dieting and hospital treatment, but in grave infections it may be severe and persistent.

Meteorism with a distended, tense, tympanitic abdomen signifies a virulent infection. It may or may not be accompanied by severe diarrhœa, and is often a harbinger of hæmorrhage or perforation.

The incidence of intestinal hæmorrhage, sufficiently gross to be detected by inspection of the stools, varies in different reports from 5 to 20 per cent. of all cases. It is most common at the time when the sloughs are separating, i.e. at the end of the second or beginning of the third week. The hæmorrhage may be slight, but more often is profuse. The evacuated blood is bright red in colour, unless it has been retained in the bowel. The signs of a severe hæmorrhage are a sharp fall in the temperature, a sensation of faintness, increased frequency of the pulse and, it may be, a transient rise in blood pressure with disappearance of diastolicity. The spleen may shrink rapidly. Sometimes the hæmorrhage is fatal before any blood is voided.

There is also a hæmorrhagic form of typhoid in which melæna may be an early sign, associated with petechiæ or bruises in the skin and hæmaturia. The outlook, then, is very grave.

Perforation of the bowel causes one out of every 3 or 4 deaths. Its incidence is something under 5 per cent. It is commonest towards the end of the second or in the third week especially, but not at all exclusively, in cases characterised by severe diarrhœa or by meteorism. Its onset may be preceded by intestinal hæmorrhage. The perforation generally lies within the last 12 in. of the ileum, but may occur elsewhere. Shivering, with sharp pain in the hypogastric region is usually the first sign, but the onset may be quite insidious. Localised tenderness, localised rigidity and local immobility of the abdominal wall accompany the pain. The temperature

may show a sudden drop to subnormal followed by a rise; but sometimes no variation is detected. Both pulse and respiration rates are usually increased, and the former should be watched carefully. Obliteration of the liver dulness is especially significant when occurring in a rigid and retracted belly. Irritability of the bladder and rectal tenesmus may occur when a perforated coil lies in the pelvis. More reliance should be based on the local than on the general symptoms in making the diagnosis. After the first shock the patient may react and show deceptive signs of improvement, but before many hours the signs of spreading peritonitis will assert themselves. A polynuclear leucocytosis generally accompanies perforation, but is inconstant and not of great diagnostic value.

There are other causes of abdominal pain in typhoid fever, such as acute cholecystitis, suppurative cholangitis, portal pyæmia, suppurating mesenteric glands, appendicitis and splenic infarction, but none of these is common. Thrombosis of the iliac veins may also cause abdominal pain and tenderness; a clue to this condition may often be found by examining the veins of the lower limbs and by looking for slight œdema of the leg or foot.

A transient hepatitis sometimes occurs, but jaundice is rare. Gall-stones are a recognised sequel of typhoid infection and may contain the bacilli.

*Respiratory system.*—A mild bronchitis is present in most cases. In severe infections, hypostatic congestion of the lung bases occurs. Lobar pneumonia may supervene in the third or fourth weeks of the disease. Although typhoid bacilli may occur in the sputum, and be found in the lung, pneumococci are also present; the condition may be overlooked, as cough is often slight and rusty sputa absent. Embolic and pyæmic processes in the lungs during typhoid may give rise to abscess, gangrene and pneumothorax. Intra-pulmonary thrombosis, with infarction, is a very rare event.

Ulceration of the larynx is not infrequent in severe cases. It involves the post-arytenoid region and has been likened to a pressure sore. It may be latent or give rise to huskiness of the voice, stridor and toneless cough. There may be pain on deglutition and laryngeal tenderness. The slighter symptoms may abate, but sometimes the process terminates in necrosis of cartilage and œdema or stenosis of the larynx.

*Blood and circulatory system.*—A slight polynuclear leucocytosis is sometimes seen in the first week of infection. More characteristic is anæmia associated with leucopenia, a characteristic absence of eosinophils with a relative increase in the lymphocytes and large mononuclear cells. In uncomplicated typhoid fever the leucocyte count rarely exceeds 6000. The eosinophils reappear with convalescence. The appearance of a polynuclear leucocytosis indicates the onset of inflammatory complications.

Circulatory failure is a feature of severe attacks. The pulse-rate, usually but moderately accelerated in typhoid, rises to 120 or more, diastole disappears, the cardiac sounds weaken and the blood pressure falls. Acute collapse, with sudden drop of temperature, coldness of the skin, cyanosis and feeble or irregular pulse, may ensue. The collapse may be recovered from, but its occurrence is ominous.

Femoral thrombosis is apt to occur during early convalescence. It is usually left-sided, and may commence in the veins of the calf, popliteal space or in the internal saphenous trunk. The symptoms are pain and tenderness at the site of the thrombosis, with fever, tachycardia, and later, swelling of the limb, usually moderate in degree. The affected vein may often be felt as a tender spot or cord. In a few weeks the thrombus is absorbed, and the circulation re-established, but sometimes permanent obstruction and œdema result. The clot, if dislodged, may cause pulmonary embolism.

Arteritis, leading to occlusion, is an uncommon complication. The vessels affected are those of the lower limbs, sometimes those of the upper extremities, neck or brain.

*Urinary system.*—Febrile albuminuria is often present, but is transitory. Typhoid

bacilluria occurs in some cases, the urine presenting a slightly turbid, opalescent appearance; but a similar appearance may be due to the colon bacillus. Symptoms of pyelitis, pyelo-nephritis or cystitis may supervene. Urinary carriers continue to discharge typhoid bacilli for long periods. Acute nephritis is uncommon, it may occur either at the commencement or height of the disease. Retention of the urine may supervene during typhoid, but suppression is rare. During the fever the excretion of urea and of uric acid is increased, but the chlorides are diminished. A moderate oliguria is the rule. A considerable reduction, in spite of free fluid intake, is evidence of a severe attack. Polyuria occurs at the onset of convalescence, and is of good omen.

*Generative system.*—Orchitis and prostatitis have been observed. In females vulvitis and also mastitis may occur.

*Nervous system.*—Meningeal symptoms at the onset have already been mentioned (p. 101). Rarely meningitis occurs in a purulent form during the third or fourth week of the disease. Its mortality is high (50 to 100 per cent.). Delirium is often present at the height of typhoid fever and is usually of a quiet type. Drinkers may develop delirium tremens. Convulsions are rare. They may occur at the onset, or when occurring later may be due to cerebral thrombosis, encephalitis or meningitis. Multiple neuritis or neuritis of such nerves as the ulnar or peroneal may supervene, in the latter cases often due to pressure. Acute tenderness of the toes during convalescence is also attributed to neuritis. These polynuritic phenomena are far less common when careful attention is paid to the patient's diet; they probably result from vitamin deficiency. During the course of the fever hemiplegia or aphasia may supervene.

Mental disturbance is occasionally a sequel, taking the form of mania, melancholia or dementia. For many months after a severe attack the patient may remain in a fatuous condition but ultimately recover.

As regards the special senses, temporary deafness is characteristic of the fever, and sometimes suppurative otitis occurs. Double optic neuritis is a rare complication which may lead to blindness.

*Osseous and muscular systems.*—During convalescence localised osteo-periostitis of the tibia, sometimes of the femur, ribs or other bones may appear. It may terminate in suppuration with limited necrosis. The inflammation is chronic and relapsing. Typhoid bacilli may persist in the pus for long periods. A painful inflammatory affection of the ligaments, intervertebral disks and vertebral periosteum is the basis of the "typhoid spine". The lumbar and sacral regions are chiefly involved, with stiffness and pain on movement. The condition is chronic, but the ultimate outlook is said to be good. Arthritis of large joints is a rare occurrence; it may lead to dislocation of the hip.

Rupture of the rectus abdominis, sometimes of the adductors or other muscles, may take place. This is accompanied by local hæmorrhage. The resulting fluctuating and discoloured swelling may clear up or go on to suppuration.

*Cutaneous system.*—Abscesses and boils may prove troublesome. Lincæ atrophica tend to form in the skin of the abdomen and thighs. In severe cases pressure sores may form on the sacrum, the heels or other pressure points. These bed-sores are a source of danger from septicæmia or pyæmia.

*Diagnosis.*—Of the symptoms of onset, headache, slight epistaxis, disturbed sleep, a mild degree of bronchitis, abdominal uneasiness and some disturbance of the action of the bowels are very suggestive. Gradual daily increase in the pyrexia and its maintenance after the lapse of a week at a steady level of 103° or 104° F., with slight morning remissions, is significant. Relative slowness of the pulse and the presence of microtism are additional diagnostic points. The dry furred tongue peeling in lateral and central strips, slightly tumid abdomen, moderately enlarged spleen and the appearance of rose spots are confirmatory. The abdominal reflexes are often absent.



**SPECIAL DIAGNOSTIC METHODS.**—1. *Blood examination.*—Culture is particularly valuable in the first week before the agglutinative reaction has appeared or the rose spots are evident, but is also applicable during the second and third weeks and in relapse. Ten to 20 ml. of blood drawn aseptically from a vein at the bend of the elbow are allowed to run directly into plenty of broth or peptone solution or, better, into a medium which contains filtered bile or bile salts. At the same time a blood count should show a characteristic leucopenia with a relative lymphocytosis.

2. *Cultures from bone-marrow* obtained by sternal puncture are said to be more often and more persistently positive than blood cultures.

3. *Cultures from the stools.*—Owing to the presence of other intestinal bacteria this is not always an easy process, but by enrichment methods and the use of litmus-lactose agar, or MacConkey's medium or the bismuth sulphite medium of Wilson and Blair, bacilli have occasionally been found during the incubation stage and in about 50 per cent. of the cases examined in the first week, a proportion which increases in the third week. Stool culture is also of value for the detection of intestinal carriers, and for determining whether a convalescent is fit to mix with other members of the community. The discharge of bacilli often being intermittent, more than one examination is necessary.

4. *Cultures from the bile.*—In suitable cases these may be obtained from bile removed by duodenal siphonage with the Rehfuß tube. The results of bile culture, like those of bone-marrow culture, are more persistently positive than blood cultures and are especially valuable in obscure, subsiding and relapsing infections.

5. *Cultures from the urine.*—The typhoid bacillus hardly ever appears in the urine before the tenth day, and, as a rule, not before the fifteenth. The infected urine is generally opalescent and slightly albuminous. Cultures are made without difficulty and are useful not only for diagnosis but also for the detection of urinary carriers.

6. *Agglutination tests.*—Towards the end of the first week of typhoid fever the blood serum begins to agglutinate the typhoid bacillus. This power reaches its maximum about the eighteenth to the twenty-third day. The test is performed with standardised suspensions and repeated every 4 or 5 days. An agglutination titre of 1:128 is regarded as positive. Normal blood rarely shows an agglutination higher than 1:64. Rising titres are highly diagnostic. Dreyer standard suspensions, being formalised, produce H or flagellar agglutination mainly. This is specific in the case of *Salm. typhi* and *paratyphi A*. *Salm. paratyphi B*, however, may occur either in the specific or in the group phase, and in the latter case possesses agglutinative elements which are common to other members of the Salmonella Group and so its antiserum may agglutinate these organisms.

A second agglutinin, known as O or somatic, should be investigated at the same time. The actual titres obtained with this usually are less than those obtained with H. An O agglutination is also possible with other members of the Salmonella Group, so O agglutination is not so specific as H.

A third agglutinin, known as the Vi appears early and is usually transitory. It affords strong evidence of recent infection. In chronic typhoid carriers it persists and is said to be of value in their detection.

As a continued fever of the enteric type may, although rarely, be caused by other members of the Salmonella Group, it is now customary to employ formalised suspensions not only of *Salm. paratyphi B*, H specific, but also of it or some other member of the family in the group phase.

T.A.B. vaccine, in consequence of its mode of preparation, evokes H agglutinins chiefly, and these may persist for some years. The appearance of O agglutinins in an inoculated person shows an enteric infection. Blood culture or examination of the excreta may reveal its identity. A rising titre of H agglutination for a particular organism may also do this, but it is known that other, quite different, infections may also raise the H titre (*anamnesic reaction*).

**DIFFERENTIAL DIAGNOSIS.**—Prominence of respiratory or bowel symptoms in typhoid fever may cause the infection to be overlooked. A deep-seated or apical *pneumonia* or, in children, *broncho-pneumonia* with intestinal disturbance, may simulate typhoid. Careful and repeated physical examination, blood and stool culture and agglutinative reactions will lead to a correct diagnosis. Labial herpes is rare in typhoid. When typhoid is prevalent, caution is necessary in diagnosing primary bronchitis, pneumonia, broncho-pneumonia and, especially in children, gastro-enteritis.

Differentiation from *acute miliary tuberculosis*, from *tuberculous meningitis* and from *tuberculous peritonitis* is often difficult. Acute miliary tuberculosis may simulate typhoid in its insidious onset with malaise and headache, its rising temperature with morning remissions, its occasional slow pulse, its bronchitis and perhaps some enlargement of the spleen. But the temperature tends to be more irregular, sweats are present, the dyspnoea and cyanosis are suggestive, and signs of pleurisy may develop. There are no rose spots, and agglutinative tests and blood culture give negative results (tubercle bacilli are rarely found). Tuberculous meningitis is differentiated by such symptoms as vomiting, convulsions, the persistence of headache after the first week, or when delirium is established. A pulse hardly raised above the normal rate, stiffness and retraction of the neck, the presence of Kernig's sign and of retraction of the abdomen or the onset of ocular paralysis are very significant. The irritability and curled-up decubitus of meningitis contrasts with the apathy and dorsal decubitus of typhoid. Lumbar puncture will clinch the diagnosis; in tuberculous meningitis lymphocytes are in excess in the cerebrospinal fluid, and sometimes tubercle bacilli may be demonstrated. The question of meningo-typhoid has already been discussed. Tuberculous peritonitis may resemble mild typhoid fever. The presence of tuberculous masses in the abdomen or the development of peritoneal or pleural effusions is significant. In cases with indefinite symptoms and no signs of tubercle elsewhere, negative blood culture and agglutination tests afford assistance in eliminating typhoid infection.

*Suppurative and pyæmic conditions* may give rise to fever and constitutional disturbance bearing some resemblance to typhoid. Among these must be mentioned appendicitis and the intraperitoneal abscesses which may result from it, perinephric abscess, cholecystitis, pelvic, or puerperal infections, infective endocarditis and deep-seated osteomyelitis. The diagnosis is made by careful attention to the history of onset and course, thorough and complete physical examination, and the frequent presence of a pronounced polynuclear leucocytosis. Profuse sweats and rigors are more likely to occur, and the temperature chart is more irregular. The blood serum fails to agglutinate typhoid bacilli, nor can they be obtained by blood culture, which may, however, reveal the presence of other organisms.

Typhoid fever in its early stages is often mistaken for *influenza*, but in the latter the onset is generally sudden and the early symptoms are more severe. The temperature reaches its maximum much sooner. The pains in the limbs and the backache are more intense, and the headache, which has a neuralgic character, is frequently supra-orbital. Catarrh of the conjunctivæ and nose may be present, and perspirations are often marked. Desquescence usually takes place within a few days. A sharp drop of temperature after 2 or 3 days with a sudden rebound 12 or 24 hours later is very characteristic. If a supposed influenzal fever persists without definite cause, typhoid should be suspected.

A mild infection with *typhus* may bear a close resemblance to typhoid, and severe typhoid with grave toxæmia, stupor and a profuse eruption may be mistaken for typhus. Points in favour of the disease being typhoid are a slower onset, later appearance of the eruption, which is never petechial and presence of bowel symptoms. Typhus, on the other hand, has a sudden onset with high fever which sooner attains its maximum and does not show morning remissions. Conjunctival injection, con-

tracted pupils and a drunken expression are the rule. The rash appears on the fourth day, becomes petechial and is accompanied by subcuticular mottling. Prostration is marked and there is a greater tendency to early delirium or stupor. Defervescence, more or less abrupt, occurs about the fourteenth day. The Weil-Felix reaction is present, but agglutination tests for typhoid are negative except in inoculated persons (p. 296).

*Undulant (Malta or Mediterranean) fever* is distinguished from typhoid by its persistently relapsing character, the prominence of arthritic pains and joint swellings, and the fact that the blood agglutinates the *Brucella melitensis*, which organism can also be recovered by blood culture. Closely allied to this is the fever produced by *Br. abortus* of cows and pigs.

When *malarial fever* assumes the continuous type, which is likely to occur with the malignant infections, the diagnosis turns on known exposure to malaria, sudden onset, the detection of malarial parasites in the blood or bone marrow and the reaction to anti-malarial drugs. Malaria and typhoid fever, however, may coexist.

The fever of *secondary syphilis* is sometimes sufficiently severe to suggest typhoid, especially when accompanied by headache, malaise and muscular pains. In the *tertiary stage* with gummata of the liver prolonged fever may also occur. Diagnosis depends on the history or detection of a primary lesion, the possible presence of a secondary roseolar eruption and on laboratory tests. Deep-seated *malignant disease* or *hypernephroma* may also cause prolonged fever.

Amongst other diseases at times confounded with typhoid must be mentioned amœbiasis, psittacosis, kala-azar, glanders, trichiniasis, fever due to *Ascaris lumbricoides*, scarlet fever in which pyrexia is prolonged, that type of glandular fever in which the glandular swelling is delayed, and especially fevers of the Salmonella Group, i.e. paratyphoid A, B or C.

**Prognosis.**—Taking all ages, the death-rate varies from less than 5 to 25 per cent. as it is higher in some epidemics than in others. Age has a decided influence, especially on the mortality, which is least in children from 5 to 10, after which there is a steady increase with advancing years. Infants are believed to stand the infection very badly. Obesity, alcoholism, privation and fatigue are adverse factors. The influence of pregnancy has already been discussed. Indications of a grave attack are a pulse-rate of 130 or 140, cyanosis with signs of failing circulation and hypostatic congestion of the lungs, marked delirium and subsultus or actual coma, oliguria, persistent diarrhœa, tympanites, incontinence of urine and fœces. A temperature of 103° or 104° F. is not necessarily unfavourable unless it is sustained beyond the usual period or accompanied by signs of heart failure. Delayed appearance of the agglutinative reaction in some instances indicates a severe attack.

Of the complications, next to toxæmic circulatory failure, perforation is the most grave. Without operation it is almost invariably fatal. With operation the recovery rate is difficult to fix—some surgeons claim success in over 30 per cent., but the intervention must be immediate. The average recovery rate is very much lower. Hamorrhage from the bowel is undoubtedly serious, especially if repeated. Such complications as meteorism, meningitis, lobar pneumonia and acute nephritis are dangerous but not very common.

Sudden death sometimes occurs, either at the height of the fever or in convalescence. It may be caused by intense toxæmia and circulatory failure, coronary or pulmonary thrombosis or pulmonary embolism. Rarely no definite cause can be assigned.

**Treatment.**—**PROPHYLACTIC.**—Patients should be isolated. Adequate disinfection of the fœces, the urine, the pus from abscesses, the vomit and the sputa is necessary. Blood discharged from the nose or bowel should also be looked upon as infectious. Equally essential is the disinfection of the bedclothes and personal linen of the patient, the feeding utensils, thermometer, bed-pan, urinal, spittoon and enema

syringe. The stools and urine should be mixed with an excess of some such disinfectant as carbolic acid, and allowed to stand for several hours before being thrown down a drain. The sputa should be received in small cloths which can be burned, or expectorated into a disinfectant solution. The clothing and bedclothes of the patient should be kept wet and soaked in a 1 in 20 solution of carbolic acid before being sent to a laundry.

Nurses in attendance should submit to prophylactic inoculation and take special precautions for their own safety. Overalls will obviate soiling of the clothes. Rubber gloves may be worn when giving enemas, touching bed-pans and urinals or dealing with soiled linen, but always it should be realised that typhoid acquired by contact is a disease conveyed by unclean hands, and the danger may be obviated by washing with plenty of soap and water after touching the patient or anything which has been in contact with him. Everything leaving the patient or used by him must be sterilised at once. Feeding utensils should be boiled after use.

In most cases the bacilli disappear from the excreta in convalescence, only persisting for a few weeks, but bacteriological examination several times repeated affords the only proof of safety. This may be supplemented by an examination of the blood for the Vi agglutinin. About 5 per cent. of those attacked become carriers. In most the carrier state is temporary and an arbitrary period of 6 or 12 months is allowed before the condition is deemed chronic. Intestinal carriers are more common than urinary carriers. In both the discharge of bacilli may be intermittent. Symptoms referable to the gall-bladder and periodic bowel disturbance occur in some intestinal carriers, and urinary carriers in like manner may suffer from kidney trouble or cystitis. Female carriers are said to be more common than male. Carriers do not necessarily give a positive Widal reaction, but Felix states that use of the Vi antigen will detect them (see p. 105).

Carriers are often responsible for the endemic persistence of typhoid in certain communities or localities and are particularly dangerous when employed in the preparation of food or in dairy work or in connection with water supplies. They should be prohibited from following these occupations. Since they may spread infection by contaminating their own hands during defæcation or micturition they should be scrupulous in washing after attending to the calls of nature and have towels reserved for their own use. Their soiled bed and body linen must be disinfected. Medical treatment by the use of intestinal and urinary antiseptics, surgical by excision of the gall-bladder, and treatment by autogenous vaccines have up to now alike failed to solve the problem of the chronic carrier. It is said that sulphaguanidine is sometimes effective. Preventive inoculation of contacts is the most effectual method of limiting their danger and is adopted in special circumstances. Some carriers give no history of an attack of typhoid and may themselves ultimately develop an attack of the fever or suffer from typhoid septicæmia after operations on the gall-bladder or kidney.

A pure water supply and an efficient system of drainage are important factors in the prevention of typhoid epidemics. When the disease is prevalent, drinking water and milk should always be boiled, and travellers in localities where it is endemic should adopt similar precautions. Uncooked vegetables and, in particular, radishes, celery, salads, cress, tomatoes, cucumbers, strawberries and other fruits are liable to contamination. Oysters and other shell-fish should be avoided unless their source is known to be above suspicion. The disease has been contracted by bathing in sewage-contaminated water.

*Prophylactic vaccination.*—Immunity can be artificially induced by typhoid vaccine. There are several methods of preparation, one of which is to heat a suspension to 58° C., and complete the sterilisation by the addition of 0.5 per cent. of phenol. Exposure to higher temperatures diminishes the potency of the vaccine. Felix advocates an alcohol killed and alcohol preserved vaccine made from smooth cultures

virulent to mice. This stimulates formation of Vi and O agglutinins and has proved highly effective. The vaccine commonly used contains 1000 million *S. typhi* and 750 millions each of *S. paratyphi A* and *B* per ml. The standard dose is 0.5 ml., followed by 1 ml. after an interval of 10 to 14 days. Smaller doses of alcohol-killed vaccine are required; for men 0.3 ml. and 0.6 ml. Thereafter an annual dose is desirable to maintain immunity.

Vaccine injection is made subcutaneously and preferably not after a heavy meal or exposure to fatigue. A mild local reaction and sometimes constitutional symptoms may occur a few hours after injection, hence the patient should rest. If the patient is already infected the reaction may be more severe. The duration of the immunity conferred is said to average 1 to 2 years and to be proportional to the dosage employed. An individual inoculated at the beginning of the incubation period of typhoid has a good chance of escaping the fever, but in rare cases the inoculation appears to precipitate its onset and aggravate its course (*provocation typhoid*).

**CURATIVE.**—The sulphonamides exert little or no influence upon typhoid fever and, of the antibiotics, chloramphenicol alone has been shown to be truly effective. Administration of this drug by mouth is followed by defervescence of the fever in 3 or 4 days and by disappearance of the toxæmia. However, relapse has been noted after its use, and the dangers of hæmorrhage and perforation are not completely abolished. The dosage originally recommended was 4 g. followed by 0.25 g. 2-hourly for 5 days. Only recently has the occasionally devastating effect of chloramphenicol on the bone-marrow been recognised, and it is not yet known how frequently its use is followed by aplastic anæmia. At present it seems justifiable to continue its employment in typhoid fever, although wise to administer it only for a period of 5 days. It should, perhaps, be mentioned that the foregoing account of typhoid fever is of the disease unmodified by the use of chloramphenicol.

Skilful nursing and suitable diet are of the first importance. The room should be kept at a temperature of 60° F., the bed narrow and of convenient height. A hair or rubber mattress is covered with two folds of blanket and a waterproof sheet over which is placed a sheet, and under the hips a draw-sheet. A water-bed is unnecessary. A sheet and coverlet with a blanket over the feet are usually sufficient covering. Night and morning the patient should be sponged with tepid water, and parts exposed to pressure should be rubbed with surgical spirit, and dusting-powder applied. Rucking of bedclothes should be avoided. The urinal and bed-pan should be used in the recumbent position, and the buttocks sponged, dried and powdered after each motion. The mouth should be cleansed after each meal. From time to time it may be advisable to move the patient from the dorsal position to avoid hypostatic congestion of the lung bases. Stools and urine should always be reserved for inspection by the medical attendant, who should never neglect daily examination of the abdomen, and should also satisfy himself that the patient, especially if restless, has not retention of urine. Examination of the veins of the legs should never be omitted. The temperature, pulse and respirations should be charted 4-hourly, and more frequently should complications be suspected.

The principles of the dietetic treatment of typhoid fever are to provide an adequate allowance of fluid, calories and vitamins while avoiding foodstuffs which leave a bulky residuc. The requirements of fluid vary, but may reach 5 to 6 litres a day with high fever. An adult will require 3000 calories daily which may be derived from eggs, steamed white fish, minced meat, milk, cream, ice-cream, purée of potatoes and thickened soups and should be given as frequent small feeds. Fluid and calories may be provided in the form of strained fruit juices, sweetened with glucose or lactose. A supplement of vitamins is essential.

When the temperature has been normal for 3 days more bulk is cautiously added to the diet.

Tepid, cold or ice sponging should be adopted when the temperature is high, or

the cold pack used, especially when nervous symptoms are pronounced. The ice cradle is another useful means of refrigeration; the patient is covered with a sheet, and a cradle, in which small rubber bags of ice are suspended, is placed over the body, the whole being covered with a thin blanket. The cradle may remain in position indefinitely, the effect on the temperature being carefully watched.

Constipation should be met by a simple enema every second day. In defervescence liquid paraffin may be substituted. *Diarrhœa*, if accompanied by curds, calls for reduction of the milk. A starch and opium enema is useful, or gr. 10 of Dover's powder by the mouth. In *hæmorrhage from the bowel* the most absolute rest is essential. Food should be reduced to a minimum or withheld for 12 or 24 hours. No stimulants or beef-tea are permissible. Ten minims of laudanum or a hypodermic injection of gr.  $\frac{1}{4}$  of morphine should be given. A watch should be kept for signs of perforation. Blood transfusion will be necessary if the hæmorrhage is voluminous. *Perforation of the bowel* calls for immediate operation. *Meteorism* may be controlled by reducing the diet, administering copious enemata of hot water and inserting the rectal tube. A turpentine stupe or ice-poultice may be applied to the abdomen. Turpentine by the mouth or by enema (half an ounce in 8 oz. of mucilage of starch) is useful. For *delirium*, *sleeplessness* and *headache*, the reduction of temperature by sponging or cradling and the administration of gr. 10 or 15 of Dover's powder should be tried. Sometimes soluble barbitone (Medinal) and aspirin are effectual. In *circulatory failure* nikethamide, leptazol and digitalis are of very doubtful value. The supervention of *femoral thrombosis* calls for strict immobility of the limb. Evidence of the value of anticoagulants in typhoid is not yet forthcoming, but these drugs are to be avoided until all risk of hæmorrhage is past. *Bacilluria* and *cystitis* are treated by hexamine in gr. 10 doses, three or four times a day; if persistent, sulphonamides may be effective. Of the suppurative and septic complications, *periostitis* may be influenced by rest, local applications and typhoid vaccine, but suppuration calls for surgical intervention. *Parotitis* usually comes to incision. *Cholecystitis* may subside, and should be given a chance to do so, but if it persists operation becomes necessary. Crops of *boils* call for local treatment, and penicillin or sulphonamides.

**CONVALESCENT.**—In an infection of moderate severity the patient should be able to be up for a short time 10 days after the temperature has become normal. Few are fit to work until 2 or 3 months have elapsed.

Three negative stool cultures at intervals of 7 days should be obtained before discharge. The Vi agglutination should be tested. If it remains positive the carrier state is suspected and it should be repeated in 3 months.

## PARATYPHOID FEVER

**Ætiology.**—Paratyphoid fevers, like typhoid, are ubiquitous, but the type differs in different countries and different climates. The infecting organisms belong to the group *Salmonella*. Paratyphoid A is prevalent in India and other tropical countries; it may possibly be endemic in the Mediterranean and parts of Western Europe, but in European countries Paratyphoid B is much more common. Paratyphoid C has occurred chiefly in Eastern Europe but also elsewhere. Paths of infection in the body and the lesions produced resemble those of typhoid fever, but ulceration of the bowel is more superficial, hæmorrhage being slight and perforation rare. The infection may even take the form of a septicæmia without bowel lesions. In other cases there is a diffuse dysenteric inflammation and ulcers are found in the colon only. The bacilli leave the body by the same channels as in typhoid.

The greatest incidence of paratyphoid infections is in the summer, earlier in the year than that of typhoid fever. All ages and both sexes are susceptible. The primary source is a patient suffering from an attack, often in an ambulatory form, less com-

monly a chronic carrier. The contagion may be direct or through food, drinking water or fomites. Foods not safeguarded by cooking after purchase are common vehicles of infection. Amongst these are bread; cream, synthetic or natural; ice-cream; cream pastries; cooked beef, ham and some shell-fish. Extensive water-borne outbreaks are rare, but the organisms may flourish in sewage or sewage-effluents for 3 weeks. Milk infection is usually through the agency of infected water or of a carrier. The incubation period varies from 10 to 12 days. Extremes of 4 to 24 days are known. Precocious carriers have been known to harbour the bacilli for as long as a month before developing the disease.

**Symptoms.**—The clinical manifestations of paratyphoid are similar to those of typhoid fever, but are generally of a milder character with a speedier ingravescence and a shorter course. *Ambulatory, or almost symptomless, attacks are common, and during outbreaks the number of transitory carriers is much in excess of the cases of overt infection.* On occasions, however, paratyphoid may show a severity equal to that of true typhoid. Simulation of attacks of acute irritant food-poisoning is also alleged, but these are more likely to be due to *Salm. typhi-murium* or to mixed infections. The septicæmic stage of paratyphoid is short, rarely lasting more than a week and blood cultures for diagnostic purposes should be taken as early as possible. They are said to prove positive in 90 per cent. of the cases.

The onset is usually insidious, the invasive symptoms resembling those of typhoid, but a sudden onset is believed to be more common than in the latter disease. Shivering and vomiting are not infrequent symptoms of such invasion. Sometimes gastrointestinal symptoms are for a time very prominent, and are particularly misleading in childhood. As with typhoid, bronchitis, influenza or pneumonia may at first be simulated, and sometimes the symptoms simulate an acute abdominal condition or meningitis.

The fever attains its maximum sooner than in typhoid, and may be at its height by the third or fourth day, by which time, if not before, the patient will have taken to bed. The head aches, also the back and limbs and sometimes the joints. The patient is apathetic, and the spleen usually becomes palpable; it is firm and sometimes tender. The liver may be slightly enlarged, and the gall-bladder tender if cholecystitis is present. The abdomen is generally somewhat tumid, but marked distension is uncommon. Diarrhoea may occur at the onset, but constipation is more common. Sweating is often more pronounced than in typhoid. Rose spots are present in unusual profusion in some cases. They usually appear towards the end of the first week. Their distribution resembles that seen in typhoid fever. They often appear larger than those seen in ordinary typhoid infection, and the rash may continue to come out after the temperature has fallen. Pulmonary complications are mild, but bronchitis and broncho-pneumonia may occur. In the more severe cases, circulatory failure may be evident.

After the first week the toxæmia rapidly diminishes and it is exceptional for the patient to pass into the "typhoid state". The fever has a shorter duration and is more often remittent than in typhoid. Within a fortnight, sometimes sooner, it has generally fallen by rapid lysis to normal. The slow pulse and low blood pressure of typhoid are also seen in the paratyphoid variety, and the blood picture, in minor degree, also resembles that of typhoid fever. Relapse is said to be just as frequent. Convalescence is rapid.

**Complications.**—In some cases bronchitis, or broncho-pneumonia, are prominent and may mask the real nature of the infection. Intestinal hæmorrhage is much less common and less severe than in true typhoid. Perforation is rare. Thrombosis of the femoral or saphenous veins or their radicles is not uncommon, and pleural effusions may occur. Cholecystitis may be due to paratyphoid organisms, as also bacilluria, cystitis, pyelitis and even pyelonephritis. Orchitis is an occasional complication. Other complications, which have mostly been observed in army practice,

are laryngeal ulceration, parotitis, periostitis, peritonitis, sometimes without perforation of the bowel, and pylephlebitis, attributed to lesions of the appendix.

**Diagnosis.**—For the differentiation of paratyphoid from typhoid and of the varieties of paratyphoid from each other, recourse must be had to bacteriological methods, *i.e.* to blood culture, agglutinative reactions and cultures from the stools and from the urine. Of these methods, blood culture in the early stages is the most satisfactory. In the inoculated, if agglutination occurs in high dilutions with one of the paratyphoid organisms and little or not at all with the others and with the organism of typhoid, the nature of the infection is evident; but in other cases the examination has to be repeated at short intervals and the results compared. A rising agglutination for one organism indicates it as the causal agent. The possibility of confusion with *Salm. typhi-murium* and of anamnestic reactions should be borne in mind.

**Prognosis.**—The prognosis in paratyphoid infections is better than in those due to the *Salm. typhi*, the proportion of severe infections being much smaller, and the mortality much lower. The fatality in recent outbreaks has ranged from 1 to 35 per cent. The causes of death are chiefly hæmorrhage, perforation, lung inflammations and toxæmia.

As regards differential diagnosis, phage typing, prophylaxis and treatment, what has already been said with regard to typhoid applies. Sulphonamides are of very doubtful utility.

R. BODLEY SCOTT.

## BACILLARY DYSENTERY

Bacillary dysentery is one of the most important diseases encountered in the tropics, and until the introduction of sulphonamide therapy was associated with serious mortality—especially in infections with *Sh. shigæ*. It is the only form of dysentery giving rise to large epidemics and in the War of 1914–1918, caused much sickness and death in British armies campaigning in Africa and Macedonia. In the War of 1939–1945, the incidence was markedly reduced in allied troops owing to (1) a higher standard of field and camp sanitation with a greater appreciation of the fly menace and need for water sterilisation, (2) the introduction of specific drugs like sulphaguanidine and sulphadiazine.

**Definition.**—An acute inflammation of the colon, often associated with superficial ulceration of the mucosa and occasionally with extensive coagulation necrosis, caused by specific dysentery bacilli. The disease is characterised clinically by a sudden onset, with colicky abdominal pain, followed by urgent diarrhœa, malaise, vomiting, headache, muscular pains and fever; in the early stages the stools may be brown, watery and contain flakes of mucus; later, they are mainly composed of glairy mucus, perhaps admixed with blood or yellowish muco-pus. Many cases of dysentery, however, are so mild that they are frequently regarded as diarrhœa.

**Ætiology.**—Dysentery bacilli may give rise to sporadic infections, outbreaks or definite epidemics. No country is exempt and natives and Europeans of all ages and both sexes are susceptible. In England and Europe, Flexner and Sonne dysentery bacilli may cause outbreaks in military barracks, prisons and asylums, and along with *Proteus morgani* are responsible for certain outbreaks of summer diarrhœa in children. Filth, overcrowding, malnutrition and intercurrent disease predispose, notably when sanitary conditions are bad, as in prison camps. Dysentery is common in warm climates, especially during the early summer, rainy season and autumn months, and the epidemic wave closely follows the increase in flies. It is most frequent where sanitation is defective, flies prevalent and garbage disposal inadequate. Dysentery is spread by (1) faecal pollution of water, or (2) contamination of food, either directly from a carrier or indirectly by faecal-feeding flies. In some countries,



such as the Netherlands East Indies, where the natives defæcate directly into flowing water or streams running into rivers, the disease is predominantly water borne and prevention consists essentially in water sterilisation. In the Middle East, however, infection is mainly fly borne. Uncooked vegetables, particularly salads, should be suspect, as human excrement is so often employed as manure. Cooks and food-handlers who are carriers are also a potent source of infection. Recent technical advances in culturing dysentery bacilli have shown that a larger proportion of dysentery patients become carriers than was formerly thought.

Shiga (1898), in Japan, first discovered *Sh. shigæ*, which is a most virulent organism producing a true exotoxin. This was rapidly followed by the isolation of several other strains of dysentery bacilli. Boyd, who has recently re-classified the organisms, causing bacillary dysentery, recognises two non-mannitol fermenting bacilli, *Sh. shigæ* and *Sh. schmitzi*. Of the mannitol fermenting dysentery bacilli there is *B. dysenteriae* Sonne, which is a late lactose fermentor, and two groups of non-lactose fermenting organisms which include six types of *Sh. flexneri*, i.e., I, II, III, IV, V and VI, and three types of *Sh. boyd*, i.e., I, II and III. The latter types have been found in India, the Middle East and New Guinea, and probably have a still wider geographical distribution. More than half the dysentery in warm climates is caused by organisms of the Flexner-Boyd group. In the Middle East, *E. histolytica* accounted for 12.3 per cent., *Sh. shigæ* for 15.8 per cent., and Flexner-Boyd I for 52.3 per cent. of Army cases in 1941.

**Pathology.**—While the naked-eye pathology of fatal cases is well known, the macroscopic appearances of the bowel in non-fatal cases can only be investigated during sigmoidoscopic examinations of the rectum and pelvic colon. Combined studies have shown a wide range of pathological lesions, including (1) transient catarrhal inflammation with hyperæmia associated with increased mucoid secretion but without ulceration; (2) more severe generalised inflammation with hyperæmia, œdema, scattered hæmorrhages and localised areas of coagulation necrosis of the mucosa, exfoliation of which subsequently leads to superficial ulcers covered with muco-pus; and (3) widespread coagulation necrosis of the mucosa, which, in fulminating cases, is characterised by a greyish-white or greenish gangrenous membrane. Cases dying in the acute phase of the disease often show extensive ulceration, which may involve the whole colonic mucosa, and sometimes the terminal 12 in. of the ileum as well; in others maximal lesions are found in the rectum, sigmoid colon and cæcum. Fatal cases have also shown hæmorrhagic inflammation and swelling of the meso-colonic lymph glands, parenchymatous degeneration of the liver and kidneys and central necrosis of the suprarenal glands. The pathological findings in subacute and chronic bacillary dysentery are considered later.

**Symptoms.**—The incubation period is from 1 to 7 days. The clinical features vary with the resistance and age of the patient, and the type of the invading organism. Thus, Flexner-Boyd and Sonne infections are generally mild and Shiga infections frequently severe. In infants, however, Flexner infections may be rapidly fatal, greenish fluid stools containing typical bacillary exudate being passed.

Acute, subacute and chronic clinical types of dysentery may be encountered.

#### ACUTE DYSENTERY

**The Flexner-Boyd Group.**—Many cases are of mild catarrhal type, and, as a rule, symptoms of severe toxæmia and dehydration do not develop.

The onset is characterised by colicky abdominal pain, followed by urgent diarrhœa. Nausea, transient vomiting, headache, shivery feelings and aching in the limbs may accompany, follow or precede the onset of abdominal symptoms. Fever is present soon after the onset of diarrhœa in most cases. Examination reveals diffuse tenderness, most marked over the right or left iliac fossa, or the upper part of the abdomen.

The abdominal pain is predominantly colicky in character. Between the paroxysms the patient may get relief or complain of a persistent dull ache. Tenesmus due to rectal spasm is less frequent in mild than in severe infections.

Diarrhœa is generally most intense on the first and second day of attack, the stools, as a rule, decreasing in number thereafter, but in some cases the maximum number is reached on the third, fourth or fifth day. At first the stools are fairly copious and watery, but, if looked for, flakes of mucous and blood will generally be found. Most cases of febrile diarrhœa in which numerous liquid stools are passed are bacillary dysentery. As the condition develops, the stools are found to consist almost entirely of mucus or of blood and mucus. The mucus is like egg white, practically odourless, tenacious and sticks to the bed-pan. The blood varies in quantity, and may be seen as mere flecks in otherwise colourless mucus or may be more copious. In more severe cases the mucus becomes yellow and definitely purulent in character. As the case advances towards recovery blood disappears, mucus becomes more scanty and thicker, and brown fecal matter reappears. In mild cases fever and diarrhœa may last only 1 or 2 days, while in others it goes on for a week or more. If sulphonamide treatment is being given and the pyrexia or diarrhœa persists more than a week, sigmoidoscopic examination should be made.

*Shiga Type.*—(1) Fulminating cases of Shiga dysentery are occasionally encountered. The onset is sudden, with vomiting and severe watery diarrhœa. The patient rapidly becomes collapsed and dehydrated, muscular cramps ensue and death with subnormal temperature may supervene in 24 to 36 hours. In these cases the terminal portion of the ileum is frequently involved. As mucus secretion from the necrosed colonic mucosa is impossible, the typical mucosanguineous stools of dysentery may never appear. The copious fluid stools may suggest cholera or food poisoning, and the correct diagnosis may only be made at necropsy.

(2) In severe Shiga infections the onset may be sudden or insidious. In patients with a sudden onset the illness commences with a rigor or feeling of chilliness, associated with fever, headache, nausea or vomiting, colicky abdominal pain and frequent urgent bowel actions. Tenesmus commonly follows. At first the fluid brown stools contain only flecks of mucus or blood; soon they become mucoid or muco-purulent in character and may contain blood and greenish sloughs of mucous membrane. The presence of considerable quantities of blood or of greenish sloughs should always suggest a Shiga infection. As the condition progresses the bowels may act twenty to sixty times daily and symptoms of dehydration and toxæmia, detailed below, rapidly appear unless specific drug treatment be given.

In cases with an insidious onset, severe intestinal symptoms and fever do not supervene for several days, during which period the patient may not feel ill enough to go to bed. As the infection progresses and more mucosa is destroyed, bowel symptoms increase and toxæmia appears. The cheeks then become flushed, the eyes bright, the expression anxious, fever increases, the pulse is more rapid and the tongue coated and yellow. Restlessness, sleeplessness and delirium develop. When fluid loss continues without compensation, dehydration results; there is increasing thirst, a dry brown tongue, muscular cramps, a dry shrivelled skin, collapsed peripheral veins, a feeble rapid pulse, a low blood pressure, oliguria and an increase in nervous symptoms. Occasionally renal failure complicates the picture; then there is albuminuria with granular casts and nitrogenous retention. Oliguria, abdominal distension and hiccough are characteristic. In the most severe cases, anuria supervenes and the patient dies in uræmic coma. Another complication is peripheral circulatory failure which arises from a combination of toxæmia, dehydration and possibly hypoproteinæmia consequent to the loss of serum protein through the extensively ulcerated colonic mucosa.

Sometimes infection of the colon extends more deeply, involving the muscular coat and even the peritoneum, which becomes inflamed; subacute or chronic peri-

tonitis with serous effusion results. Under these circumstances the abdomen becomes distended, the abdominal muscles tender and somewhat rigid and there may be dullness in the flanks or free fluid demonstrable. Flatulence, vomiting and colicky abdominal pain prove troublesome. A polymorphonuclear leucocytosis is characteristic. The condition is non-surgical, and must be differentiated from acute peritonitis secondary to perforation which demands immediate laparotomy.

(3) The less severe Shiga infections present much the same picture as the Flexner-Boyd group already described. They cannot be differentiated clinically and can be diagnosed only by bacteriological methods.

*Sonne Type.*—This type particularly affects children, but may also occur in epidemic form in adults. The clinical picture is frequently mild, resembling that described in the Flexner-Boyd group.

Since the introduction of sulphonamide therapy, subacute and chronic dysentery are rare and only encountered in untreated or inadequately treated patients.

### SUBACUTE DYSENTERY

In the subacute stages of dysentery, looseness of the bowels and the passage of stools showing mucus and traces of blood persist. Fever may or may not be present.

Sigmoidoscopy generally reveals ulcerative lesions which are not necessarily associated with generalised inflammation of the mucosa. The ulcers seen may be (1) small, superficial and clear cut with well-defined edges; (2) like aphthæ with yellowish-white exudate; (3) punched-out in appearance, with vertical walls and covered with muco-pus; or (4) small discrete nodular-like lesions with a yellow crust; on scraping a bleeding crater is left containing exudate of bacillary type from which dysentery bacilli can be cultured. Patients with these small local ulcers and normal intervening mucosa may have periods of complete remission of symptoms, interspersed with mild attacks of looseness of the bowel, and the passage of stools containing mucus and possibly blood.

### CHRONIC DYSENTERY

Rogers found that chronic bacillary dysentery mainly involved the rectum, sigmoid and ascending colon. Two types are encountered.

(1) The patient gives a history of dysentery from which he has failed to recover. Looseness of the bowels ensues, the stools containing mucus, muco-pus and sometimes blood. In some cases the bowels may have acted 5 or 6 times every day for 6 months or longer. Sigmoidoscopy reveals normal mucous membrane interspersed with circular or oval ulcers up to 1 cm. in diameter. Microscopic examination of the muco-pus obtained during this examination shows bacillary exudate, and culture is positive for bacilli, especially of Shiga variety.

(2) The patient gives a similar history, but is more ill, and during exacerbations fever may recur. Evidence of malnutrition is more marked; the loss of weight is greater and such patients tend to become miserable and emaciated. Secondary anæmia and œdema of the legs may develop. The abdomen is scaphoid, and the thickened descending colon is readily palpable during physical examination. Sigmoidoscopy reveals that the large bowel is tubular in outline, thickened and contracted and difficult to distend. The surface is composed of red granulation tissue, which bleeds readily on instrumentation. The general appearance resembles that seen in ulcerative colitis, and in severe cases the patulous condition of the anus, the atrophied appearance of the perianal skin, and the wasting of the gluteal and perineal muscles are common to both diseases. The radiological picture also shows a smooth tubular bowel with loss of haustration. In chronic dysentery of this type the inflammatory process extends deeply, involving the muscular coats leading to thickening, fibrosis

and loss of function. Culture of muco-pus obtained at sigmoidoscopy may reveal dysentery bacilli, and so differentiate the condition from ulcerative colitis.

**Complications and Sequelæ.**—Complications in both Flexner-Boyd and Shiga types of dysentery are infrequent, and are mainly encountered in the severe infections. Intestinal complications include hæmorrhage, which may be severe, especially in Shiga infection, perforation with peritonitis, chronic peritonitis with localised or general effusion of peritoneal fluid, hæmorrhoids, rectal prolapse and painful excoriation of the anus. Peripheral circulatory failure and renal failure are not uncommon complications in severe Shiga infections, and have been already described. Peripheral neuritis, toxic arthritis, conjunctivitis, iritis, pneumonia, parotitis, petechial and purpuric skin rashes occasionally occur. Toxic arthritis is found in both Flexner and Shiga dysentery. It takes the form of effusion into joints and peri-arthritis, and generally comes on from the third to fifth week, or during convalescence. The large joints are prone to be attacked. It often persists for many weeks, but recovery without permanent deformity follows.

**Diagnosis.**—Many cases regarded as simple diarrhœa are caused by dysentery bacilli. In bacillary dysentery the attack is almost invariably heralded by colicky abdominal pain, followed by urgent diarrhœa. Fever is generally present at the first examination, which may reveal localised abdominal tenderness in the course of the colon. The stools may be liquid in consistency and brown in colour at onset, but even at this early stage careful examination will generally reveal flakes of mucus containing exudate of bacillary type. In a typical case the stools show clear glassy mucus, with or without bright-red blood, and later muco-pus. Any case suddenly developing colicky abdominal pain, urgent diarrhœa with flakes of mucus or naked-eye mucus with or without blood in the stools and fever should be regarded as bacillary dysentery until proved otherwise. When feasible this tentative diagnosis should be confirmed by laboratory investigation and, if necessary, by sigmoidoscopy. Typical bacillary exudate is composed predominantly of polymorphonuclear leucocytes, with or without macrophages, epithelial cells and red blood corpuscles. Stools sent for culture should contain mucoid exudate, be absolutely fresh and uncontaminated by urine or antiseptics; they carry well in a solution of 30 per cent. glycerin in physiological saline. Dysentery bacilli may be isolated at any stage of the disease, especially if material for culture be obtained during sigmoidoscopy or by rectal swab. Using modern media positive cultures may also be obtained from stools containing no macroscopic mucus.

**Sigmoidoscopy.**—This can be carried out for diagnostic purposes early in the disease, but at this stage is generally not necessary. When the symptoms persist for more than 10 days the information obtained is valuable in prognosis, as the healing or extension of the lesions can be followed. From a diagnostic viewpoint not only do the appearances of the bowel wall indicate the nature of the disease, but by swabbing the ulcers ideal material can be obtained for culture and determining the type of exudate, while gentle curettage of the ulcer surface will supply material enabling vegetative forms of *E. histolytica* to be demonstrated if amoebiasis be present. In bilharzial dysentery papillomata or other lesions may be found; microscopic examination of material obtained from scrapings will reveal numerous ova. In the differentiation of the chronic dysenteries sigmoidoscopy is indispensable.

Bacterial food poisoning with organisms of the *Salmonella* group may need differentiation. The sudden and simultaneous onset of severe gastro-intestinal symptoms, with prostration, in a group of people who have consumed the same meat, milk or other food within 6 to 36 hours previously is suggestive. Culture of *Salmonella* organisms, such as *Salm. typhi-murium* or *Salm. enteritidis* will confirm the diagnosis, though it is not always possible to isolate the responsible organism. Blood is rarely present in the stools in *Salmonella* infections.

Chronic ulcerative colitis and carcinoma of the rectum or colon are commonly

misdiagnosed as subacute or chronic bacillary dysentery. Sigmoidoscopy and radio-barium after a barium enema may be essential in their differential diagnosis.

**Course and Prognosis.**—Most non-Shiga dysentery infections run a benign course, and many cases of catarrhal type are so mild that they clear up in a few days without specific treatment; in others, fever and intestinal symptoms persist for 1 to 3 weeks before subsiding; and in a minority, subacute or chronic dysentery may result. Fatal cases are generally of Shiga type, death occurring in from 30 hours to 3 months of onset. In some epidemics, especially amongst Japanese and debilitated natives, the mortality rate has been 25 to 50 per cent. In infants and young children, the aged and people who are malnourished or suffer from intercurrent disease, bacilli of Flexner, Schmitz and Sonne types may cause death. The mortality rate in British Forces in Egypt, Macedonia and Mesopotamia during the War of 1914–1918 was 27 per 1000. In Australian troops in New Guinea in the War of 1939–1945 it did not exceed 0.5 per 1000, a result attributable to the lower incidence of Shiga infections and the efficacy of early sulphaguanidine therapy. (See also Specific Chemotherapy, below.)

**Treatment.**—**PROPHYLACTIC.**—As dysentery is spread by water or food contaminated either directly from a patient or human carrier or indirectly by flies, measures similar to those adopted for enteric fever and cholera are indicated. No satisfactory prophylactic vaccine is available. Sulphonamides, by limiting the number of stools and rendering them non-infective, constitute a potent means of controlling epidemics, and by curing the patient they prevent the development of carriers.

**CURATIVE.**—Rest in bed and good nursing are essential. Special attention should be directed to the correct dosage of the particular sulphonamide administered, maintenance of a positive fluid balance to prevent dehydration, regular feeding, the hygiene of the mouth and the prevention of bed-sores.

**Dietary.**—In all cases for the first 24 hours only water is allowed, to which may be added glucose, lactose or cane sugar. Subsequently, albumen or barley water, tea and chicken broth are given, followed by soups, Marmite, orange juice, jelly, biscuits, dry toast, clear honey, whey, Sprulac and apple purée. Later, arrowroot, cornflour, ground rice, sago puddings and, as improvement continues, by eggs, non-fatty fish, chicken, butter, milk drinks, junket and stewed fruit may be taken. Adherence to this type of low residue diet is only necessary in severe cases, especially Shiga infections, in order to rest the bowel; in dysentery of ordinary severity and of non-Shiga type, milk drinks, milk puddings, toast and cereals may be introduced as first additions to the initial diet of clear fluids and jellies once the stools have been reduced to 6 to 10 per day; and proteins are allowed shortly afterwards.

**Specific Chemotherapy.**—Various sulphonamides, including sulphaguanidine, succinylsulphathiazole and sulphadiazine, have been shown to exert specific curative effects in bacillary dysentery. Owing to its poorer absorption, lower toxicity and absence of renal complications, sulphaguanidine (p-amino-N guanylbenezene sulphonamide) has special advantages over most of the other sulphonamides for use in hot climates in dehydrating intestinal diseases like Shiga dysentery and cholera which may be complicated by renal failure and anuria. Crystals of acetyl-sulphaguanidine do appear in the urine, but they are deposited as a soft mush and not in the form of hard renal concretions, as in the case of most other sulphonamides. Once a tentative diagnosis has been made on clinical grounds, specimens of the stool should be obtained and forwarded to the laboratory for a report on the microscopic and cultural findings. Treatment, however, should not be delayed pending the laboratory report for by so doing valuable time is lost.

Sulphaguanidine in acute dysentery is given in a dose of 0.05 g. per kg. 4-hourly for the period during which the number of stools passed exceeds 5 per day, and subsequently a dose of 0.05 g. per kg. every 8 hours until the stools have been normal in number and consistency for 2 days. The duration of treatment should not exceed

12 days, but if necessary the course can be repeated after the lapse of a week. Thus, a patient weighing 11 stone would receive 3.5 g. 4-hourly, and later the same dosage 8-hourly. An initial dose of 0.10 g. per kg. body weight is often given. With Shiga dysentery, if the patient is not treated until the third day or later, it is not uncommon for 150 to 200 g. to be administered over a period of 8 to 12 days.

The response of acute dysentery to sulphaguanidine therapy is remarkable. If the drug be given within a few hours of onset, the attack of dysentery is generally aborted; fever disappears, the diarrhoea and abdominal pain cease in 24 hours and the stools soon become normal. In Shiga cases when treatment is delayed 2 or 3 days or longer, inflammation and destruction of mucous membrane have already resulted. Despite this, the response is generally striking. There is an early feeling of well-being, rapid relief of abdominal pain and a decrease of abdominal symptoms. In uncomplicated cases an early reduction of the temperature and pulse is noted, the normal being reached in most cases in 1 to 3 days. There is also a remarkable reduction in the number of stools, and blood disappears rapidly from the faeces and mucus a few days later. When the treatment of Shiga dysentery commences from the third day to the third week of the disease, normal bowel action can be expected in about 5 to 6 days, and formed stools in about 8 days.

In subacute and chronic cases, in which the bowels are acting some 3 to 8 times daily, the treatment consists of 0.05 to 0.1 g. per kg. every 8 hours for 7 to 10 days. Should this not be effective it will be necessary to repeat the course later or to substitute one of the other sulphonamides for sulphaguanidine.

Full dosage and a complete course of treatment as prescribed for chronic dysentery is the most effective means of eliminating the carrier state.

If colicky pain or tenesmus are severe during the first 24 hours, morphine gr. 1 may be given and repeated next day, but this is rarely necessary. Heat in the form of antiphlogistine or turpentine stupes applied to the abdomen may also be helpful before sulphaguanidine has exerted its maximal beneficial effects. Dehydration should be prevented by administering as much fluid per os as can be comfortably taken. The fluid intake should be sufficient to ensure the secretion of 2 pints of urine daily. When there is severe vomiting or copious fluid stools, intravenous injections of saline (0.85 per cent.) or glucose (5.0 per cent.) solution are administered either intermittently or by continuous drip. Blood transfusion is advisable if the patient is markedly anæmic or intestinal hæmorrhage is severe.

Succinylsulphathiazole (Sulfasuxidine) and phthalylsulphathiazole are other sulphonamides which are being used successfully in the treatment of dysentery, and are said to be more effective than sulphaguanidine in the treatment of Sonne dysentery and in the eradication of *B. dysenteriae* Sonne in carriers. They are poorly absorbed, not more than 5 per cent. being excreted by the kidneys. Like sulphaguanidine, the dosage is considerable, being 0.25 g. per kg. initially and 0.04 g. per kg. 4-hourly thereafter.

Sulphadiazine, in a dosage of 4 grammes daily, is widely advocated in U.S.A. It has the advantage that a smaller dosage of the drug is required, but it is not suitable for use in dehydrated patients in the tropics until the fluid balance has been restored and can be maintained.

Streptomycin has some therapeutic effect but has proved to be inferior to the sulphonamides. It may be useful in the treatment of dysentery caused by sulphonamide-resistant dysenteric organisms.

*Specific Anti-Dysenteric Sera.*—Now that specific drugs are available there is little need for immunological therapeutic reagents.

Refined monovalent anti-dysenteric Shiga serum has a limited field of usefulness in fulminating Shiga infections to control circulating exotoxin while the sulphonamide is exerting its local bacteriostatic action on the bacillus. The daily dosage should not be less than 200,000 I.U. administered intravenously; in fulminating cases

200,000 I.U. may be repeated every 4 to 6 hours. This anti-serum possesses the advantages of rarely, if ever, causing serum sickness or other adverse reactions. Its disadvantage lies in the fact that it is purely anti-toxic and possesses no bacteriostatic or bacteriolytic action on *Sh. shigæ*; for this reason its beneficial effects are only temporary. Polyvalent and multivalent anti-dysenteric sera frequently give rise to serum reactions, and are of very doubtful therapeutic value. No satisfactory anti-sera have yet been produced for the Flexner-Boyd group. Bacteriophage therapy has also proved disappointing. Boyd has recently demonstrated that strains of dysentery bacilli may persist along with their specific bacteriophages in the stools of uncured dysentery patients.

*Sodium or Magnesium Sulphate.*—This was the standard treatment for dysentery before the introduction of specific sulpha drugs. It is now only used if these specific drugs are not available. The initial dose is 2 drachms; subsequently 1 drachm is given 2-hourly for the first 12 to 24 hours, and then 4-hourly, 6-hourly and finally 8-hourly for the next 3 or 4 days or until the stools become feculent. It is inadvisable to continue sulphate therapy longer than 4 or 5 days, as in many cases it merely keeps up the diarrhœa.

*Treatment of complications.*—Intestinal hæmorrhage is best treated by sulphaguanidine, morphine injections and blood transfusions. Surgical intervention is rarely justified. Perforation of the bowel calls for immediate laparotomy; the prognosis is very grave for the bowel wall is generally necrosed. Joint complications do not generally respond to specific therapy and require treatment along general lines.

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## FOOD POISONING

The original use of the term food poisoning was based on a misconception. An alternative was "ptomaine poisoning", the belief being that the symptoms were due to toxic products of protein breakdown formed in the course of bacterial decomposition. It is true that highly toxic substances can be formed in this way, but decomposition is by then so far advanced that the smell and taste of the food would be repulsive. What may have been a minor form of this was common during the War of 1939-1945 following the consumption of "torpedoed meat". This came from ships reaching port with damage to their refrigeration plant; at a time when meat was scarce inspectors were reluctant to condemn cargoes in doubtful condition, and such meat, particularly if made into pies, was the cause of severe afebrile diarrhœa lasting only a few hours. Whether products of decomposition or perhaps the endotoxins of the various non-specific bacteria concerned were responsible for this effect is not certainly known.

On the other hand, most food poisoning is due to the action of specific bacteria or their toxins, and has nothing to do with decomposition. Staphylococcal food poisoning and botulism are produced by pre-formed bacterial exotoxins, and are not infections in the ordinary sense. *Salmonella enteritis*, the commonest form, is simply an infection of the bowel by specific micro-organisms which the food happens to convey. This is really no more food poisoning than are enteric fever or dysentery, which can be conveyed in similar ways.

### ACUTE INFECTIVE ENTERITIS (*SALMONELLA*)

*Ætiology.*—The *Salmonella* group of organisms (named after a bacteriologist: the popular supposition that tinned salmon is apt to contain them is quite erroneous) is almost indistinguishable in general characters and fermentation reactions from the group of paratyphoid bacilli. They can be identified only by agglutination tests, and since each may possess from 1 to 3 O antigens and as many as 6 H antigens,

including those characteristic of its two phases, specific and non-specific, an elaborate investigation is often required. Many of these antigens are common to a large number of species, between which the differences, even in antigenic composition, are small, while in all other ways they are indistinguishable. It is thus perhaps unfortunate that over two hundred of these organisms have been accorded the rank of species and given names, often those of places in which they were first isolated. Other bacteria, notably the hæmolytic streptococcus and the pneumococcus, are divisible into many "types" by the same method, but these are merely denoted by numbers.

Much the commonest of these organisms is *Salm. typhi murium*, formerly known as *B. aertrycke*, and next in frequency of occurrence is *Salm. enteritidis* (Gaertner's bacillus).

**Sources of Infection.**—The source of infection, as in enteric fever, may be a human case or carrier and, if so, the vehicle may be any uncooked food liable to contamination with human intestinal bacteria (milk, ice-cream, confectionery, salads, shell-fish, etc.). But whereas this is always the ultimate source of either enteric fever or dysentery, diseases which occur naturally only in man, the food-poisoning *Salmonellas* are pathogens of various animals, among which the infections they cause are common and widespread: human infections have therefore usually an animal source.

The animals concerned fall into three classes. Cattle, including both oxen and pigs, are susceptible, suffering from an enteritis which, if severe, may be accompanied by septicæmia. "Emergency slaughter" of animals so affected leads to the marketing of meat containing the bacilli owing to their presence in the blood, the numbers of which can increase greatly by post-mortem multiplication. A temperature of only about 55° C. for half an hour is required to kill them, but this is often not reached throughout in cooking sausages and other pork products or in joints of beef: hence the living bacilli are in the meat as consumed. Another possible method of transmission from cattle is by the milk of an infected cow.

Rodents are also susceptible: indeed, commercial "Rat Viruses" are cultures of a *Salmonella*, sometimes said to be non-pathogenic to man and domestic animals, although this claim is disputable. The contamination of food by rat and mouse droppings is thus a possible source. Finally, poultry and eggs may be concerned. Various *Salmonella* infections are common in hens, and several, previously unknown in Great Britain, were conveyed here from America in dried egg imported during the War of 1939-1945. This product was dangerous only if made up with water and left long enough to permit extensive bacterial multiplication before cooking. Duck eggs are exceptional in that not only the shell but the interior of the egg may contain the bacillus, usually *Salm. typhi murium*. A lightly cooked (e.g. poached) duck egg is often found to have been the cause of an isolated case of this infection.

**Pathology.**—The characteristic lesion is an acute catarrh of the entire alimentary tract, least marked in the stomach (a point of distinction from chemical irritant poisoning, such as that caused by arsenic) and increasing in degree towards the lower end of the small intestine. The mucosa is swollen and congested, and there may be small submucous hæmorrhages; the lymphoid follicles and Peyer's patches are prominent owing to acute inflammatory changes. The colon is similarly affected and its contents, which are exclusively fluid, include much mucus. Ulceration does not normally occur, but in elderly or debilitated subjects or those suffering from other diseases, the disease pursues a longer course, and ulceration of Peyer's patches, as in typhoid fever, is commonly found.

Changes elsewhere include the effects of dehydration, some degree of cloudy swelling, particularly in the kidney, and fatty degeneration in the liver. In severe cases accompanied by bacteriæmia, the spleen is congested, enlarged and soft. Post-mortem investigation should include the preparation of cultures from the heart blood, spleen and intestinal contents—the latter only if a positive culture has not been obtained during life.



**Symptoms.**—Most patients wake with definite symptoms on the day following the consumption of the contaminated food, but the onset may be earlier, or may be delayed for 48 hours or rather longer. The severity of the disease varies considerably, and it is in the mildest attacks with a more indefinite onset that the incubation period may appear to be most prolonged. Malaise, headache, fever and nausea are accompanied by colic, which may be very severe and is soon succeeded by diarrhoea with frequent liquid stools containing much mucus and sometimes unaltered bright green bile pigment, a clear indication that hyperactive peristalsis involves the whole of the intestinal tract. Vomiting is common at the onset but does not persist, and is a much less prominent feature than diarrhoea. Dehydration may be extensive enough to occasion some degree of circulatory collapse, the pulse being of very small volume and the extremities cold and blue. When there is an accompanying bacteriæmia, fever is higher and more irregular and rigors may be repeated: a rigor at the onset is common. Another unfavourable sign is extreme restlessness. Skin rashes may occur, usually in the form of erythema and urticaria.

**Diagnosis.**—This may be easily made in the presence of an epidemic, but calls for laboratory verification in any isolated or obscure case. The essential investigation is cultivation of the faeces and the identification in them of the causative organism. The results of blood culture may also be of interest in more severely ill patients. An agglutination test performed with the patient's serum is rarely helpful in the early stages, the appearance of agglutinin in the blood being delayed for several days.

It is important to distinguish between this disease and poisoning by arsenic, antimony and other such chemicals, the features of which may be very similar. Examination of vomit, faeces and urine for these substances at once renders this diagnosis clear.

**Course and Prognosis.**—This disease is very rarely fatal in a young and healthy subject. In the old, or those whose resistance is impaired by other disease, it may continue and come to resemble enteric fever not only in its morbid anatomy, as already noted, but in its clinical features; in such patients the mortality has hitherto been considerable. Normally the fever and diarrhoea abate within 3 days, and recovery thereafter is uninterrupted.

**Treatment.**—General measures include rest in bed, and the withholding of food other than water or glucose solution until the more acute symptoms subside. Severe colic at the onset may be an indication for pethidine or, exceptionally, morphine. Dehydration owing to fluid loss may call for intravenous replacement, preferably in the form of glucose saline.

This infection is now also amenable to specific treatment. The sulphonamides of low solubility (e.g. succinylsulphathiazole) have some effect, as has streptomycin given by the mouth, but the most effective drug is chloramphenicol. Whether this antibiotic, the use of which is not entirely free from risk, should be given to patients in whom the outlook causes no sort of anxiety, is a matter for individual decision, bearing in mind that in the healthy subject this is a self-limited disease of very short duration. On the other hand, if bacteriæmia exists or is suspected, or if the prognosis is unfavourable for any of the reasons already mentioned, chloramphenicol is definitely indicated: 500 mg. should be given, at first at 4-hour and later at 6-hour intervals until fever and other symptoms abate.

The stools should be examined repeatedly during convalescence to determine that the patient is not remaining a carrier.

#### TOXIC SALMONELLA ENTERITIS

If organisms of the *Salmonella* group have multiplied extensively in food and have subsequently been killed by cooking, the food will nevertheless cause a condition similar to that already described. These organisms possess an endotoxin which is

heat-stable and is the main cause of the inflammatory reaction in the alimentary mucosa: hence if sufficient numbers are present the immediate effect is the same as that following the multiplication of the living organism.

This variety of food poisoning is distinguished by a much more rapid and often more sudden onset. Colic and diarrhoea begin within 2 to 6 hours of the consumption of the contaminated food. This is a useful point of distinction from infection by the living organism, which is not usually apparent until the following day unless very large numbers have been ingested. On the other hand, the two conditions may be combined, dead organisms initiating the attack early and a few living ones multiplying to continue it: such a mode of infection may account for incubation periods of intermediate length. An early onset certainly does not exclude the possibility of living infection, and the stools should always be examined.

The typical attack due solely to dead bacteria in the food is not only of more rapid onset but is also, as would be expected from the fact that the cause is not a continuing one, of shorter duration. Fever is slight or absent and although dehydration may be dangerous in the elderly, the prognosis is better. Diagnosis and the identification of the cause may be difficult or impossible: cultures are of course negative and agglutinin formation is slight or absent. Cultivation of the suspected food, which, when this is available, should always confirm the source of the living infection, is also unhelpful, although its injection into animals will sometimes cause the formation of specific agglutinins and thus betray the presence and identity of the organism despite its being dead.

#### STAPHYLOCOCCAL FOOD POISONING

This recently recognised form of food poisoning is more entitled to be so described, since a bacterial poison or toxin is its sole cause.

**Ætiology.**—Some strains of *Staphylococcus pyogenes aureus*, in addition to the various toxins which operate when they cause boils and carbuncles, osteomyelitis and pyæmia, etc., form an *enterotoxin*. This is liberated during their growth in food-stuffs: these may be either milk, ice-cream or cheese, or—as in several recent extensive outbreaks—meat. Such meat has usually been handled (literally) by a cook or factory employee who either has a staphylococcal infection of a finger or carries staphylococci in his nose, whence they can be transmitted by the air or manually to any material with which he works. The operation of preparing cold meats such as pressed beef, as ordinarily carried out, involves extensive handling. The staphylococci then multiply either in the meat itself or in the jelly or “glaze” surrounding it. Four simultaneous outbreaks in the summer of 1948, one involving passengers in the *Flying Scotsman*, the others in London and towns in eastern and southern counties, were all traced to an establishment where meat was so prepared. Both operatives engaged in this work were carriers of staphylococci proved by phage typing to be identical with those recovered from samples of incriminated meat and from the vomit of affected persons.

**Symptoms.**—Vomiting, which may be frequent and prostrating, begins within 2 to 4 hours of consuming the responsible food. There is also usually diarrhoea, but this is a less prominent feature than the vomiting, and fever is absent. The condition is thus quite distinct from *Salmonella* infection or intoxication. Recovery begins within 24 hours and only symptomatic treatment is possible or necessary.

**Diagnosis.**—The occurrence of severe vomiting in a group of people who have all partaken of the same meal a few hours before is strongly suggestive of this diagnosis. Its verification depends on the fact that very large numbers of staphylococci are present in the food: they can be cultivated from it and from the vomit of sufferers. The mere presence of large numbers of pathogenic staphylococci is almost certain proof of the nature of the condition, and their identification by phage typing as belonging to a type known to form enterotoxin may be taken as settling the matter.

Direct proof that an individual strain forms enterotoxin has hitherto demanded tests in human volunteers or monkeys, although a less satisfactory one can be done in kittens, but there is recent evidence that an *in vitro* test depending on the contraction produced in a strip of animal intestine may serve instead.

### BOTULISM

This fortunately rare and frequently fatal form of food poisoning is also caused by a pre-formed bacterial exotoxin, with the important difference that the toxin is absorbed and acts elsewhere in the body. In this feature the disease is unique; no other bacterial toxin can be absorbed from the alimentary tract, although others act there locally.

**Ætiology.**—The responsible organism is *Clostridium botulinum*, an anaerobic spore-forming Gram-positive bacillus belonging to the same genus as the species causing tetanus and gas gangrene. Such organisms are widely distributed in soil, and the presence of some of them there is attributed to manuring, since they also occur in the faeces of animals, including man. On the other hand, some at least must be regarded as primarily soil inhabitants and occurring only accidentally in the mammalian alimentary tract. This seems particularly true of *Cl. botulinum*, since it is rarely demonstrable in faeces and occurs in virgin soil from remote areas as well as that from cultivated land. Its presence has been demonstrated in samples of soil from various part of England as well as the United States and other countries, and in view of this wide distribution the rarity of the disease is at first sight surprising. Two types, designated A and B, the former being much commoner, and producing different toxins, cause human botulism: several other types exist which cause similar diseases in animals.

Growth of *Cl. botulinum* is only possible under anaerobic conditions—i.e., in the complete or almost complete absence of oxygen. These conditions are attained when food is canned or bottled: they may also exist in the interior of a mass of meat, such as a ham. Commercial canned and bottled products are subjected to temperatures which destroy even the spores of Clostridia; home canning is a less safe procedure and its prevalence in the United States accounts for the greater frequency of botulism in that country than in ours. If many spores of *Cl. botulinum* are present (small numbers are less likely to germinate) and survive the heat treatment applied they will subsequently multiply and during their growth the exotoxin is formed. The food may be meat, fish or vegetable (commonly string beans, peas, corn and spinach have also been affected); fruits, the juice of which is acid, do not usually permit growth. "Spoilage", i.e. alterations in colour, consistency, smell and taste ending in frank putrefaction, will eventually result, and it seems that the rarity of botulism may be due in part to the fact that only a short period may elapse between the beginning of toxin formation and the development of changes which should at least excite suspicion if they do not render the food quite unpalatable.

The toxin of *Cl. botulinum* is by far the most powerful poison known: 1 gramme of it would furnish a lethal dose for many millions of people. It is a protein, and readily de-natured by heat; hence food containing it can be rendered innocuous by re-cooking. It is absorbed from the alimentary tract and exerts its effects on the nervous system.

**Symptoms.**—The onset may be early on the day following the responsible meal or delayed for up to 48 hours. Vomiting is inconstant, but commoner when the onset is earlier and hence the amount of toxin swallowed presumably larger. Diarrhoea is also inconstant and never pronounced or persistent: constipation is more common. The earliest characteristic symptoms are diplopia and unsteadiness on standing: these are accompanied by fatigue, dizziness and muscular weakness. There is no fever and little or no headache. What follows is the result of the paralysis first

of the motor cranial nerves: no sensory changes occur. All the ocular muscles are affected, complete ptosis depriving the patient of sight: the tongue cannot be protruded and the power of speech and of swallowing are eventually lost. Paralysis may then extend to the diaphragm and intercostal muscles, the dorsal muscles of the neck and the arms. Full consciousness is retained, and the plight of a patient struggling for breath and unable to see, speak or swallow, is described as pitiable. Death may occur after as long as 7 days, or may result apparently from cardiac failure within 24 hours before difficulty in respiration has developed. The mortality in different outbreaks has varied, but is always high and sometimes 100 per cent.

**Treatment.**—The only specific measure is the administration of antitoxin, which should be polyvalent (*i.e.* containing antitoxins for both types, A and B). Since the Loch Maree disaster of August 1922, when all 8 members of a fishing party provided with sandwiches made of potted wild duck paste died of botulism, stocks of this antitoxin have been maintained at centres in different parts of the British Isles. Only one small outbreak and one other isolated case have been recognised since then: hence there has been little opportunity to use the antitoxin, and such use as has been made was ineffectual. It is an axiom that antitoxins, although fully effective in prevention, are effective in treatment only if given early, before toxin has done irreparable damage. The likelihood of early administration in so unfamiliar a disease is small.

The supposed value of giving alcohol to de-nature unabsorbed toxin is doubtful. Morphine is indicated for the relief of distress and is also said to delay the progress of the disease. In protracted cases fluid should if necessary be supplied rectally or intravenously. A respirator should be used if paralysis of respiratory muscles develops, but it is doubtful whether recovery is possible after this stage.

#### CL. WELCHII FOOD POISONING

It has recently been recognised that *Clostridium welchii*, strains of which are the commonest cause of gas gangrene, can also cause food poisoning, apparently of two forms. Both are due to types of this organism which are exceptionally resistant to heat. The spores of *Cl. welchii* are in general much less heat-resistant than those of other species, and are destroyed by boiling or steaming for 10 minutes: the food-poisoning types are not, and can thus be easily recovered from food or faeces steamed for 1 hour.

The mild form, of which there have been many outbreaks in recent years, has invariably been caused by meat or meat preparations which have been cooked, allowed to cool slowly and not refrigerated, and eaten a day or more later. This practice was less common before the war, as was the provision of meals in canteens, where the occurrence of food poisoning is much more likely to be recognised and investigated than in the home. The growth of the organism, which is a feebly toxigenic and otherwise atypical Type A, usually causes no detectable change in the meat. The results of its consumption are simply colic and diarrhoea, without vomiting or headache, beginning 8 to 20 hours after consumption and lasting no more than a day.

The other form, which is severe and often fatal, has been described chiefly in Germany, produced in some cases by home-canned meat such as rabbit, and is known as enteritis necroticans. It is a diffuse enteritis involving especially the jejunum but also the ileum and colon, in which acute inflammatory changes with marked oedema of the mucosa are followed by necrosis of its superficial layers and hence the formation of sloughs. The onset is abrupt, with severe pain, some abdominal rigidity, vomiting and profuse diarrhoea leading to dehydration and circulatory collapse. The mortality is high. The responsible organism is *Cl. welchii* of type F, forming a large amount of  $\beta$ -toxin.

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## UNDULANT FEVER OR BRUCELLOSIS

**Synonyms.**—Malta or Mediterranean Fever; Abortus Fever; Brucellosis.

**Definition.**—An endemic or epidemic disease characterised clinically by prolonged fever with a tendency to long wavy relapses, splenomegaly, transient painful swellings of the joints, neuralgia and secondary anæmia. In Malta *Brucella melitensis*, conveyed in goats' milk, proved the causative organism, but indistinguishable diseases of widespread geographical distribution may be caused by the bovine and porcine strains of *Br. abortus*.

**Ætiology.**—Undulant fever of caprine origin is endemic in the Mediterranean basin, and has a widespread geographical distribution. The indigenous population sometimes appears to have a certain immunity to the disease as in Malta, where the Maltese, prior to the boiling of goats' milk by the garrison, were less affected than English soldiers and sailors. All ages and both sexes appear equally susceptible, and in Malta, at least, the disease proved more prevalent in the dry summer months.

Bruce, in 1886, isolated *Br. melitensis* from cases of undulant fever and experimentally reproduced the disease in monkeys. Eighteen years later it was proved that infection was conveyed in goats' milk. The organism causes a bacteriæmia and may be isolated from the blood, bile, fæces, urine and milk. Primarily it is a disease of goats which, while themselves showing few symptoms, may yield a good quality milk containing large numbers of *Br. melitensis*. Other varieties include the bovine and porcine strains of *Br. abortus*, and are only distinguishable by agglutinin-absorption tests. The latter organism, which infects the chorionic cells, causes contagious abortion of swine and cattle, and produces a disease in man indistinguishable from undulant fever; it has been reported from the United States, Europe, Southern Rhodesia, South Africa, etc., is of bovine or porcine origin, and is contracted from cow's milk or contact with carcasses, infected animals or their excreta.

**Pathology.**—The disease is essentially a bacteriæmia and organisms may be isolated from the blood, spleen and lymph glands at necropsy. The spleen is constantly enlarged, averaging about 20 oz. in weight. Sometimes the mesenteric glands appear swollen, but there is no ulceration of Peyer's patches. The liver, kidneys and pulmonary bases show congestion, and occasionally broncho-pneumonia and glomerulo-nephritis are found.

**Symptoms.**—The incubation period is about 14 days, but may last a longer or shorter period. Monkeys develop fever 5 days after subcutaneous inoculation, and 15 days after ingestion of infected material. Five clinical varieties are recognised: (1) Ambulatory; (2) Undulant; (3) Intermittent; (4) Continuous; and (5) Malignant.

(1) **AMBULATORY OR MILD.**—In some cases the symptoms are so slight that infected persons go on with their work as usual; in others there are slight fever and minor symptoms which disappear rapidly, serum tests alone indicating infection. Out of 525 dock hands examined by Shaw in Malta, 79 gave positive agglutinin reactions, whilst 9 out of 22 of those specially tested showed the organism either in the blood or urine or both. Such cases constitute human carriers.

(2) **UNDULANT OR ORDINARY.**—The onset is generally insidious like typhoid, and the symptoms often resemble those seen in other fevers, but the temperature chart is characteristic. Bouts of fever lasting 2 or 3 weeks alternate with periods of remission, so producing the typical undulant fever chart. Illness in the ordinary case lasts 3 to 4 months, the extremes being 3 weeks to 2 years. The fever is often associated with profuse sweating, lassitude, secondary anæmia, debility and transient painful swelling of the joints resembling rheumatic fever, but not responding to salicylates. Enlargement and tenderness of the spleen and liver also occur, and neuralgic pains, especially involving the intercostal and sciatic nerve, are common. The tongue frequently has a central white fur, and anorexia, flatulence, abdominal discomfort

and constipation are often troublesome features. The leucocyte count is generally normal, but there is a relative lymphocytosis; the urine may contain albumin. After running a more or less chronic course, the remissions become more prolonged, the febrile exacerbations less high, and recovery gradually ensues. No patient should be regarded as convalescent, however, until the temperature and pulse have been normal for at least a fortnight and all other symptoms have disappeared. Neuritis, debility and anæmia may persist for a considerable period.

(3) **INTERMITTENT TYPE.**—There is a swinging temperature resembling benign tertian malaria, a normal morning temperature being succeeded by a sudden afternoon rise to 105° F. or higher, accompanied by chilliness and a definite rigor; by evening the temperature falls again with drenching sweats. The condition is differentiated from malaria by the absence of parasites.

(4) **CONTINUOUS TYPE.**—Here there is continuous fever for a period of from 1 to 3 months.

(5) **MALIGNANT TYPE.**—The patient is attacked suddenly with high fever, severe generalised pains, diarrhoea and vomiting. Broncho-pneumonia, cardiac weakness and a typhoidal state frequently develop, while hyperpyrexia may precede death.

**Complications.**—These include bronchitis, broncho-pneumonia, neuritis, parotitis, orchitis in the male and mastitis in the female. Purpura and suppurative osteitis have also been described. Menorrhagia, abortion or premature labour may also result.

**Diagnosis.**—The differential diagnosis includes the enteric fevers, acute rheumatism, malaria, kala-azar, tuberculosis, subacute bacterial endocarditis, thoracic lymphadenoma associated with the Pel-Ebstein syndrome, amœbic abscess of the liver and occult pyogenic infections. Macroscopic agglutination reactions are of great diagnostic value after the first fortnight of fever, the serum being tested in an ascending series of dilutions (1/25–1/1000) against dead *Brucella* suspensions. Absorption of agglutinin may be necessary to distinguish infections with *Br. melitensis* and *Br. abortus* respectively. Blood culture in liver infusion broth is often positive for *Br. melitensis*, and the period of examination should extend over a fortnight before reporting the result as negative. *Br. abortus* is best grown in an atmosphere of 10 per cent. carbon dioxide or, better still, 1 ml. of suspected blood is inoculated into the peritoneal cavity of a guinea-pig, culture from the peritoneal cavity being generally positive in about a week and from the spleen at a later date. Burnet's intradermal test is frequently positive; it is characterised by the development of localised redness and œdema some 6 hours after inoculation, the reaction lasting 1 to 2 days.

**Prognosis.**—Mortality rates of from 2 to 9 per cent. have been recorded. Death generally results in malignant cases during the first 3 weeks of fever. At any time, however, fatal recrudescence may occur, a typhoidal state, broncho-pneumonia, cardiac failure and hyperpyrexia being grave signs. Chronic cases may present great debility, emaciation, anæmia and neuritis.

**Treatment.**—**PROPHYLACTIC.**—Laboratory workers should be very careful in handling *Brucella* cultures for, as in tularemia, infection is easily acquired. Adequate boiling of goats' milk renders it safe, but its prohibition in endemic centres and the destruction of infected animals are more effective. Cream and cheese may also convey infection. In the case of *Br. abortus* the disease may arise from cows' milk or the carcasses or excreta of bovines and porcines.

**CURATIVE.**—Careful nursing and a nourishing dietary which should include milk puddings, eggs, fish, fruit juice, yeast and other vitamin-containing foods, are desirable. Cool sponging is indicated whenever the temperature exceeds 103° F. Specific therapy is still under trial. Autogenous vaccines, "brucellin", anti-undulant fever serum and immune-transfusion of compatible blood from a recovered case are all of doubtful value. A course of sulphonamide terminates the fever in some cases, but recurrences are frequent. Recently the administration of small doses of sulphadiazine

er sulphamerazine combined with blood transfusion has been advocated. Cures are recorded following T.A.B. vaccine intravenously, commencing with 50 millions and working up to 250 millions, injections being given every fourth day. Promising results are now being reported following combined treatment with a full course of sulphadiazine and streptomycin. The course lasts for 10 days, 2.0 g. of streptomycin being given in divided doses each day. Penicillin is ineffective. The best antibiotic seems to be chlortetracycline given in doses of 0.5 g. 6-hourly for 10 days. This treatment quickly arrests the clinical attack but is likely to be followed by relapses, which require repetition of treatment.

Various symptoms and complications, such as sleeplessness, headache, arthritis and orchitis, should be treated as they arise.

## PLAGUE

**Synonyms.**—Oriental Plague; Pest; Black Death.

**Definition.**—Plague is primarily a disease of rodents caused by the *Pasteurella pestis*. Transmitted to man by rat fleas, it runs a rapid course with high fever, and marked tendency to septicæmia and tender enlargement of lymphatic glands. More rarely a pneumonic form develops.

**Ætiology.**—Plague may occur anywhere; it is more common in subtropical regions, but towards the equator tends to die out. High temperatures and a dry atmosphere or high saturation deficiency reduce its incidence in the hot weather in India by killing the flea vector. It spread from Hong Kong to India, Egypt and Japan in 1896, and three years later to the Philippines and South America. People of any race, age or sex are susceptible. The plague bacillus, *Pasteurella pestis*, was isolated by Kitasato and Yersin in 1894. It is readily cultured, and is a short, Gram-negative rod showing bipolar staining. Guinea-pigs and other laboratory animals are susceptible. Rat fleas, especially *Xenopsylla cheopis*, which have fed on the blood of infected rodents such as the large grey rat (*Rattus norvegicus*) and the smaller black rat (*Rattus rattus*), desert these animals after death and inoculate man by regurgitating *P. pestis* during the act of biting and sucking blood. Epizootics in rats invariably precede human epidemics, and an extension of plague to man can be accurately foretold 2 or 3 weeks beforehand from a rising curve of infection in the rat population. Pneumonic plague, on the other hand, is intensely infectious, being directly transmitted by droplet spray infection from person to person. Doctors and nurses often acquired the disease during the Manchurian epidemic.

**Pathology.**—At the site of entrance, especially in resistant cases, plague bacilli may occasionally produce a primary vesicle. Generally the adjacent chain of lymph glands are acutely inflamed (primary bubo) while others are secondarily involved. Frequently bacilli enter the circulation, producing various degrees of septicæmia and in the most fulminating cases primary buboes may be absent altogether. The toxic substances elaborated by *P. pestis* also affect the endothelial lining of the blood vessels, giving rise to congestion and hæmorrhage in the mucous and serous membranes and skin, while the cardiac muscle shows fatty degeneration and the right heart is dilated. On section the primary bubo shows intense congestion and hæmorrhage, with periglandular, gelatinous and hæmorrhagic œdema matting adjacent glands together. More distant glands, secondarily implicated, are congested and greyish red in colour. Bacilli are numerous in the early stages and also often occur in the spleen and blood. The liver and kidneys are congested, showing cloudy swelling and fatty change, and fibrinous thrombi may be present in the Malpighian tufts. The spleen, which is two or three times its normal size, is hyperæmic and often hæmorrhagic. The meninges are very congested and hæmorrhages may occur in the brain. Pneumonic plague starts as a broncho-pneumonia, but later may involve the

entire lobe; pleural ecchymoses, congestion of the bronchial tree and involvement of the bronchial glands are characteristic.

**Symptoms.**—The incubation period varies from 2 to 12 days, generally being 3 to 4 days. In severer infections there is a marked tendency towards septicæmia and in the types of *pestis major* a sudden onset with chill or rigors, irregular high fever, nausea, vomiting, cardiac weakness and great mental prostration is characteristic. Splenomegaly and also hæmorrhagic rashes may occur, hence the ancient synonym "black death". Nine clinical types have been described.

(1) **BUBONIC.**—Prodromata include backache, pains in the limbs, and mental depression, but generally the onset is abrupt and the constitutional features severe. The blurred speech, reeling gait and mental dullness may suggest alcoholic intoxication. Examination reveals fever, injected conjunctivæ, rapid soft pulse; the urine contains albumin and the blood count shows a moderate leucocytosis. On the second or third day a tender primary bubo appears, the affected group of glands (femoral and inguinal=70 per cent.; axillary=20 per cent.; submaxillary and cervical=10 per cent.) rapidly swelling to the size of a hen's egg or larger. Pain is severe and suppuration generally occurs during the second week. Death usually eventuates between the third and fifth day; with recovery the symptoms gradually ameliorate, but convalescence tends to be protracted. Secondary broncho-pneumonia may occur, and the sequelæ include sepsis, carbuncles, etc.

(2) **SEPTICÆMIC.**—The disease is rapidly fatal; there may be splenomegaly and slight general enlargement of lymphatic glands, but no bubo. Frontal headache, fever and vomiting are characteristic, but in the severest cases there may be only a slight rise of temperature. Cutaneous petechiæ and melæna may be noted. The diagnosis is made by a positive blood culture.

(3) **PNEUMONIC.**—Chill and a rapid rise of temperature occur at onset, followed by headache, dizziness, pains in the limbs, clouding of consciousness, pain and tightness in the chest, with cough and expectoration of a copious, sanguineous, watery sputum teeming with plague bacilli. Dyspnœa with cyanosis, crepitations and possibly areas of diminished resonance are found. Cardiac failure is common and death almost invariably occurs within 4 days.

(4) **INTESTINAL.**—A rare form, described by Wilm in the Hong Kong epidemic of 1896, as an intestinal disorder with vomiting, incessant purging and liquid, offensive, bile-stained stools often mixed with blood. Buboes were absent, but pathological lesions were present in the intestine.

(5) **CEREBRAL.**—In this type, which may resemble cerebral malaria, the mental hebetude characteristic of ordinary bubonic plague progresses to delirium, convulsions and coma. Definite plague meningitis has also been recorded, and may run a chronic course.

(6) **CELLULO-CUTANEOUS.**—Carbuncles appear having a necrosed and ulcerated centre, with a hard edge surrounded by a red areola, sometimes covered with minute vesicles. The condition is distinguished from coccal carbuncle by the demonstration of *P. pestis*.

(7) **VESICULAR OR VARIOLOID.**—In this form the vesicles and pustules may be so abundant as to simulate varicella. *P. pestis* is readily isolated from the vesicles.

(8) **ANGINAL OR TONSILLAR.**—Cervical buboes may implicate the tonsils, or violent plague tonsillitis and pharyngitis, with secondary cervical adenitis, may arise from killing vermin with the teeth—a habit of Indians in Ecuador.

(9) **ABORTIVE OR AMBULATORY (*Pestis minor*).**—Such cases are common in all epidemics: buboes develop and may suppurate or be absorbed without serious indisposition or fever, or the lymph glands may simply swell and become painful, associated with transient headache.

**Complications.**—Acute bubonic cases may develop plague septicæmia or pneumonia with fatal results, or after the fever has disappeared the local buboes may



become indolent and take many weeks to heal. Broncho-pneumonia and septic complications such as subcutaneous abscesses, cellulitis, adenitis and parotitis sometimes ensue.

**Diagnosis.**—Bubonic plague early in an epidemic may need to be differentiated from climatic bubo, chancroid or syphilitic buboes, rat-bite fever and possibly tularaemia. Gland puncture reveals bipolar bacilli on culture or in smears, the crucial test being transmission of plague to the white rat by smearing infective material on its skin. In pneumonic plague herpes is absent and the sputum is sanguinolent and watery, not viscid and rusty as in pneumonia: furthermore it is teeming with plague bacilli. Septicæmic plague is diagnosable only by positive hæmo-culture.

**Prognosis.**—Pneumonic and pure septicæmic plague have in the past been practically always fatal. In bubonic plague the mortality rate was much higher in natives (75 to 80 per cent.) than in Europeans (25 to 30 per cent.) and axillary buboes were less favourable than inguinal ones. Positive hæmo-culture is of serious significance, and Liston showed that where the bacilli exceed 40 per 1 ml. of blood, death almost invariably resulted.

Modern chemotherapy is very effective in all forms of plague, including pneumonic.

**Treatment.**—**PROPHYLACTIC.**—*This consists essentially in the destruction of rats and fleas, in preventing their coming into contact with man, and in increasing individual resistance by Haffkine's prophylactic vaccine, which gives an immunity lasting 6 to 12 months or more. The building of ratproof houses and grain stores, rat destruction by poisoning and trapping, fumigation of ships with sulphur dioxide and hydrocyanic gas, and evacuation of infected villages and houses during epidemics are all important measures in controlling the spread of plague. Fleas are killed by a dust containing 10 per cent. of D.D.T.; this is best applied to rat runs by a pressure sprayer.*

Overalls, masks, caps and gloves should be worn by those dealing with plague cases. D.D.T. impregnated clothing reduces the risk of flea bite.

Contacts of pneumonic cases should be isolated and watched. Successful chemoprophylaxis has recently been achieved. Adults who have been in intimate contact with cases receive 6 g. sulphadiazine daily for 3 days to 1 week after contact; others may be given 3 g. daily for the same period. Contacts of bubonic cases should also receive chemoprophylactic treatment.

**CURATIVE.**—Bed rest, liquid diet and careful nursing are essential. The buboes should be treated by hot fomentations, kaolin poultice or belladonna and glycerin applications with incision if suppuration occurs. Morphine may be necessary for the pain. Stimulants and cardiac tonics should be used early, and intravenous injections of dextrose are of value. Specific treatment, with large doses of antiplague serum intravenously during the first 2 days has reduced the mortality. Favourable results ensue from treatment with sulphonamides, particularly sulphamerazine, sulphadiazine and sulphathiazole. Examples of dosage régimes are: *sulphadiazine* orally, 4.0 g. immediately; 2.0 g. after 4 hours; 1.0 g. every 4 hours until temperature has been normal for 2 days. Some workers recommend continuing a dose of 0.5 g. 4-hourly for up to 10 days. *Sulphamerazine* intravenously, 2.5 g. in 50 ml. of 5 per cent. glucose solution at 8-hourly intervals for three doses, followed by two further injections containing 1.5 g. each at 8-hourly intervals and then 1.0 g. orally every 8 hours. When sulphonamides are given, abundant fluids are administered, the urine is kept alkaline by the oral administration of bicarbonate of soda and citrates, and a careful record is kept of the urinary output during each 24 hours; this should not be permitted to fall below 50 oz.

Streptomycin is effective alone or in combination with one of the above sulphonamides. The following régimes have been used successfully:

(a) *Streptomycin* intramuscularly, 0.66 g. immediately; 0.33 g. every 4 hours night and day until the temperature has been normal for 1 or 2 days. Very severe

cases may be given 0.66 g. 4-hourly until the temperature has been normal for 2 days.

(b) *Streptomycin* intramuscularly, 0.25 g. to 1.0 g. every 4 hours until temperature is normal. *Sulphadiazine* given orally concurrently, 4.0 g. immediately; 2.0 g. 4 hours later; 1.0 g. every 4 hours subsequently until the temperature has been normal for 2 days.

Pruritus and urticaria may occasionally complicate streptomycin injections, but serious toxic effects have not been described.

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## TULARÆMIA

**Synonyms.**—Deer-fly Fever; Pahvant Valley Fever; Ohara's Disease.

**Definition.**—A plague-like general infection of small rodents, hitherto confined to the United States, Japan and a district in Siberia; also recently in Norway, communicable to man. The disease has the peculiarity, in which it resembles Malta fever, of being extremely infective to laboratory workers handling the causative organism, *Brucella tularensis*.

**Ætiology.**—In 1911 M'Coy, during plague work among ground squirrels in California, discovered a plague-like disease not due to *Pasteurella pestis*, and in 1912 M'Coy and Chapin isolated the specific organism from the blood of infected animals, and it was named *Bacterium tularensis*. Subsequently the organism was found in various rodents, and endemic centres of the infection have been recognised in many areas of North America. The first human case of infection appears to have been reported by Pearce in 1910, but bacteriological proof connecting it with *Br. tularensis* was provided by Francis subsequently. Where the infection is endemic among rodents, human cases are not uncommon, and possibly some have recovered unrecognised. The infection is conveyed from animal to animal by various blood-sucking parasites. The faces of infected bugs have been shown to be infective. Polluted water has recently been thought to be a source of infection in Norway and U.S.A. There is thus no difficulty in understanding how endemic centres of infection are kept up, and human infections in the field are readily understood. But it is difficult to explain the cases of infection in laboratory workers. It is suggested that a possibility is respiratory infection during the anæsthetising of experimental animals, when coughing is not uncommon, and the bacillus is certainly contained in bronchial secretions, as well as the excreta generally. The question appears to be parallel to the difficulty of explaining the great liability to laboratory infections with *Br. melitensis*.

*Br. tularensis* is a minute, Gram-negative cocco-bacillus, measuring, according to M'Coy and Chapin,  $0.3\mu$ , with a breadth of  $0.2\mu$ . It is not easily stained by the ordinary dyes, unless a mordant, such as carbolic acid or aniline, is added. It is refractory to growth on ordinary media, the original cultures being obtained on a medium composed of egg-yolk. It will grow readily on serum glucose agar if a piece of rabbit spleen be added thereto.

**Pathology.**—In animals, nothing characteristic is found. At the site of inoculation some diffuse necrosis may be seen, and occasionally swelling of the corresponding lymph nodes. The spleen, liver, lungs and kidneys may show small necrotic areas. Human cases contracted in the field, probably from some blood-sucking fly, will show a local ulceration at the site of the bite, with swelling, and possibly suppuration, of the local lymph nodes. Cases contracted in the laboratory provide no pathological data, for there is no evidence of the portal of infection, and the blood shows no characteristic changes.

**Symptoms.**—The infection expresses itself in two ways: (1) Dealers in rabbits may develop a necrotic papule, which is followed by acute lymphadenitis in the area affected. Suppuration may occur, with considerable pyrexia and toxæmia. (2)

Laboratory workers studying the infecting agent have suddenly developed pyrexia, with marked malaise and often evidence of pneumonia or pleurisy. The temperature subsided at the end of 3 weeks. The marked features of the majority of the cases were the malaise, the recurrent nature of the fever and the prolonged inability to work. Neuroglandular, oculoglandular, glandular and typhoid forms of the disease have been described.

**Diagnosis.**—In endemic areas, people handling rabbits and other rodents, who develop fever, with or without localising signs of insect bites, should be under suspicion. In this country, only laboratory workers are likely to be infected. In either case, the diagnosis depends upon specific agglutination of *Br. tularensis* antigen. Very definite agglutinations were noted towards the end of the second week after the commencement of the disease, and the titre rose rapidly and remained high during the long convalescence. *Br. tularensis* can usually be obtained by inoculating rabbits or guinea-pigs intraperitoneally with 1 or 2 ml. of blood or other infected material.

**Prognosis.**—The mortality rate varies with the clinical type of infection from about 4 per cent. in the ulceroglandular form to 50 per cent. in the typhoid variety. These figures date from before the introduction of streptomycin and chlortetracycline.

**Treatment.**—Various antitularæmic sera have been employed with doubtful results, but the use of streptomycin and more recently of chlortetracycline has completely altered the outlook in this disease. Administration of either of these antibiotics is followed by rapid subsidence of fever, disappearance of constitutional symptoms and recovery.

## GLANDERS

**Definition.**—An infectious disease, occurring not infrequently in the horse and in the ass, occasionally transmitted to man, and characterised by the formation of granulomatous nodules in the nose (glanders), and in the subcutaneous tissues (farcy).

**Ætiology.**—The bacillus of glanders, or *Pfeifferella mallei*, is a short rod, straight or slightly bent, of 3 to 4 $\mu$  in length by 0.5 to 0.75 $\mu$  in thickness. It is non-motile, and possesses no flagella, nor does it form spores. It can be cultivated on ordinary media at 37° C., but gives a more characteristic growth on potato.

The bacillus stains somewhat faintly with the usual aniline dyes, so that a mordant, such as carbolic acid, is usually employed, but even when deeply stained there is a tendency to decolorise rapidly. The staining is markedly irregular, this irregularity being a diagnostically helpful point. It is Gram-negative.

**Pathology.**—The disease chiefly affects horses, mules and asses—the latter being the most susceptible. Horned cattle are immune, but goats and sheep are occasionally infected.

In the horse, infection may take place through any abrasion of the skin, but most frequently through abrasion of the nasal mucous membrane from infected water-troughs or feeding-mangers. The infection may be acute or chronic. In the acute form (glanders proper) there is fever and prostration, and in 2 or 3 days there occurs ulceration of the nasal mucosa with a sero-purulent discharge, leading on to involvement of the lungs, and death within a few weeks. In the chronic form—farcy—there is involvement of the lymphatic system associated with the original site of entry. The lymph vessels become enlarged—farcy pipes—and irregular thickenings—farcy buds—occur, which may soften and suppurate.

The disease may be latent, and can then only be diagnosed by the "mallein" test. In the human being the infection is generally derived directly from the horse, and is therefore usually confined to those in close connection with horses; but the disease has been contracted in the laboratory.

The toxin of *Pf. mallei* or mallein is an endotoxin, being derived from the bacterial

bodies, in which respect it differs markedly from the toxins of tetanus and diphtheria bacilli. One of its chief characteristics is its resistance, it being capable of withstanding temperatures of 120° C. and prolonged storage with but little loss of strength. It is prepared by growing cultures in glycerin broth for 3 or 4 weeks, and sterilising these by boiling or autoclaving at 115° C. The cultures are then allowed to stand, and the supernatant fluid being decanted off, this is then filtered through a Chamberland filter. The resultant filtrate, to which one-half of 1 per cent. of carbolic acid is added, constitutes *mallein*. It contains the soluble portions of the bacteria, and substances from the altered medium, and is a similar product to tuberculin. It is used in doses of 1 ml. to detect a glanders infection in the horse. As the reaction in a "glandered" animal is severe, both locally and constitutionally, it is unsuitable for use in man.

**FORMS OF THE DISEASE.**—Both glanders and farcy have been known to occur in man in acute and in chronic forms. All forms are rare.

**Symptoms.**—1. **ACUTE GLANDERS.**—The incubation period varies, but is in most cases 4 days. At the site of infection in the nose there occurs an inflammatory swelling surrounded by œdema and lymphangitis, with a papular eruption soon becoming pustular. In a few days other and similar swellings appear, which soften and ulcerate, so that the mucosa of the nose becomes generally infected, leading to profuse mucopurulent discharge. The whole nose swells, sometimes considerably. The ulceration extends deeply so as to involve the cartilage and bone. The cervical lymph nodes are usually enlarged and may soften, forming abscesses. Constitutional symptoms are present by this time, and death, usually with pneumonia, occurs about the middle of the second week.

2. **CHRONIC GLANDERS.**—This form resembles closely the disease as seen in the horse. There is a chronic profuse coryza, associated with widely scattered muscular and subcutaneous nodules. Unless the nature of the disease is suspected, it may go undiagnosed for some time.

3. **ACUTE FARCY.**—This is the form of the disease resulting from accidental inoculation of the skin. A local lesion of a highly inflammatory kind leads quickly to a spreading zone of lymphangitis, subcutaneous nodules (farcy buds) appearing in the track of the infection, softening and forming abscesses. The patient becomes severely ill, with symptoms of a general infection, and the course of the disease is of much the same duration as in acute glanders.

4. **CHRONIC FARCY.**—This only differs from acute in that the "buds" are associated with much less inflammatory reaction, the constitutional symptoms are much less severe, and the course of the disease is much longer. A few of the cases have extended over 12 months.

**Diagnosis.**—Acute glanders has been mistaken for small-pox, owing to the likeness of the papulo-pustular eruption to the specific eruption of this disease. The chronic forms are at times mistaken for the other infective granulomata (syphilis, tuberculosis and actinomycosis). Exact diagnosis turns upon bacteriological methods, direct or indirect.

The *bacteriological diagnosis* in man may be simple if a superficial swelling exists which may be opened. Direct cultures may be made therefrom, preferably on potato, and a rapid diagnosis made. It may be, however, that weeks elapse before such an opportunity occurs, or before some deeply situated swelling calls for operative interference; in such cases serum reactions, such as the complement-fixation test and agglutination, are indicated.

If material containing *Pf. mallei* be injected intraperitoneally into a male guinea-pig, tumefaction and suppuration occur in 2 or 3 days in the tunica vaginalis, and the bacilli can be recovered therefrom after about 6 days.

**Treatment.**—**PROPHYLACTIC.**—The utmost care must be taken in nursing, destruction of old dressings, etc.

The site of inoculation, if obvious, should be excised, and the underlying tissues should be treated drastically by strong antiseptics. All abscesses should be opened promptly and efficiently drained. The general symptoms are met by treatment similar to that given in any septicæmia. Experience with chemotherapy and the antibiotics has been limited on account of the rarity of the disease; sulphadiazine was thought to have some effect in six patients and the recovery of another was attributed to streptomycin.

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## MELIOIDOSIS

**Definition.**—A fatal disease, resembling glanders in symptoms and pathology, caused by *Pfeifferella whitmori*; it has been found in Burma, British Malaya, Cochin China and Ceylon, and is primarily a disease of rodents; the mode of human infection is unknown.

**Pathology.**—The characteristic lesions are small caseous nodules which sometimes coalesce, forming large honeycombed abscesses in the viscera. The lungs, liver, spleen and, less commonly, the intestines and kidneys may be implicated, while pustules and bullæ may involve the skin. *Pf. whitmori* is readily cultivated from these lesions as well as from the blood during the septicæmic stage, but the safety-pin-like bipolar staining organisms are scanty in smears of the pus obtained from the nodules.

**Symptoms.**—In severe cases the vomiting, purging and collapse may simulate cholera, and death from septicæmia may occur in 3 days; other cases may show remittent and intermittent pyrexia for weeks and months. The clinical picture varies with the organ predominantly attacked, and according to Stanton and Fletcher the clinical types may resemble: (1) plague; (2) broncho-pneumonia; (3) typhoid or malaria; (4) liver abscess; (5) infective endocarditis or general tuberculosis; (6) pyelitis.

**Diagnosis.**—This is always difficult clinically, and is dependent on the cultivation of the organisms from the blood, sputum, urine, cerebrospinal fluid or material aspirated from the liver or spleen. Relatively few cases have been diagnosed during life.

**Treatment.**—Food should be protected from contamination by rats and other rodents. In man the disease is almost invariably fatal. Autogenous vaccines are worth a trial, but neither vaccines nor anti-sera possess protective power in infected animals.

## CHOLERA

**Definition.**—A specific disease due to Koch's comma vibrio, characterised clinically by violent vomiting, painless diarrhœa with copious rice-water stools, dehydration, muscular cramps, aphonia, collapse and urinary suppression.

**Ætiology.**—Cholera exists endemically in India, China and certain other Far Eastern countries. In India Rogers demonstrated three main endemic foci from which epidemics spread in the spring and summer through mass movements of pilgrims who acquired the disease from infected water. War may lead to the spread of cholera, and herding of people in famine and prison camps also favours outbreaks. Occasionally cholera has reached Europe. People of different race, sex and age are all susceptible.

The causative organism is *Vibrio cholerae*, described by Koch (1883). The true cholera vibrio (1) ferments mannose and sucrose but not arabinose, (2) does not hæmolyse goat's erythrocytes and (3) agglutinates with O-group 1 serum. The status of the hæmolytic El Tor and Celebes strains of vibrio remains undecided. Water

transmission is an important mode of spread. When the general water supply becomes infected, as in the Hamburg epidemic (1892), a sudden widespread outbreak follows. If wells or other local water supplies are infected, cases appear from day to day in the locality so supplied. Flies also may disseminate the disease by contaminating food, milk, etc., with infected faeces. Cholera vibrios occur in great numbers in the rice-water stools, but disappear rapidly. Both the cholera convalescent and the contact carrier lose their vibrios within a few days of the termination of the attack or contact with a cholera case. Chronic carriers, as in typhoid fever, are unknown, and the actual cholera patient remains the main source of spread. Choleraeophage is said to be absent from the stools of the most virulent cases, and present in mild and convalescent ones.

**Pathology.**—After death rigor mortis sets in early. The blood is thick and tarry. The small intestines are collapsed and shrunken, the mucosa is denuded of its epithelial lining, congested and perhaps hæmorrhagic, and the lymphoid follicles are enlarged. The stomach and liver are congested, and the gall-bladder distended with viscid thick bile, difficult to expel—hence absence of bile in the intestine. The kidneys show swelling, congestion and ecchymoses, the spleen is small and shrunken and the lungs collapsed and dry.

The cholera vibrio is readily isolated from the contents of the small intestine and occasionally from the gall-bladder. The vibrios undergo disintegration on the surface epithelium, especially of Lieberkühn's glands, with liberation of a powerful endotoxin. Denudation of intestinal epithelium, outpouring of fluid from the blood vessels into the lumen of the bowel and absorption of toxin into the circulation result. Toxæmia and fluid loss underlie the pathological findings and clinical picture. Diarrhœa and vomiting lead to chloride depletion, to decrease in blood volume with increased viscosity of the blood and to tissue dehydration. Biochemical investigations show reduced blood chloride, diminished plasma alkalinity, phosphate retention and increased blood urea. A polycythæmia of 6 to 8 million red corpuscles per c.mm. and a leucocytosis of from 15,000 to 30,000 per c.mm. are frequently found; hæmatocrit estimations have shown an average loss in serum of 35 per cent. in mild and up to 64 per cent. in severe cases. Dehydration associated with increased viscosity of the blood frequently leads to cardiac and peripheral circulatory failure; renal anoxia (cortical ischæmia) is probably the main basis of the anuria.

**Symptoms.**—The incubation period is 2 to 5 days.

Five clinical types have been described. (1) *Ambulatory cases*. (2) *Choleraic diarrhœa*. (3) *Cholérine*: the patient suddenly develops severe abdominal pains, passes numerous fæcalent motions, then typical rice-water stools, followed by rapid recovery. (4) *Cholera sicca*: the patient becomes rapidly collapsed and dies before the typical gastro-intestinal features develop. (5) *Cholera gravis*: typical cholera, constituting 95 per cent. of the cases in most epidemics. Premonitory symptoms are frequently absent but occasionally there may be looseness of the bowels, headache, epigastric discomfort, nausea and possibly vomiting some 24 hours before true choleraic diarrhœa develops. In the ordinary severe cases three stages may be recognised.

1. Stage of evacuation. This lasts 3 to 12 hours. The onset is generally abrupt, with painless diarrhœa and vomiting. Soon the stools lose their fæcalent character, purging becomes marked and the evacuations are frequent and copious; the stools now resemble rice-water and contain flakes of epithelium. Colicky pain is absent; evacuation of the bowels brings relief, but this is soon followed by a sense of prostration. Vomiting commences early: at first the stomach contents are ejected; later, several quarts of rice-water vomitus may be lost in a few hours. Severe retching is common and hicough may be troublesome. As a result of sodium chloride loss, agonising cramps now appear, often commencing in the hands and feet and extending to the extremities or abdominal muscles. The patient also suffers from intense thirst.

and becomes restless and exhausted. The skin is cold and wrinkled, the lips and lobes of the ear bluish, the face appears pinched, the conjunctivæ are injected, the eyeballs sunken and the voice husky and weak. Aphonia often supervenes. The respirations become rapid, the blood pressure lowered, the peripheral veins depleted and collapsed and the pulse almost imperceptible. Though the skin temperature is subnormal, in the rectum it may reach  $101^{\circ}$  to  $104^{\circ}$  F.

2. Algid or collapse stage. In this stage the vomiting and purging lessen or cease, but symptoms of collapse increase. Circulatory failure follows. Despite this, the mind generally remains clear. The cholera facies becomes even more accentuated, the skin cold, clammy and dusky, and cyanosis is marked. The pulse, which is irregular and weak, may disappear completely at the wrist. The systolic blood pressure may fall to 40 to 70 mm. Hg. Cardiac sounds are weak, and a friction rub, caused by dryness of the serous surfaces, may be heard over the pericardium and pleura. Urinary secretion is markedly decreased as a result of hypotension and dehydration, and the scanty urine contains albumin and casts. Unless the low blood pressure be maintained, oliguria may be replaced by anuria. Death may occur within 3 to 48 hours of the onset of these symptoms; peripheral circulatory failure and uræmia are the most frequent causes. About 50 per cent. survive this stage of collapse, and pass on to the stage of reaction.

3. Stage of reaction. With recovery, the temperature rises, the circulation and blood pressure improve, cyanosis decreases, the urinary secretion increases and the stools become fæculent and contain traces of bile. Recovery may ensue within a week. In less favourable cases, especially when the collapse stage has been prolonged, a typhoid state may develop. The face is flushed, the temperature rises, the pulse and respirations are accelerated and the tongue is dry and brown; and erythematous rashes may appear and low muttering delirium ensues. The blood pressure in these cases may be elevated above normal (150 to 175 mm. Hg.). The cause of the syndrome is believed to be absorption of cholera or other bacterial toxin from the damaged bowel after the circulation has been restored. Fatal cases may die with hyperpyrexia. In other cases, despite circulatory recovery, urinary secretion is not re-established, no urine or only a small quantity of albuminous urine being passed. Increased respirations, Cheyne-Stokes breathing, hiccough, twitching muscles, stupor, delirium, convulsions and coma follow. Death is due to renal acidosis and uræmia.

Polycythæmia and leucocytosis have been noted under Pathology.

**Complications and Sequelæ.**—Cardio-vascular collapse, renal acidosis and uræmia, and toxæmia producing a typhoid state are common modes of death. Despite the frequency of uræmia, chronic nephritis rarely follows cholera. Complications also include broncho-pneumonia, cholecystitis, parotitis and bed-sores; and gangrene of the fingers, toes, ears, penis and scrotum have been recorded. Extreme local cyanosis may be mistaken for gangrene. Lack of lacrimal secretion may lead to conjunctivitis, corneal ulceration and sloughing of the cornea. Miscarriage and premature delivery are not infrequently caused by toxæmia, severe purging and cramps in the abdominal muscles.

**Diagnosis.**—When cholera is prevalent the only safe rule is to treat every case of diarrhœa as suspect until proved otherwise. Laboratory confirmation in all atypical cases should be sought.

During an epidemic little difficulty will arise, but in atypical and sporadic cases the diagnosis will largely be made on a positive stool culture. Outbreaks of food poisoning (cholera nostras) due to organisms of the *Salmonella* group may be differentiated by the history, the presence of bile in the stools and laboratory investigation. In mushroom poisoning the history is important and particles of the fungus may be identified in the vomitus or stools. Malaria, dysentery, early trichinosis and infection with *Gastrodiscus hominis* may occasionally produce acute gastro-intestinal features somewhat resembling cholera; laboratory investigations will clinch the diagnosis.

In poisoning by arsenic or mercury perchloride, vomiting generally predominates, the stools contain bile and sometimes blood, and there may be a marked metallic taste in the mouth.

**Prognosis.**—The mortality rate has varied in different epidemics from 30 to 80 per cent., being most fatal at the start. Modern treatment has reduced it to about 10 per cent. Over 90 per cent. of cases admitted with a blood pressure above 70 mm. recover. Young children, pregnant women, aged and debilitated people, alcoholics and chronic nephritics do badly. A severe and prolonged collapse stage, early anuria with uræmic symptoms and hyperpyrexia are unfavourable, but with modern treatment these can often be avoided. (See also Cholera Vaccination below.)

**Treatment.**—**PROPHYLACTIC.**—Personal prophylaxis is vital. Since cholera vibrios originate in the first instance from patients with cholera, isolation of the patients in fly-proofed wards, destruction of vomitus and excreta and sterilisation of soiled linen and clothing are most important measures. Milk must be boiled, water sterilised by boiling or chlorination and water and food adequately protected against pollution or contamination by flies. Cold meat, shell-fish, salads and raw fruit should be avoided, and the hands invariably well washed in antiseptic solution before eating. Drinking vessels and eating utensils should be cleaned in boiling water and dried by heat. *Scrupulous care of the ice chest is essential. Houses should be fly-proofed where possible.*

Cholera vaccination produces some degree of temporary immunity and is valuable in epidemics, provided virulent strains of vibrios have been used in the manufacture of the vaccine. The vaccine contains 10,000 million vibrios per ml.; the first dose is 0.5 ml., followed in 10 days' time by 1.0 ml. A "booster" dose of 1.0 ml. should be given at least every 6 months if continued protection be desired. In India, vaccines containing Inaba and Ogawa strains have yielded promising results. Immunity develops rapidly in from 4 to 10 days, and probably lasts 4 to 6 months. The mortality rate in the vaccinated remains high, but is reported to be about two-thirds that of the uninoculated. The value of cholera-phage as a causal prophylactic during an epidemic is undetermined, while its practical value in eliminating cholera vibrios from wells and cisterns is also uncertain.

**CURATIVE.**—Specific treatment resulting in the destruction of cholera vibrios and toxin remains a therapeutic ideal yet to be achieved. Intestinal antiseptics have failed. Sulphaguanidine has been favourably reported on when therapy is instituted early. No unanimity of opinion exists in regard to bacteriophage, which is administered orally at short intervals in a dose of 4 ml.

Apart from specific therapy, intravenous fluid medication and other measures have lowered the mortality from approximately 60 per cent. to 10 per cent. The principles involved are designed to: (1) rest the small intestine; (2) replace fluid and salts lost from the blood and (3) restore the acid-base equilibrium of the blood and tissue fluids. By so doing circulatory failure, hypochloremia, renal acidosis and uræmia are prevented or combated.

The patient is kept strictly in bed, and only water and rice or barley water are given by the mouth for the first few days. Frequent drinks, not exceeding 2 oz., should be administered. During the collapse stage efforts should be made to conserve the body heat; hot-water bottles are useful for this purpose. Morphine is only used in the stage of premonitory symptoms; it is contraindicated later. Intravenous medication is all important, solutions of isotonic or hypertonic saline with or without sodium bicarbonate being largely employed. Various indices have been used to estimate the amount of fluid required to be injected in the individual case. These include: (1) the specific gravity of the blood; (2) the blood pressure and pulse and (3) the hæmoglobin concentration. Rogers advocates two solutions: (a) Hypertonic saline (sodium chloride gr. 120, calcium chloride gr. 4, water 1 pint) for reinforcing blood volume and chloride loss; and (b) an alkaline solution (sodium bicarbonate



gr. 180, sodium chloride gr. 90, water 1 pint) to counteract acidosis and uræmia. During the *collapse stage* 1 pint of (b) is first given, and then the total quantity as estimated from the specific gravity of the blood is made up with Rogers' hypertonic saline solution (a). Thus a specific gravity of 1063 to 1064 calls for 3 pints, and between 1065 to 1070 for 4 to 6 pints, the aim being to keep the figure below 1060. Injections are repeated as often as the specific gravity of the blood rises to or above 1063, or the blood pressure falls to 70 mm. Other solutions in use consist of isotonic saline, 5 per cent. glucose, and a combined sodium chloride (1.4 per cent.) and sodium bicarbonate (1.5 to 3.0 per cent.) solution. The latter should be sterilised, either by filtration or by adding the sodium bicarbonate to the cooling salt solution after it has been sterilised by heat. It is not permissible to boil or autoclave sodium bicarbonate, as it is converted into the toxic carbonate.

Fluid should be administered intravenously, either intermittently or by continuous drip. The all-important consideration is to restore and maintain blood volume by isotonic saline injections, and if for any reason isotonic saline cannot be injected into the veins it can be introduced intrasternally or subcutaneously.

The pulse and blood pressure probably serve as the best indicator of blood fluid requirements. A blood pressure below 70 mm., especially if there is associated cyanosis, restlessness, cramps and cold extremities, necessitates immediate transfusion with isotonic saline solution. The result is dramatic, provided an adequate quantity of fluid be injected. Profound collapse is relieved, the skin becomes warmer, cyanosis disappears and the pulse and blood pressure are markedly improved. Injections should not be continued after the pulse and blood pressure have been restored. Cases of moderate severity require 2 litres of fluid every 6 or 8 hours for 1 or 2 days. As much as 31 pints in 4 days have been given in a severe case with resultant recovery. Special care should be taken (1) to avoid pyrogens in the water used for intravenous injection, (2) to see that the temperature of the injected fluid does not exceed 80° F. (room temperature in the tropics), if the rectal temperature be elevated. The former precaution is necessary to prevent rigors, and the latter to prevent hyperpyrexia.

In the *reaction stage*, cold sponging is advisable whenever the temperature exceeds 103° F. Threatened uræmia is treated by alkaline drinks, injection of alkaline saline solutions per rectum and intravenously and dry cupping. Hot packs should not be used. Throughout this stage constant care is necessary, the chief dangers being hyperpyrexia and renal failure. In the treatment of hyperpyrexia, cold sponging, an ice cap to the head and cold saline enemas may be tried; if these fail the patient should be placed on a rush mattress, and covered by a sheet over which water is sprinkled and on which a fan plays to cause evaporation. When the blood pressure fails to rise, repeated adrenaline injections are said to be helpful.

As long as the renal function is depressed no increase in the diet should be made, and even after all acute symptoms have subsided the patient should be nursed in bed in the recumbent position for several days, as fatal syncope may ensue if he sits up prematurely. When patients can tolerate food, the diet should at first be low in residue. Broths, jellies, white of eggs, underdone minced meat and farinaceous foods reinforced by vitamins are permitted.

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## WHOOPIING-COUGH

**Synonym.**—Pertussis.

**Definition.**—An acute specific disease of high infectivity, characterised by catarrh of the respiratory tract and by paroxysmal cough which may or may not be associated with an inspiratory laryngeal spasm producing the distinctive "whoop".

**Ætiology.**—Whooping-cough is mainly a disease of temperate climates, being rarer and less severe in hot countries. Spring and autumn are the seasons of its

In poisoning by arsenic or mercury perchloride, vomiting generally, the greatest mortality, the stools contain bile and sometimes blood, and there may also occur in the taste in the mouth.

**Prognosis.**—The mortality rate has varied in different epidemics, being most fatal at the start. Modern treatment has reduced it to 10 per cent. Over 90 per cent. of cases admitted to hospital recover. Young children, pregnant women, alcoholics and chronic nephritics do badly. Most susceptible children in intimate families are those under 10 years of age. Attacks are comparatively early in adults even in those over 60, and, in modern treatment these can often be cured. The *fœtus in utero* has been known to contract the disease. The new-born child. More females than males are attacked. It may occasionally be a precursor of laryngeal diphtheria.

**Treatment.**—**PROPHYLAXIS.**—Vibrios originate in the soil, in the faeces of patients in fly-proof houses, in soiled linen and in polluted water. It may occasionally be a precursor of laryngeal diphtheria. The frequency with which whooping-cough follows an attack of measles is variable. On rare occasions convalescents are said to have acted as carriers of the disease for several months.

The infection is usually conveyed by the mucous droplets expelled by the cough. Since the bacillus can resist drying for several weeks the infection may lurk in rooms and fomites, but this is uncommon. One attack almost invariably confers lifelong immunity.

**BACTERIOLOGY.**—The causative organism is *Hæmophilus pertussis* or the bacillus of Bordet and Gengou. This is a minute, slender rod closely allied to the bacilli of the influenza group. It is Gram-negative, and only flourishes on artificial media which contain blood or serum. It grows best at blood heat. The bacilli swarm in the larynx and on the ciliated epithelium of the air passages. Cultures are most easily obtained from the small pellets of viscid mucus which are expectorated at the end of a paroxysm of coughing. The blood of convalescents agglutinates the bacilli.

There are no post-mortem appearances which are distinctive, the changes found after death being due to complications. Of these, congestion of the air-passages, bronchiolitis and broncho-pneumonia are the most common, and are accompanied by general acute vesicular emphysema. The tracheo-bronchial lymph glands are usually soft and swollen.

The paroxysmal cough is attributed to hyperæsthesia of the respiratory mucous membrane with heightened excitability of the vagus nerve.

**Symptoms.**—The incubation period is difficult to fix with accuracy, owing to the insidious nature of the onset and the delayed appearance of the characteristic whoop, but it is probably 13 to 15 days. Extremes of 3 days and over 3 weeks have been claimed. During a typical attack three stages may be recognised—catarrhal, paroxysmal and convalescent.

The catarrhal stage lasts from 7 days to a fortnight—it is febrile, and resembles a somewhat severe respiratory catarrh; but the cough is more troublesome and bronchitic signs ill-marked. Recognition of the disease at this, the most infectious, stage is difficult unless the patient is known to have been exposed to the infection. Suggestive signs towards the end of the period are a tendency of the cough to assume a paroxysmal character, with greater severity at night, giving rise to suffusion of the face and occasionally to retching or vomiting. Bacteriological investigation by swab or cough plate and the detection of lymphocytosis will assist early diagnosis.

When the paroxysmal stage is reached the disease is unmistakable. Fever will usually have subsided; but the cough occurs in paroxysmal bouts, often spontaneous, but frequently the result of external stimuli, such as excitement, draughts, the ingestion of food or examination of the throat. Several paroxysms may occur in quick succession with longer or shorter intervening periods of freedom. The victim senses the cough impending, and may attempt to suppress it. If lying in bed a child will sit up, or if about may run to mother or nurse. A brief, deep inspiration is followed

rapid succession of short coughs, with open mouth and protruded tongue, which continued until the chest is almost emptied of air. The face becomes congested, the superficial veins are engorged, and the eyes fill with tears. The eyeballs the skin is bathed in sweat and suffocation appears imminent; but relief afforded by relaxation of the laryngeal spasm and the occurrence of the drawn-crowling inspiration, which refills the lungs with air. The occurs, and may be repeated several times, leaving the child perspiring. The bout often terminates with the discharge from the air-passages of transparent mucus. A quantity of thin sticky secretion, which retained, may also flow from the mouth and nose. During the often last for 2 or 3 minutes, the child may faint or become. The contents of the stomach are often ejected, and the some instances incontinence of feces occurs. Epistaxis more severe attacks. Subconjunctival hæmorrhage may appear in the skin of the eyelids, root of the neck and other parts. *membrana tympani is ruptured, and blood escapes from the ear. In asphyxia may occur.*

In the early paroxysmal stage the cough is only occasional, but its frequency soon increases, and in a case of moderate severity from 15 to 20 paroxysms occur in the 24 hours; in some attacks, however, they are much more numerous. They are characteristically most frequent and most severe at night.

Physical examination at this stage will still reveal signs of diffuse bronchitis; but this is now accompanied by a greater or less degree of acute emphysema and moderate abdominal distension is not uncommon. The forcible protrusion of the tongue over the lower incisor teeth often produces a shallow ulcer on the frænum linguæ.

The duration of the paroxysmal stage is from 3 to 10 weeks, and after this convalescence begins. Whooping-cough is more prolonged in winter than in summer, and its duration is increased if complications ensue. After the whoop has ceased a fresh attack of respiratory catarrh may cause it to reappear; but this should not be regarded as a relapse, it does not render the patient again infectious.

A leucocytosis occurs even in the early catarrhal stage. The lymphocytes are increased out of proportion to the other cells; a typical count would be 15,000 to 25,000 white cells per c.mm. with from 50 to 70 per cent. lymphocytes. (At the age of 6 months, in health, the proportion of lymphocytes is 57 per cent. and at 2 years 53 per cent.) Myelocytes may also appear. The leucocytosis is increased after each paroxysm of coughing, and the highest counts are found during convulsions. The supervention of pneumonia increases the polymorphonuclear cells. In contrast with other infectious diseases the sedimentation rate in whooping-cough is usually retarded during the paroxysmal stage.

**Course.**—Attacks vary in their severity and duration. During outbreaks abortive attacks, only recognised by bacteriological methods, are said to be common. Mild infections may run their whole course in a week or two, and the whoop may be absent, whilst severe ones may last several months. As mentioned above, the number of paroxysms in 24 hours is some measure of the severity. The danger of supervention of complications is proportional to the severity of the attack.

When whooping-cough attacks the adult violent fits of coughing with a sense of impending suffocation but no whoop are common. Cyanosis, vomiting and even temporary attacks of unconsciousness may also supervene and subcutaneous ecchymoses appear. The legs may become cedematous and muscle rupture may ensue from the violence of the cough, which retains its paroxysmal character and nocturnal severity.

In infants, too, the whoop may be very imperfectly developed.

**Complications.**—These belong mainly to the paroxysmal stage—they are partly

diet of milk or whey may be considered in some instances. Orange juice with glucose should be given freely.

The bacillus is insensitive to penicillin, but both this and sulphonamides may be of use in some secondary complications. Chloramphenicol gives satisfactory results in some cases, but a number of instances of aplastic anaemia have arisen from its use in pertussis, and its continued employment is unjustifiable. Some strains of the organism are sensitive to streptomycin. Chlortetracycline has been effective in other cases. Two other closely related antibiotics, aerosporin and polymyxin have also been used with some successful results. During the catarrhal stage simple expectorant mixtures are sufficient, and later the paroxysms may be modified by such sedatives as belladonna, phenazone, bromoform, phenobarbitone, paregoric, codeine and heroin, all of which have their advocates. Tincture of belladonna in increasing doses (2 or 3 minims 4-hourly cautiously increased until the pupils are widely dilated) and phenazone are the most generally useful; the latter may be given to a child in doses of gr. 1 or 2 with small doses of potassium iodide and expectorants every 4 to 6 hours. Ephedrine (one twelfth of a grain in infancy to one-half grain for a child of 5 years in a simple linctus) is also a good antispasmodic given three times a day. Remarkable amelioration of the cough and vomiting may be effected by the use of heavy doses of sodium bicarbonate, the urine being made and kept fully alkaline. Vaccine treatment with the Bordet-Gengou bacillus is still on its trial. Its prophylactic is greater than its curative value. Smooth, recent, virulent strains are essential. Spaced at monthly intervals three injections are given, starting with 5000 million organisms and rising to 10,000 million. Horse, rabbit and hyper-immune human antisera have been used; there is some evidence that the last is of value if used early in infants under 1 year of age, but the other two do not appear to affect the course of the disease. Attention should be paid to the condition of the nose and throat, and adenoids removed as soon as possible in convalescence, since they tend to maintain the cough. As after-treatment, tonics and a change to the seaside are advisable.

Complications should be treated on general lines. Obstinate vomiting needs careful feeding, and phenobarbitone one-sixth to one-quarter grain three times a day, or intramuscular injections of soluble phenobarbitone. Gastric lavage with 0.6 per cent. solution of sodium bicarbonate may help. Asphyxial attacks are treated by pushing forward the lower jaw and applying artificial respiration. The mouth and pharynx should be cleared of mucus. Inhalation of  $O_2$  and  $CO_2$  is said to be of good effect. Intubation has been practised in some very severe cases. Convulsions call for the mustard-bath or hot pack, with an enema of paraldehyde (1 to 1½ drachms) in olive oil. A whiff of chloroform may give relief, and sometimes lumbar puncture with free escape of cerebrospinal fluid is effective. Broncho-pneumonia should be treated with sulphonamides or the appropriate antibiotic. Atelectasis requires similar treatment, followed by stimulant expectorants, breathing exercises and postural drainage.

The injection of the serum of convalescents, on the same lines as in measles and in similar doses (*q.v.*), has been advocated as a prophylactic but has proved disappointing.

Although the infectivity of the paroxysmal stage, especially of its latter part, is problematical, patients should be isolated for 5 weeks from the commencement of the whoop, provided the paroxysmal cough and whoop have ceased for a fortnight; or, better, until the infecting organism has disappeared, which may occur after 3 weeks of illness, or a week or two later. The quarantine period for non-immune contacts is 21 days. Disinfection of rooms and clothing is desirable.

## CHANCROID

**Synonyms.**—Soft Chancre, "Ulcus Molle" and Ducrey's Infection.

**Definition.**—An acute localised specific infectious disease due to the entrance of a micro-organism (*Haemophilus ducreyi*) into the tissues of skin or mucous membrane.

**Ætiology.**—The infection is nearly always transmitted during sexual intercourse. Accidental infection is rare. The disease is widespread throughout the world but the incidence is highest in tropical countries. In this country it is not common and is limited, for the most part, to seaports. It is found much more often in men than in women. The figures of incidence in the Report of the Chief Medical Officer of the Ministry of Health show 389 new cases in males and 14 new cases in females in England and Wales during 1952. The total number, 403 cases, compares with 19,659 cases of gonorrhœa, the most prevalent venereal disease. It is generally regarded as a disease of the highly promiscuous and the unhygienic. Symptomless carriers are known to exist.

**Pathology.**—The organism, *H. ducreyi* or streptobacillus of Ducrey, is a small, slender Gram-negative bacillus which is often seen in chain formation but may be found singly or in groups. It may be difficult to find in smears from the open sores because of secondary infection. It is a fastidious organism and usually difficult to grow in culture, although in expert hands media containing defibrinated human or rabbit's blood have given good results. The microscopic picture of chancroid is said to be distinctive and biopsy to be a useful method of diagnosis.

**Symptoms and Signs.**—The incubation period is short, namely, 3 to 5 days in most cases. Occasionally it may be as short as 24 hours. At the site of inoculation, which is nearly always on the genitalia, there first appears a small red painful papule or pustule which quickly breaks down to form an ulcer. The ulcer is usually very painful and extends quite quickly by local tissue spread. It may also ulcerate deeply and be very destructive. It tends to be irregular in outline, with undermined edges and a narrow zone of bright red erythema at the spreading margin. Surrounding issue may show an erythematous blush. The floor of the ulcer is covered with yellowish slough which exudes pus. The granulations bleed freely on manipulation. The base of the sore is not indurated. Occasionally the granulations become exuberant and elevated above the surrounding surface, so-called "ulcus molle elevatum". Multiple sores are more common than single sores, in contrast to primary syphilis from which the diagnosis must be made. Auto-inoculation is common. In many cases the regional inguinal lymphatic glands become involved, after periods varying from 2 days up to 3 weeks from the appearance of the sore. The adenitis is very painful and develops quickly. The skin over the swelling is reddened; the glands become matted together and soon suppurate with the formation of a large single abscess, the "inflammatory bubo". This is likely to break down on the surface of the skin to form a large chancroidal ulcer in the groin. Painful lymphangitis may also occur. Other complications which have been described include hæmorrhage from the ulcer, urethral stricture, urethral fistula, phimosis and spreading gangrene.

**Diagnosis.**—The diagnosis is frequently made on clinical grounds, but it is important to try to find the organism by smear or by culture. An intradermal test, the so-called "Ito-Reenstierna" test, is performed by injecting a quantity (0.25 ml.) of a saline suspension of killed *H. ducreyi* into the skin. The commercial vaccine, dmelcos, which is made up into concentration of 450 millions of organisms to the millilitre, is usually used. A positive result may be found after 24 to 48 hours and takes the form of an inflammatory papule of diameter 0.5 cm. or larger, surrounded by erythema of the skin. A positive test is not to be expected until 7 days or more after the appearance of the sore. Once the sensitivity has developed a positive test will be found over a period of years and perhaps always. If the patient gives a history

and legs, but similar ones may involve the mucous membranes of the eyes, nose, pharynx and larynx, giving rise to cough, hoarseness, epistaxis and even sudden death. The *nodular type* of lesion may attain the size of a chestnut; these tumours often ulcerate, forming large, bleeding, fungating masses situated in the flexures of the joints and appearing in successive crops. Little difficulty is experienced in diagnosis and fatal results are rare, though the disease may last 2 to 3 months.

**Treatment.**—When the nodules ulcerate they should be dressed with antiseptics, and if they undergo necrosis or hæmorrhage severely they may be excised.

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## PNEUMOCOCCUS INFECTIONS

LOBAR PNEUMONIA (see p. 1048).

BRONCHO-PNEUMONIA (see p. 1058).

BOTULISM (see p. 123).

## B. DISEASES CERTAINLY, OR ALMOST CERTAINLY, DUE TO FILTRABLE VIRUSES

### INTRODUCTION

A number of human diseases, examples of which are small-pox, rabies, yellow fever, chicken-pox, measles and epidemic poliomyelitis, are now known to be caused by ultra-microscopic viruses, and, arguing from analogy, encephalitis lethargica is thought to belong to the group, though proof is still lacking.

As a rule, these viruses measure less than 250  $m\mu$ , and some of them measure much less. Particles less than 250  $m\mu$  cannot be resolved by ordinary microscopes, though Barnard, by the use of a short-wave ultra-violet light and lens systems of quartz has resolved objects as minute as 75  $m\mu$ . Of recent years the physical characteristics of many viruses have been revealed and studied by means of the electron microscope. Great diversity of size occurs amongst the viruses. With few exceptions, however, the viruses are ultra-microscopic, and will pass through filters that fail to pass the pathogenic bacteria.

Though differing much in size and effects, most of the viruses have characteristics in common. Many of the diseases caused by filtrable viruses in man and animals are highly infectious, very minute doses of virus causing infection—an infection that spreads with great rapidity. Many of the virus diseases produce special intracellular bodies, termed inclusion bodies. These may be restricted to one particular tissue, or may be found in various tissues. They may occur in the cytoplasm or nuclei of cells, or in both, and vary greatly in size. In some diseases the diagnosis can be made histologically by the recognition of these bodies, e.g. the Negri bodies in rabies. The fact that the inclusion bodies have been seen to develop *in vitro* in tissue-cultures suggests that the filtrable viruses are intracellular parasites, in which respect they differ from the majority of bacteria.

Some of the virus diseases, such as yellow fever, dengue and papataci fever, are insect-borne.

No virus has been cultivated *in vitro* in the absence of growing cells, though many can be propagated in tissue cultures, and on account of this exception, many, if not the majority of workers, hold the opinion that pleuro-pneumonia is not a virus disease. Generally speaking, therefore, viruses can only be propagated by animal passage.

Most of the viruses produce an active immunity which is very lasting, and in

some of the diseases immune serum confers passive immunity. In measles the injection of immune serum will produce such a degree of passive immunity as to prevent an attack of measles in a contact, but such immunity is not lasting. If given about 6 days after contact, a modified attack of measles of very attenuated type will occur, subsequent to which permanent immunity ensues. Work published by the Rockefeller Institute shows that fully inactivated yellow fever virus will not confer immunity. Inactivated distemper virus will, however, immunise, and is indeed used as a preliminary measure in the prophylaxis of distemper, and inactivated virus also confers immunity in cattle plague, fowl plague, rabies, influenza (in mice), herpes and some other animal diseases.

Most of the filtrable viruses are resistant to glycerine, especially at low temperature, and remain unaltered for long periods in 50 per cent. thereof at 4° C., whereas the lethal effect of glycerin on bacteria generally is well known.

Complement fixation reactions between virus and antibody have been shown in many virus infections, and flocculation has been shown in the case of variola virus. Ledingham has shown that homogeneous suspensions of the elementary corpuscle from vaccinia and fowl-pox are agglutinated by the sera of convalescent animals, while normal serum has not this effect.

The following list comprises some of the human virus diseases under two headings :

### 1. Certain

Small-pox.	Herpes Febrilis.
Chicken-pox.	Herpes Zoster.
Mumps.	Infectious Warts.
Yellow Fever.	Acute Anterior Poliomyelitis.
Dengue Fever.	Psittacosis.
Phlebotomus Fever.	Rabies.
Rift Valley Fever.	Encephalitis (St. Louis Type).
Lymphogranuloma Inguinale.	Influenza.
Common Cold.	Measles.

### 2. Almost Certain

Encephalitis Lethargica.	Molluscum Contagiosum.
Primary Atypical Pneumonia.	Rubella.
Epidemic Infective Hepatitis.	Homologous Serum Hepatitis.

## THE COMMON COLD

**Synonyms.**—Acute Coryza; Cold in the Head.

**Definition.**—An inflammatory process affecting the upper respiratory tract in which the air sinuses and tubes in connection therewith may also be involved.

**Ætiology.**—Colds are very common in the damp variable weather of the autumn, winter and spring in temperate climates. Susceptibility to infection tends to diminish with age, yet shows great variation amongst different individuals and even in the same individual under different conditions. Both sporadic and epidemic forms are met with, and infection may spread through a community with great rapidity. Amongst important predisposing causes are frequent changes of atmosphere, as by entering and leaving hot, stuffy, ill-ventilated, crowded rooms; the presence of a focus of chronic infection in the upper respiratory tract, *e.g.* adenoids, infected tonsils and chronic cranial sinusitis; structural anomalies which interfere with free ventilation of the nose, *e.g.* deflected septum and polypi; and chronic irritation of the mucosa

The virus resides in the secretions of the respiratory tract and direct infection is the rule, very intimate contact is not essential. Infectivity may be present 5 days before the appearance of the rash, possibly longer, and then rapidly declines. Only on rare occasions do intermediaries convey the infection, and rooms and fomites do not retain it for more than a short period. There is no evidence incriminating water, milk or other articles of food.

**Pathology.**—The causal agent is a filtrable virus. The disease has been reproduced in man and monkeys by inoculation with blood, bronchial secretions or tears. The infective agent can be cultivated in chick embryos. The primary morbid change is a generalised hyperplasia of lymphoid tissue in which many cells resembling histiocytes appear. In fatal cases the most striking visceral change is broncho-pneumonia. Secondary infections chiefly with hæmolytic streptococci are common. Catarrhal or ulcerative laryngitis may be found. The bronchial glands are inflamed and the lymphoid aggregations of the small intestine may be very conspicuous. Measles is prone to activate pre-existing tuberculous lesions.

**Symptoms.**—*Incubation.*—The rash appears on the fourteenth day of infection, sometimes a day earlier or a day later, but it may be delayed in patients who have been infected with the serum of convalescents. This interval is more constant than that which elapses between infection and the first catarrhal symptoms. Reckoning to the onset of fever and catarrh 9 or 10 days usually pass. In some cases the incubation period is slightly febrile and a transitory feverish catarrh with fleeting rash has occurred even a few hours after exposure to infection (Goodall's *illness of infection*). A polynuclear leucocytosis is characteristic of the incubation stage. Slight enlargement of the cervical, inguinal, axillary and other glands may herald the eruption. Koplik's spots on the buccal mucosa may precede the rash by 2 or 3, sometimes by 5, days. Prodromal rashes are not uncommon; a precocious macular eruption is the commonest, but a punctate scarlatiniform erythema is the most important, since it simulates scarlet fever. It is apt to appear on the second day of invasion. An urticarial rash may also occur.

*Invasion.*—This is signalled by catarrh of the respiratory tract, fever and the outbreak in the mouth of Koplik's spots. It culminates in the appearance of the skin eruption. Sneezing, irritating cough, watery eyes and conjunctival injection are the early signs. There is chilliness, and the temperature may reach 103° F. by the end of the first day. Photophobia and sharp diarrhœa may occur. In the early stage of invasion slight blotchiness of the skin about the mouth and nose may be evident. The cutaneous rash usually appears on the fourth day, and a deceptive remission of symptoms and fall of temperature sometimes occur just before its outbreak. In some instances laryngeal symptoms are marked during the invasive stage, and give rise to suspicion of diphtheria; exceptionally, catarrh is insignificant, and an attack of severe simple tonsillitis is simulated.

Koplik's spots are of great importance in the early diagnosis, since they are usually recognisable some 72 hours before the rash, with the appearance of which they rapidly disappear. They are minute superficial specks of a bluish-white tinge, and show tendency to aggregate into small clusters or granular patches. Their common site is on the inner aspects of the cheeks, opposite the line of apposition of the molar teeth but they may be more widely scattered over the buccal mucous membrane, on the inner surfaces of the lips and on the conjunctivæ. There is evidence that they also occur on the mucosa of the colon. Sometimes they are surrounded by bright red areolæ. In addition, the mucous membrane of the mouth becomes congested and dusky, and a decided blotchy exanthema may here precede the cutaneous eruption.

*Period of eruption.*—With the approach of the rash the symptoms become aggravated. The temperature rises sharply, it may be to 104° or 105° F. The hurried respiration and slight cyanosis may suggest broncho-pneumonia. Diarrhœa may persist, and sometimes urinary irritation is noticeable. The nasal and conjunctival



discharges become more purulent. The eruption makes its first appearance about the brows, behind and below the ears, and in the circumoral region. Rarely, it appears first on other parts, such as the buttocks, thighs or wrists. It spreads rapidly, sometimes after a short hesitation, over the face, neck, trunk and extremities, and is usually fully out on the fifth or sixth day of the attack. Small brownish macules are the first elements, but they soon become papular, and show a tendency to fuse into groups with irregular sinuous outlines. Profuse eruptions may become confluent on the face, neck, back and extensor aspects of the limbs. Petechial hæmorrhages in the rash are not uncommon. The skin is usually moist and exhales a peculiar musty smell. Rarely, it is hot and dry. Itching or burning sensations may accompany the rash.

The eruption fades in the order of its appearance, and usually disappears in the course of 2 or 3 days; but brownish staining may persist for some time, particularly on the back. A fine branny desquamation speedily follows. At its first appearance, the rash may fail for a time to spread; retrocession is also sometimes observed. A badly developed and retarded rash is characteristic of some severe attacks, and in asphyxial states the rash may be cyanotic. As the rash develops, the temperature continues to rise, reaching its maximum with the climax of the eruption in from 24 to 48 hours. When the rash begins to fade, the temperature falls more or less abruptly by a crisis which is rather prolonged.

The pulse-rate is increased in proportion to the fever, but the respiration is disproportionately rapid. The catarrhal symptoms also reach their greatest intensity at the height of the eruption. Headache, slight delirium, insomnia and a feeling of intense wretchedness are characteristic of this period. The throat may be sore, the buccal mucous membrane show an intense catarrh and the glands at the angle of the jaw become tender. The tongue at first is heavily coated, but before long red papillæ are evident, and when peeling is complete a clean, red papillated tongue, very like that of scarlet fever, may often be seen. With the crisis rapid amelioration of all symptoms should occur.

The blood now shows a leucopenia with a high percentage of large lymphocytes. All complications induce a polynuclear leucocytosis.

The urine presents the ordinary febrile characters. Transitory albuminuria may occur. Ehrlich's diazo-reaction is nearly always present, and is most marked when the temperature begins to fall. An acetone reaction is obtained in most cases.

**VARIETIES.**—Attacks may be mild or severe. Some of the mildest attacks are abortive, the rash failing to appear, and only Koplik's spots giving a clue to the disease. Such attacks may also be seen after serum prophylaxis. Severe attacks are classified as toxic, pulmonary and hæmorrhagic. The *toxic type* includes those cases in which the patient may succumb during the eruptive period without evident complication. Ill-defined rashes, high fever, muscular tremor, delirium, dyspnoea and circulatory failure are characteristic features. In the *pulmonary or suffocative type* the infection falls with *especial stress upon the lungs*. The temperature is high, the respirations rapid and hissing, and the condition suggestive of slow asphyxia. Consolidation of the lungs cannot be detected, but rhonchi are present everywhere, accompanied by fine crepitations. A stuporose condition may precede death or terminal convulsions may occur. The true *hæmorrhagic type* of measles is rare. In this the patient may bleed from the mucous membranes with hæmorrhages into the skin and subcutaneous tissues. Recovery takes place in some instances. Hæmorrhage into the rash, and confined to it, has not a very grave significance.

**Complications.**—These are numerous, but those involving the respiratory tract, the middle ear and the bowel are the most important.

Laryngitis may accompany the onset, develop with the eruption or appear early in convalescence. Arising in the invasive stage it may simulate laryngeal diphtheria. Laryngitis is more common during the eruptive period, and may persist for some days—it may be complicated by laryngeal ulceration, sometimes by oedema of the

glottis; but necrosis of the laryngeal cartilages and abscess formation are rare. Severe laryngitis arising during convalescence should always arouse suspicion of diphtheria.

Bronchitis is often present during the eruptive stage, but bronchiolitis with spreading broncho-pneumonia is a much more serious complication, and is a common cause of death. Its incidence is favoured by adverse climatic conditions, overcrowding and contact with similar cases. It is generally attributed to secondary pneumococcal or streptococcal infection; but, especially when occurring early in the infection, may be due to *H. influenza*. This early broncho-pneumonia is associated with a high temperature and considerable toxæmia. It is suffocative in type, and the lung signs are rather those of capillary bronchitis than of consolidation. During the eruptive stage, broncho-pneumonia should be suspected if the temperature fails to fall or rises again with subsidence of the rash, and the pulse remains quick and respiration rapid. It may clear up in a week or 10 days, but often persists for weeks, or relapses. The temperature chart often shows remarkable daily remissions and exacerbations which may lead to suspicions of tuberculosis. The incidence of broncho-pneumonia, formerly about 13 per cent., has fallen with prophylactic chemotherapy to less than one-quarter of this figure. Feeble infants succumb rapidly, and in those who recover convalescence is protracted.

True lobar pneumonia is uncommon. Massive collapse of the lower lobe of a lung has been described; its onset is sudden with intense dyspnoea, cyanosis and cardiac failure. It is distinguished from pneumonia by the feebleness of the breath sounds, upward displacement of the diaphragm and dislocation of the heart towards the affected side. Rarely mediastinal and subcutaneous emphysema have occurred. Effusions into the pleura have been noticed in some epidemics, and empyema may follow. Fibrosis of the lung and bronchiectasis often originate in the broncho-pneumonia of measles.

Rheumatic arthritis with pericarditis, endocarditis and sometimes chorea has been known to supervene on measles.

Blepharitis and phlyctenular ulcers are common sequels. In cachectic children intense conjunctivitis may lead to ulceration and even perforation of the cornea.

The stomatitis of measles occasionally becomes ulcerative. Very rarely a gangrenous inflammation (*noma*) may attack the lips, cheeks, vulva or other parts. A discoloured patch appears on the mucous membrane and quickly ulcerates, extending both in area and in depth. A zone of inflammatory induration surrounds the lesion, and a fetid odour is given off. Noma is terribly destructive both to soft parts and bone, and is very fatal. It occurs in debilitated children, and is attributed to secondary infection. Vincent's spirochaeta and fusiform bacilli are often present. It is said to be sometimes due to the Klebs-Löffler bacillus or to streptococci. Pronounced leucopenia may accompany it.

Otitis media was formerly a frequent and troublesome complication. Its incidence has been much reduced by prophylactic chemotherapy and is probably now not above 2.5 per cent. It may be catarrhal or suppurative; the suppurative form is more common in children, and is responsible for much chronic ear disease. Mastoid inflammation may occur, and deafness may result.

Cutaneous eruptions of eczematous, impetiginous or pustular type are common. Sometimes they are widespread, and very resistant to treatment.

Enlargement and suppuration of the cervical glands, entero-colitis and ascites are rarer complications.

Encephalo-myelitis of a demyelinating type (see p. 1411) may occur towards the end of the first week, with a course which is either rapidly fatal or tends to spontaneous recovery. Meningeal symptoms or convulsions may signalise its onset. Hemiplegia, aphasia, coma or mental defect may ensue but are rare. Myelitis, sometimes of the ascending form, has been known to occur in measles; also symptoms suggestive of disseminated sclerosis. Paralysis of extra-ocular muscles, papilloedema and optic

atrophy have all been encountered. The mortality of encephalomyelitis is about 10 per cent.

Measles was formerly thought to favour the activation of tuberculous foci hitherto latent in the bronchial glands or elsewhere. It seems more likely that the coincidence of measles with the active stage of a primary tuberculous complex is the real danger, and caseous broncho-pneumonia, miliary tuberculosis of the lungs, or general tuberculosis with meningitis may follow immediately or occur after a quiescent period. Outbreaks of measles often occur in close association with whooping-cough, diphtheria and scarlet fever, which have a very similar seasonal incidence.

Relapse in measles is rare. Second attacks, although uncommon, undoubtedly occur, and some unfortunate individuals fail to acquire any lasting immunity. Fourth, and even seventh, attacks are known.

**Diagnosis.**—In the prodromal stage, measles may be mistaken for ordinary nasopharyngeal catarrh or even tonsillitis. If laryngitis is pronounced, and the child croupy, diphtheria may be simulated. Mastoid operations, excision of the tonsils and even of the appendix sometimes are performed precipitately before the true nature of the infection is recognised. Febrile symptoms and loss of weight during the incubation stage may be erroneously attributed to tuberculous infection. The prodromal scarlatiniform rash may lead to confusion with scarlet fever. These errors may be avoided by bearing in mind the possibility of measles, enquiring for exposure to infection, and particularly by a careful search for Koplik's spots and shottiness of the posterior cervical glands. The pre-eruptive fall of temperature and recession of the catarrhal symptoms before the appearance of the rash should be borne in mind, and not lead to premature relaxation of precautionary isolation.

In the eruptive stage, the fevers with which measles may be confused are rubella, small-pox and perhaps typhus.

*Rubella* is distinguished by the trivial nature and brevity of its prodromal symptoms; the slightness or absence of catarrh and cough; the insignificant fever; the absence of Koplik's spots and of stomatitis; and, especially, the presence of distinct and tender enlargement of the posterior cervical, mastoid and occipital glands. The rash of rubella is smaller, pinker and more discrete; but by fusion a scarlatiniform stage may supervene. The patient never feels or appears so ill as in ordinary measles. A previous attack of measles generally excludes that disease.

*Small-pox* may be heralded by a prodromal rash of morbilliform character, which may have a similar distribution to that of measles, save perhaps on the face. Catarrh, and true Koplik's spots, however, are absent, and the onset is more abrupt, and more likely to be signalled by such symptoms as backache, acute shivering, vomiting and severe prostration.

Measles may, on the other hand, be mistaken for the early eruptive stage of small-pox, for in both an illness for a few days may precede the appearance of a pronounced papular rash on the face and upper parts of the body. Catarrh, Koplik's spots and distribution of the rash about the ears, circumoral region and margins of the hairy scalp are in favour of measles. The temperature, too, continues to rise until the maximum efflorescence, whilst that of small-pox is unique in that it begins to fall on the third day with the outbreak of the rash. As the rash develops, the shottiness of the small-pox papules and the peculiarities of their distribution and evolution become apparent.

*Typhus fever* may be simulated by measles when the rash of the latter is receding and dusky, and lung complications are present; but the rash of typhus rarely invades the face, which is always affected in measles. The Weil-Felix reaction is a valuable indication of typhus.

*Septic rashes* in scarlet fever are often morbilliform; but their distribution does not conform to that of the measles rash. *Serum rashes*, *food rashes* and *drug eruptions* may assume a measly character; but these rashes often prove to be polymorphic

when the whole body is examined, as it should be, and, besides, other signs of measles are wanting.

The *macular syphilide* is distinguished by the absence of respiratory catarrh and of Koplik's spots. History of exposure to venereal infection, a chancre and the accompanying throat symptoms afford a clue. The Wassermann test is positive.

**Prognosis.**—In different epidemics the death-rate varies greatly. Measles is most fatal to infants and young children, 70 per cent. of the mortality occurring in children under 3 years of age. After the fourth year the death-rate is low. In the London Fever Hospitals the mortality rate was 5·6 per cent. for 1931–1932; in 1942 it had fallen to 0·38 per cent. and has since remained at this level. Rickets, tuberculosis, congenital syphilis, malnutrition and chronic bowel complaints are unfavourable factors, and the disease is more fatal among the poor. In the cold season of the year the tendency to respiratory complications is more marked and the fatality rate is nearly double that in the summer months, when enterocolitis is more common. When the infection occurs in conjunction with whooping-cough or chronic lung disease the mortality is high. Diphtheria is apt to assume the laryngeal form, and is an especially fatal complication. Considerable toxæmia with high fever, cyanosis, muscular tremor and diarrhoea point to a severe attack. Laryngitis, capillary bronchitis and broncho-pneumonia are serious. Cerebral symptoms, such as prolonged stupor or convulsions, are of bad augury. Remarkable recovery has been noticed in some cases of ascending myelitis.

**Treatment.**—**PROPHYLACTIC.**—Measles is chiefly disseminated by schools. The difficulty in controlling outbreaks of measles arises from the fact that it is extremely infectious, and the infectivity is present in virulent form for 4 or 5 days before the rash appears. Notification and school closure have been tried with poor results. The best method is to make provision for the early recognition of suspicious symptoms in contacts for a period covering the ninth to the sixteenth day after the occurrence of the first case. Exclusion of contacts from school has proved ineffective and quarantine is usually limited to children under the age of 6 years who have not had measles.

In ward outbreaks children who have not had measles should be passively immunised and, if possible, isolated, or, at all events, segregated in small groups.

**Serum prophylaxis.**—Intramuscular injection of the blood serum of healthy convalescents from measles into susceptible contacts produces a *passive* immunity, which lasts about a month. Injection during the first 5 or 6 days of the incubation period prevents measles if the dose is adequate. Injection after the sixth and before the ninth day will modify the severity of attack, and allow the development of an *active* immunity which is lasting. Dried convalescent serum is also effective.

The dose is 2 ml. for each year of a child's age to a maximum of 10 ml.; more is needed for adults or if the serum is injected late. In children under 3 years of age it is better to prevent the attack altogether. The most potent serum is obtained from the sixth to the ninth day after defervescence. The donor must be free from syphilis, malaria and tuberculosis, and must not be incubating any other infectious disease.

The serum of adults, presumed to have had measles at some previous time, but not recently, is of some value, but the dose should be doubled. If citrated whole blood is substituted there may be danger of Rh sensitisation. A placental globulin extract has been prepared for use in the same way but reactions are severe.

If measles follows the subcutaneous injection of immune serum the rash fails to erupt at the site of injection; this is the *Debré phenomenon*. Immune serum does not blanch the developed rash. A disquieting feature is the occasional occurrence of infective hepatitis (*homologous serum jaundice*) after the administration of convalescent measles serum, sometimes after so long an interval as 3 months. If obtainable, the use of pooled gamma globulin which represents a 25-fold concentration of the serum and can be safely heated to 57° C. for 4 hours should prevent this. The dose is 0·1

ml. per pound of body-weight. This pooled globulin has proved quite as effective as convalescent serum.

Systematic taking of temperatures and examination for Koplik's spots and catarrh facilitate early detection of the disease. The wilful exposure of children to measles is unjustifiable, as the nature of the resulting attack can never be predicted.

Sixteen days' quarantine from the date of last exposure to infection is usually deemed sufficient, but, owing to the trivial nature of the prodromal symptoms, it is better, in the case of schools, if quarantine is imposed at all, to allow a period of 3 weeks to elapse, especially if serum prophylaxis has been attempted. Convalescent patients in the absence of complications are quite free from infectivity at the end of a fortnight and possibly even a week from the appearance of the rash.

**CURATIVE.**—The patient must be confined to bed during the febrile, and also during the prodromal stage, if this is recognised in time. The sick-room should be kept at a temperature of 60° to 65° F., and ventilation effected by means of open windows; an open fire is also an advantage. The photophobia calls for screening from direct light. Clothing should be light and consist of a flannel or woollen night-dress; this is sufficient to prevent chill, allows the respiratory muscles full play and encourages the evaporation of perspiration. Strict attention should be paid to cleansing the mouth and teeth, and the regulation of the bowels. During the febrile stage the diet should be restricted to milk, diluted if necessary with barley water. Tea may be allowed, and fruit juices or barley water given to assuage the thirst.

Twice a day during the febrile period the patient should be washed with tepid water; but should the attack assume a toxæmic form, accompanied by high fever and delirium, cold sponging or the use of the cold pack is advisable.

Laryngitis in the early stage is relieved by steam and the use of a simple expectorant mixture, to which a sedative may be added. The croupy symptoms usually subside without necessitating tracheotomy or intubation. The possibility of the presence of diphtheria renders a bacteriological examination essential.

Laryngitis which persists after the eruption may be alleviated by the inhalation of compound tincture of benzoin or lysol in the strength of 60 minims to the pint of boiling water. The cough is relieved by a simple linctus, or one containing codeine or other sedative. Late laryngitis if diphtheritic needs antitoxin. Bronchitis and broncho-pneumonia call for prompt treatment. Antibiotics, either penicillin or aureomycin, should be prescribed immediately. If the cough is dry and irritating, steam often relieves. An expectorant mixture containing ipecacuanha and a small quantity of potassium iodide is useful. Sometimes a single mustard and linseed poultice gives great relief. As the cough becomes looser, steam should be discarded and free ventilation arranged. It is well to separate cases with broncho-pneumonia from others, as the condition is believed to be infectious. Treatment of the broncho-pneumonia of measles in the open air, where circumstances and weather permit, gives excellent results. Oxygen is valuable where there is much respiratory distress and cyanosis.

Sulphadimidine given for 6 days from the appearance of the rash reduces the incidence of broncho-pneumonia and otitis media to a trivial figure.

Conjunctivitis should be treated by bathing the eyes with boric lotion and the application of boric ointment to the lids. In severe cases, penicillin or drops of silver nitrate solution, gr. 2 to the oz., should be instilled night and morning, or 2 to 10 per cent. solutions of silver protein used. Should the cornea ulcerate, atropine drops should be employed and oculent hydrarg. oxid. applied. Eye bandages are undesirable.

Stomatitis usually subsides quickly; the mouth should be cleansed with a lotion containing chlorate of potash (gr. 10 to 1 fl. oz.). Ulceration due to Vincent's organisms should be treated with intramuscular penicillin. The supervention of noma necessitates bacteriological examination, the use of penicillin, neoarsphenamine or

the appropriate antitoxin and surgical interference in the way of cauterisation or free excision and local application of zinc peroxide paste or permanganate crystals. Enterocolitis is managed on the same lines as infantile epidemic diarrhoea.

Convulsions and encephalomyelitis are treated by sedatives and lumbar puncture, repeated if the cerebrospinal fluid is under increased pressure. Intramuscular or intravenous injection of 10 ml. of blood serum from a recently recovered case with this complication, if obtainable, seems worthy of a trial.

In an uncomplicated case of measles the patient may be allowed up 2 or 3 days after the temperature subsides. Supervision should be exercised during the convalescence of severe cases, and the possibility of later tuberculosis borne in mind. Ear discharges call for skilled treatment, as they may become chronic (see also directions on p. 47).

## RUBELLA

**Synonyms.**—German Measles, R $\ddot{o}$ theln.

Rubella is quite distinct from ordinary measles and from scarlet fever. It protects only against itself. Amongst the exanthemata it is distinguished by its long incubation period, its short invasive stage, its characteristic rash and adenitis, its benign course and the time of its seasonal prevalence.

**Ætiology.**—The infectivity is less than that of measles and of short duration. Like measles it is infectious for a day or two before the eruption appears. Infection is by droplet spray and is facilitated by close contact. There is no evidence that the disease is spread by fomites. Transmission through an intermediary cannot be considered proved. The infective agent is presumed to be a filtrable virus.

Rubella is prevalent in the first half of the year. Cases increase from January to a maximum in May and June or sometimes in August or September. A series of local outbreaks usually occurs, determined by the aggregation of a number of unprotected young adults. A more or less pronounced epidemic wave occurs every third or fourth year. The maximum incidence is at a later age period than that of measles, but even the youngest infants have been known to take the disease. Its frequency much diminishes after the age of 30. Sex is without influence.

The occurrence of rubella in the first 2 or 3 months of pregnancy is known to favour the incidence of cataract, heart malformation, deaf-mutism and other congenital defects in the child. These may be multiple. The risk of a live child with congenital defects is about 25 per cent. and the frequency of stillbirth about the same when the mother contracts rubella within the first 3 months of pregnancy. Abortion, frequent in measles, is rare in rubella.

**Symptoms.**—The incubation period, although variously stated to be from 7 to 22 days, is usually 17 or 18 days.

Premonitory symptoms are mild or altogether absent, but a short catarrhal stage usually occurs, the rash making its appearance within 24 hours. Rarely a longer prodromal period of ill-defined febrile illness occurs before the eruption. The characteristic tender adenitis of the mastoid, occipital, cervical or other lymph glands can, more often than not, be detected for a day or two, exceptionally even a week or longer, before the appearance of the rash.

The rash has two stages. Macular, slightly papular and morbilliform in its progress, it frequently fuses and becomes scarlatiniform in its final stage. Discrete spots first appear on the face or neck; they invade the circumoral region and may be found behind the ears and on the scalp. Sometimes they are first found on the wrists, chest, shoulders or even on the legs. They are smaller than the papules of measles, pale pink in colour and tend to cluster in smaller groups. The rash quickly extends to the trunk and limbs and in most cases as quickly fades. On the second

day the face is no longer spotty but appears diffusely erythematous ("sunburnt"). Sometimes the outbreak of the eruption is halting in its progress. The scarlatiniform stage is not developed in all attacks; it is due to the fusion of the discrete elements, and is generally best marked on the trunk, especially so on the back. It becomes most apparent on the second day of the eruption. The rash of rubella rarely lasts more than 72 hours and hardly stains the skin, thus contrasting with measles.

Stomatitis is insignificant, and Koplik's spots never occur. The tonsils may be slightly swollen and reddened, sometimes a follicular exudate is present. Some degree of pharyngeal catarrh is evident, and the tongue may be lightly coated. A fine vesiculation and congestion of the soft palate are often seen, and the orifices of Stenson's ducts may be vividly injected. Sometimes the gums are injected and tender. The conjunctivæ are pink and the eyes slightly suffused. Photophobia is rare.

Fever is slight, even when the rash is intense. Often there is no fever at all. The pulse and respiration rates are only increased in proportion to the febrile disturbance.

A tender adenitis is very distinctive. The mastoid and occipital glands may rapidly attain the size of peas; the posterior cervical glands are also enlarged, frequently too those in the axillæ and groins. The enlarged glands are firm, tender and discrete; they never suppurate. As a rule resolution takes place rapidly when the rash subsides. Particularly in children, the spleen may become palpably enlarged. The urine presents no special characteristics.

As in the case of morbilli, a transitory polymorphonuclear leucocytosis occurs during the incubation period, but a leucopenia with a relative increase of lymphocytes is found in the eruptive stage. Very distinctive is a high percentage of plasma cells, 15 to 20 per cent., on the fourth and fifth days of the attack, when the neutrophils are at their lowest.

Convalescence is remarkably speedy. Slight furfuraceous desquamation may occur.

**Complications.**—Complications and sequelæ are, as a rule, absent. When they do occur they are trivial and take the form of mild recurrent sore throat, rheumatism, slight laryngitis, bronchial catarrh or transient albuminuria. In some outbreaks benign polyarthritis has been a feature. Otitis is very rare, and meningeal symptoms, encephalomyelitis, or polyneuritis, rarer still.

On occasions, epidemics of rubella of more severe type, approximating in symptoms and sequelæ much more closely to measles, have been described.

**Diagnosis.**—The disease has a similarity to both measles and scarlet fever, especially when the latter occurs in a mild form. In addition, the rash of rubella must be distinguished from toxic and drug rashes, from the eruption of secondary syphilis, from glandular fever and from certain skin diseases.

Measles is differentiated by the following points. Its incubation period is shorter, being 14 days from exposure to the appearance of the rash; cough and catarrhal symptoms are marked, the mucous membrane of the mouth is inflamed and Koplik's spots are present. The rash appears later, is darker, more persistent and stains. There is no late scarlatiniform stage. Fever is more pronounced, prostration more evident and the mastoid and occipital glands are not especially enlarged. Pulmonary complications are much more likely to occur.

Rubella is often mistaken for scarlet fever. Distinctive points in favour of the latter are: the short incubation period, the occurrence of such initial symptoms as vomiting, marked faucial inflammation, shivering or severe headache. The fever is high at onset and the pulse disproportionately rapid. The circumoral region is free from rash, and by the fourth day the tongue has peeled. The occurrence of such sequelæ as cervical adenitis and nephritis, also typical pinhole or lamellar desquamation, will clinch the diagnosis. Even in the scarlatiniform stage of rubella, discrete measles elements may generally be detected about the advancing edges of the rash

on the forearms, wrists, legs and ankles. An eruptive fever which simulates measles at its onset and scarlet fever later, is generally rubella. Occasionally glandular fever (*q.v.*) resembles rubella.

Toxic, enema and drug rashes may bear a resemblance to the rash of rubella, but, as a rule, these rashes are very irregular in their distribution and polymorphic in character. The characteristic tender occipital and mastoid glandular enlargement and slight catarrh of rubella are absent.

Of skin diseases, erythema scarlatiniforme and pityriasis rosea are sometimes mistaken for rubella. The first named bears a greater resemblance to scarlet fever; unlike rubella, it avoids the face, does not give rise to swelling of the mastoid and occipital glands, and shows a great tendency to recur.

Pityriasis rosea, itself possibly an infective fever, is distinguished by a herald patch which precedes the general eruption, and the fact that the latter usually appears first on the upper part of the trunk. The rash often shows commingled macular and ringed lesions. The patches are slightly scaly and are decidedly larger and more persistent than the papules of rubella. They desquamate in a characteristic manner from their centres, which are fawn coloured, towards the margins, which are slightly elevated, darker and ringed by a collarette of scales. There is no catarrh and no conspicuous glandular enlargement about the head.

Secondary syphilides bear a superficial resemblance to the rash of rubella, but are distinguished by the presence of a primary sore, the characteristic throat and the conspicuous increase in size, and shottiness of the glands in the vicinity of the chancre. The Wassermann reaction is positive.

The Paul-Bunnell reaction will distinguish glandular fever.

**Prognosis.**—Recovery is the rule; second attacks are known, but not common, and relapse is very rare.

**Treatment.**—PROPHYLACTIC.—As the incubation period is long a quarantine of 3 weeks is theoretically necessary for contacts, but is rarely imposed. They should be supervised from the tenth to the twenty-first day from exposure to infection. Early warning of the imminence of attack may be given by slight enlargement and tenderness of the mastoid and occipital glands.

Special precautions against infection should be adopted in early pregnancy. If convalescent serum or gamma globulin can be obtained serum prophylaxis should be attempted. This protection lasts but a few weeks, so repetition is necessary in those still exposed to infection.

**CURATIVE.**—The patient should be isolated and preferably kept in bed until all symptoms have subsided. In 7 days, possibly sooner, infectivity has ceased, provided there is no persistence of faucial, nasal, respiratory or other symptoms.

## SMALL-POX

**Synonym.**—Variola.

**Definition.**—An acute, highly infectious specific fever, characterised by a definite incubation period and a peripherally distributed, deep-seated, disfiguring eruption which passes through the stages of papule, vesicle, pustule and crust. A pre-eruptive, toxic or septicæmic, and an eruptive, or focal, phase are recognised.

**Ætiology.**—All races, both sexes and persons of every age are susceptible if unprotected by a previous attack, or by efficient vaccination. This universal liability is most evident when the disease is introduced for the first time into a new community; under such conditions it may decimate the population. The present-day incidence in adults is accounted for by vaccination in infancy; in endemic centres it was, prior to the introduction of vaccination, a disease of early childhood.

For centuries endemic in Asia, small-pox has at times been epidemic in every



civilised country, following trade routes and the channels of communication. It is more severe in hot climates, but its virulence has always varied greatly in different localities and different outbreaks. Coloured races take it badly. Unlike scarlet fever and measles, it frequently attacks infants at the breast.

When small-pox occurs during pregnancy, the disease in the mother tends to assume a confluent or hæmorrhagic type and infection of the fœtus is common but not inevitable. Abortion or premature delivery is to be expected in all severe attacks. The fœtus contracts the disease *in utero*, usually during the pre-eruptive (septicæmic) stage in the mother, the incubation period being shortened. Sometimes fœtal infection is delayed and may even occur at the time of separation of the placenta. Few of the children survive; sometimes they show the rash or its scars at birth.

In temperate climes most outbreaks of small-pox occur during the winter and spring, and die out with the commencement of summer. In the tropics periods of drought predispose to epidemics. Second attacks are rare. Vaccination gives complete immunity for some years and partial immunity usually persists afterwards. Complete natural immunity is very rare, as also is a persistent susceptibility in which vaccination or a previous attack fails to protect.

Infection with small-pox is, almost certainly, through the respiratory tract, and may be direct or indirect, *i.e.* by contact, which need not be very close, with a patient suffering from the disease or through the medium of objects infected by the sick person. Intermediaries may carry the contagium in their clothing or in their hair. The greater incidence in the neighbourhood of small-pox hospitals suggests the possibility of aerial convection of the virus for considerable distances, perhaps exceeding a mile, but the influence of human carriers in these cases is hard to eliminate. Bedding, clothing, rags and articles of merchandise, such as cotton, may retain their infectivity for considerable periods of time, especially when stored. Transmission by flies and domestic animals is regarded as a possibility.

With the exception of the pre-eruptive stage of hæmorrhagic small-pox, the infectivity is slight at the time of the symptoms of onset, and is much greater when the eruption appears. Infectivity in the early stages is, by some, attributed to primary and unrecognised lesions in the respiratory tract. It continues until all the scabs have separated. The virus is very resistant to desiccation and long persists in the dry crusts and seeds. Crusts dried *in vacuo* have been found infective after more than 2 years. Corpses of those recently dead from small-pox can transmit the disease. Tramps are often responsible for the conveyance of infection from one locality to another.

There is no doubt that small-pox is due to a filtrable virus. Minute, but characteristic, intracellular bodies are found in the epithelial cells of the pocks of small-pox and vaccinia, and also in the cornea of the rabbit, after scarification with the virus of these diseases. They are known as *Guarnieri bodies* and are aggregations of the "elementary bodies" of Paschen. The elementary bodies of small-pox and of its variant, variola minor, are agglutinated by the sera of patients convalescent from either form of the disease.

**Pathology.**—The cutaneous lesion of small-pox lies in the deeper layers of the epidermis. Vesiculation is due to serous exudation between and into the cells. Loculation is caused by vertical strands of the ruptured epithelial cells which radiate from the base of the pock. The tenseness of the vesicle and tethering of the covering by this reticulum cause the pock to be umbilicated. In malignant attacks, where the pocks are flaccid, and in the old and debilitated, umbilication is often absent. With pustulation the fibres of the reticulum are destroyed and the pock becomes dome-shaped. Multinucleated giant cells are formed in the prickly cell layer. The suppuration is attributed to secondary infection with hæmolytic streptococci or with staphylococci. On mucous membranes the vesicles rupture almost as soon as formed and are rapidly converted into shallow erosions.

The chief blood change is an initial leucopenia, followed after the first week by a leucocytosis in which mononuclear cells preponderate. Secondary anæmia may be pronounced. In malignant small-pox the presence of myelocytes and normoblasts with a thrombocytopenia has led to an incorrect diagnosis of acute leukaemia.

The post-mortem appearances are those usually found in acute infective processes. The rash persists, the liver is often much enlarged, the spleen swollen, and the lungs broncho-pneumonic. Particular attention has been drawn to the presence of local necroses in the liver, testicles and bone marrow. These are often infiltrated with mononuclear basophil cells. Interstitial infiltrations of the kidneys also occur.

In hæmorrhagic small-pox, petechial and purpuric hæmorrhages are found in the skin, mucous membranes, lungs and other viscera, sometimes also in the retro-peritoneal tissues and the roots of the mesenteries.

**Symptoms.**—*Unmodified or natural small-pox; Variola major.*

**Period of incubation.**—Taking the first symptoms of invasion, this is from 10 to 14 days. The average period is 12, or counting to the appearance of the rash, 14 days. Extremes of 5 to 23 days are mentioned but are rare. With increasing virulence the incubation period tends to shorten. In inoculated small-pox the generalised eruption appears on the eighth to the eleventh day.

**Period of invasion—toxic or septicæmic stage.**—In a typical unmodified attack the invasive symptoms are sudden and of great intensity. The most prominent are severe chills or rigors, marked pyrexia, severe frontal headache and intense pain across the loins. The temperature quickly reaches a maximum of  $103^{\circ}$  to  $104^{\circ}$  F., and there is severe prostration. Retching and vomiting may occur, particularly in children. Delirium, mental symptoms and even suicidal tendencies occasionally accompany this stage. With these severe symptoms are coupled more ordinary febrile manifestations, such as anorexia, thirst, coated tongue and disturbed sleep. The breath is offensive, the skin usually hot and dry but sometimes perspiring, and the bowels constipated.

There are, however, mild attacks in which the symptoms of invasion are much less severe, and even in more severe attacks pain across the loins is by no means constant. Mild invasive symptoms usually presage a mild course; with a severe invasion the attack is generally, although not invariably, grave.

**Prodromal rashes** belong to the toxic or septicæmic stage, and may precede the proper eruption for 1 or 2 days, but they are not always present. There are two types, one purely erythematous, the other petechial or hæmorrhagic with or without accompanying erythema. The pure erythemas are of a bright-red or dusky-purplish colour and may appear in the femoral triangles, the axillæ or on the trunk, where they are often patchy and evanescent, or be limited to the bony prominences and extensor surfaces of the limbs. They may suggest the rash of scarlet fever, or, less frequently, bear a superficial resemblance to that of measles. The hæmorrhagic or petechial rash, which often has at first a dusky erythematous background, is more characteristic. It appears in the groins, which are stippled with small petechiæ; invades the thighs for an inch or two and extends in an ill-defined manner on to the abdomen (*bathing drawers rash*). Sometimes it extends towards the axillæ and may be found on the back of the neck and flexures of the knees. The petechial rashes are persistent and indicate a severe attack. The erythemas are fugitive and of good prognostic import; the only exception is a very brilliant universal oedematous erythema of face, trunk and limbs known as the *astacoid*, or *lobster*, rash which sometimes ushers in hæmorrhagic small-pox. Later this may be replaced by livid sheets of deep subcutaneous hæmorrhage.

**Eruptive or focal stage—Distribution.**—On the third day the invasion is at its height and the focal eruption should appear. In malignant attacks it may erupt earlier. It is not necessarily profuse; indeed, in mild and modified attacks it may be limited to a few lesions on the distal parts of the limbs and on the face. Whether scanty &

profuse, the rash is centrifugal in distribution, appearing first on the forehead near the scalp, and on the temples, then on the backs of the wrists and hands, and a day later about the ankles and feet. Its extension is rapid and symmetrical and its elements deeply seated in the skin, uniform in size and more or less circular. In marked contrast to the prodromal petechial rash the full efflorescence is least profuse on the abdomen and groins, scanty on the chest, more evident on the back, especially across the shoulders, increasing as it descends the arms to thicken on the extensor aspects of the wrists and hands. Most profuse of all is the outbreak on the supraorbital, malar and nasal prominences of the face. The rash reaches the lower extremities within 24 hours and here is most evident about the ankles and feet, where it may still be in the papular stage whilst that on the face has become vesicular. Meantime the lesions multiply on the parts already affected, the eruption becoming thick on the face and perhaps on the scalp whilst still scanty on the parts involved later. In 3 days it will have attained its full density and typical distribution, but the earliest lesions will be in a more advanced stage of development. It is highly characteristic of the focal eruption of small-pox to avoid depressions, flexures and protected flexor surfaces such as the armpits, groins, flanks, orbital hollows, supraclavicular fossæ and flexor aspects of the toes. Abnormal irritation by bands of clothing, irritants, scratching, vaccination or exposure to sun and weather may determine a profuse eruption on areas where, ordinarily, pocks are scanty. The pocks, too, tend to aggregate along prominent bones and tendons but may strangely avoid the prominences formed by the clavicles and the malleoli.

*Evolution and maturation.*—On its first day the rash consists of small dull-red macules. Within 24 hours these become papules which feel shotty when pinched up between the finger and thumb, on the face, hands or forearms. On the third day many papules have become vesicles, but vesiculation may be recognised on the summits of the papules at an even earlier stage. By the fourth or fifth day the eruption is completely vesicular and the toxicæmic symptoms and fever of onset may have subsided. The vesicles, circular in outline, slowly increase in size and become surrounded by red areolæ. They are now the size of split peas, greyish, and set in rather than on the skin. Umbilication is evident and loculation is proved by failure to collapse when transfixed by a sterile needle. The contents of the vesicles remain clear for 24 hours only; they then become purulent, so that by the fifth day pustules are evident on the face and by the eighth day are universal. With pustulation, the pocks soften, become flat-topped and lose their areolæ.

Reaccession of fever with constitutional symptoms and often delirium, the *secondary suppurative fever*, accompanies the process of suppuration or maturation. A marked inflammatory œdema of the skin may now appear, causing the features to become swollen and expressionless and impeding the movements of the hands and fingers. Much tenderness and itching may accompany this œdema. Suppuration destroys the loculation of the vesicles and also obliterates umbilication. Adjacent lesions, particularly on the face and hands, may run together in the vesicular and pustular or even the papular stage—a process which produces the confluent rash, a sign of severe infection.

On the ninth and tenth day the pustules begin to desiccate, some first rupture or are torn by scratching, and collapse. Brown or black crusts result which separate by the end of the thirteenth or fourteenth day, but where the skin is very thick, as on the palms and soles, the dried-up unruptured pustules may form deep-seated "seeds" which may take weeks to work their way to the surface and remain infectious for months.

To summarise: the rash is papular on its first and second days; vesicular on the third and fourth; pustular on the fifth and sixth and thereafter desicating. A rash which remains papular after the third day or is fully vesicular by the second day is unlikely to prove to be due to small-pox.

The cutaneous eruption is accompanied by an outcrop of greyish infiltrations on the conjunctivæ and mucous membranes of the mouth, tongue, nose and pharynx. In severe cases the larynx, bronchi, gullet and even the stomach and small intestine may also be affected. On the mucous membranes infiltrations and vesicles are soon transformed into shallow ulcers. Vesiculation may be observed on the palate, whilst the lesions are still indeterminate on the skin. In consequence of the eruption the eyelids, fauces and tongue become sore, the nose is obstructed and deglutition is painful. Implication of the larynx will cause hoarseness or aphonia and even dangerous œdema. The mucous membranes of the vulva, vagina, prepuce and rectum do not escape.

A mild generalised superficial adenitis is common and the spleen may be palpable.

The fever of invasion reaches its acme with the appearance of the rash, then it falls, but not immediately. It is generally normal by the fifth day of the attack, often before this. Small-pox thus differs from other eruptive fevers in that the temperature falls during the appearance of the focal eruption. At this stage, in the milder attacks with scanty rash, the patient may attempt to resume his ordinary occupation, and, in modified cases, very little further febrile disturbance may ensue. Ordinarily, however, the secondary suppurative fever now sets in and reaches its acme about the ninth or tenth day of the disease. Its duration in the more severe cases is from 10 days to a fortnight. In severe and confluent small-pox the remission of temperature in the vesicular stage may be absent.

The pulse and respirations are quickened proportionately to the degree of fever present, but in grave attacks the respirations become more rapid, shallow and irregular, and the pulse accelerated and feeble. In malignant and hæmorrhagic infections death may occur from toxæmia within the first week. In the gravest cases a subnormal temperature accompanies the toxic stage and death may result from circulatory failure, even within the first 24 hours, the mind remaining clear.

The urine is febrile in character. Some albumin may be present, and a diazo-reaction may be obtained.

Owing to the depth of the lesions in the skin, depressed scars are left, the amount of pitting depending on the degree of destruction of the true skin. The pits show reddish staining which may persist for months. Some desquamation may accompany the separation of the crusts, particularly on the feet and hands. The hair often falls out freely. The nails may be shed. Convalescence is, in favourable cases, rapid and complete, but may be much delayed when sepsis has supervened.

**VARIETIES.**—Small-pox may be severe, modified or naturally benign.

**Severe types of small-pox.**—In addition to malignant or severely toxic attack these include the confluent and the hæmorrhagic varieties. *Confluent small-pox* is distinguished from *discrete small-pox* by fusion of the lesions, particularly on the face and hands. The rash may fuse while still papular, but more commonly does so in the vesicular and pustular stages. In such cases the toxæmia is severe and the remission of symptoms before the stage of pustulation may be absent or ill-marked. Delirium is common, and the secondary fever high. Inflammatory œdema is very marked; the features may become quite unrecognisable and the confluent pocks may form a continuous sheet of pus. Severe conjunctivitis, nasal obstruction, salivation, cough, aphonia and diarrhœa are common. Some patients pass into a typhoid condition. An offensive odour emanates from the body, circulatory failure is progressive and death may occur towards the end of the second week.

**Hæmorrhagic small-pox.**—In the earliest and most malignant variety (*Purpur. variolosa*), the incubation period may not exceed 7 or 8 days. Purpuric flecks and patches often appear in the skin before the development of the eruption, but spots of greyish infiltration may already be appearing in the buccal and palatine mucosæ and rapidly become pseudo-membranous and confluent. The cutaneous hæmorrhage are accompanied by subconjunctival hæmorrhages, hæmaturia and bleeding from the

mucous membranes. Initial symptoms, in particular backache and prostration, are severe, and prodromal rashes common. The respiration is hurried and the breath sickeningly fetid, but the temperature not necessarily very high. Death may occur before the outbreak of the proper eruption gives a clue to the nature of the infection, but often towards the end careful inspection may detect a few papular elements of the focal rash, possibly lying in a prodromal erythema.

In other cases the bleeding manifests itself later, and accompanies the focal eruption, in the form of petechiæ or of circular spots between the lesions and infiltrations of their bases staining their contents (*Variola hæmorrhagica pustulosa*). The pocks are often badly developed, confluent and of a violaceous hue. Bruises form easily in the skin, and hæmaturia, epistaxis, hæmatemesis or uterine hæmorrhage may add to the gravity of the outlook.

The mere presence of blood-stained contents in the vesicles, especially those on the legs, without hæmorrhages into the bases of the pocks, or in the intervening skin and elsewhere, is not of bad prognostic importance.

*Modified small-pox or varioloid.*—Small-pox of a mild type may occur in vaccinated subjects although the same virus may prove virulent in those unprotected. In some, initial symptoms may be slight, and the eruption, although typical, is precocious and scanty. More commonly, the initial symptoms are severe, but again the rash appears early, is generally sparse and discrete, tends to evolve quickly, and many of its elements fail to progress beyond the papular or vesicular stage. The suppurative fever is slight or absent. The lesions of *modified small-pox* are often small, superficial and may be unilocular, sometimes they appear fleshy and wart-like. The modification is most evident on the face. The lack of depth and the arrest of maturation, leading to the juxtaposition of papules, vesicles and small pustules, may cause a resemblance to chicken-pox, or suggest measles complicated by chicken-pox, but the distribution remains characteristic although it may remain obscure in very sparse and abortive eruptions.

Rarely small-pox aborts completely in its initial stage, the focal rash failing to appear (*Variola sine variolis*). The subjects of this form of the disease have usually, but not invariably, been vaccinated at some previous time.

*Variola minor.*—A benign type of natural small-pox has from time to time prevailed in many parts of the world. The virus of this is sometimes known as the Western strain of the United States and West Indies in contradistinction to the Eastern strain or Asiatic small-pox. The names *alastrim*, *amaas*, *varioid* *varicella* and *Kaffir* or *Cuban itch* also designate this disease. It differs from ordinary small-pox in its mild course, low mortality (0.5 to 2 per cent.), lesser infectivity, the mildness or absence of secondary fever, the occurrence of residual pigmentation rather than pitting, and incidence on adults rather than on children.

The incubation period is 10 to 15 days, or longer. Invasion is abrupt, and may be accompanied by muscular pains, backache, vomiting and sometimes high fever, although many cases are ambulatory. The rash usually appears on the fourth or fifth day. It is seen first on the face, then on the forearms and trunk, and within 12 hours on the lower limbs. The eruption may be scanty or moderately profuse. It rarely comes out in crops, but in any case the initial lesions are more advanced than those which follow. Maturation is more rapid than in *variola major*, papular and vesicular stages each lasting 2 days, pustulation beginning early, and scabbing on the face being evident within a week. There is, as a rule, no secondary fever, but its absence is not invariable.

The distribution of the eruption is centrifugal, the rash favouring the face and extremities rather than the trunk. On the limbs, the distal parts and on the trunk the upper part of the back, rather than the abdomen and chest, are involved. Much weight is attributed to the detection of a few deep-seated lesions in the skin of the thenar and hypothenar eminences.

The lesions are more superficial than in *variola major*, but not so superficial as

the vesicles of chicken-pox. They are not always spherical, and are often unilocular and not umbilicated. Mature vesicles have an opalescent rather than frankly purulent appearance, and the crusts are of a deep amber colour. It is easy to understand why the disease is so often mistaken for chicken-pox. The distribution of the rash is the important diagnostic criterion. Although vaccination protects against variola minor the converse is not invariably true. As a rule, vaccination in the eruptive stage fails, but may take in modified form later.

Serological tests fail to differentiate variola minor from variola major.

**Complications.**—During the later stages of small-pox and in convalescence boils and superficial abscesses often cause trouble. Septic rashes and erysipelatous or impetiginous infections may spread from the pocks. The cervical and axillary lymph glands may in such cases become enlarged or even suppurate. In the more severe infections, deep-seated muscular abscesses, cellulitis or sloughing of the skin may occur and bed-sores may form rapidly over pressure points. Rarely death is due to septicæmia arising from these secondary lesions.

Implication of the mucous membranes of the eyes, nasal cavities, fauces, larynx and gullet may bring its own train of serious complications. Ocular complications are important. Conjunctivitis is common. Pustules may form on the palpebral or ocular conjunctivæ. The eyelids often become inflamed and œdematous. A rapidly spreading keratitis may lead to sloughing of the cornea, but corneal ulcers are more common and sometimes lead to perforation and panophthalmitis. Irido-cyclitis is rare. Retinal hæmorrhages sometimes cause blindness. The scars of the corneal ulcers may impair the sight.

Otitis media is comparatively common.

Laryngeal inflammation may be so severe as to necessitate tracheotomy and may lead to perichondritis and necrosis. Bronchitis and broncho-pneumonia are frequent and often accelerate death, but lobar pneumonia and purulent pleurisy are rare. Endocarditis and pericarditis are also exceptional, but degenerative changes in the myocardium are not infrequent. Occasionally osteomyelitis or a destructive arthritis supervenes. Although albuminuria is often found, a frank nephritis is uncommon.

Parotitis is looked upon as a secondary duct infection from the mouth, and secondary orchitis or oophoritis sometimes occurs during the acute stage.

As in other fevers encephalomyelitis and neuritis may occur some 5 to 13 days after the appearance of the rash, but the incidence of these is exceedingly low. On recovery from small-pox speech may for a time be completely lost. Less favourable are bulbar or limb paralysis, with or without derangement of sphincter control (see p. 1411).

Deep pitting of the face, permanent blindness, deafness and sometimes alopecia may be the legacies of a severe attack.

**Diagnosis.**—Papular or vesicular rashes which even though scanty affect the face and extremities symmetrically are always suspect. The body should be stripped and examined in a good light. A preliminary bath may be needed. Attention is first focused on the distribution rather than on the characters of the rash. The individual lesions should be plotted on an outline diagram of the body, and a numerical comparison made of those on the abdomen, chest, back, shoulders and upper arms, forearms, face, buttocks, thighs and legs. Repeated observations will determine their spread and maturation. Too much reliance should not be placed on shottiness or umbilication. The condition as to vaccination should be ascertained and the nature of any prevailing epidemic borne in mind.

The initial fever may lead to the first difficulty in diagnosis; the symptoms of onset are very similar to those met with in other acute diseases, particularly influenza, acute rheumatism, pneumonia, typhus and cerebrospinal fever. Severe prostration and backache, when present, are suggestive. Often the diagnosis is not certain until the focal eruption appears on the third day and the fever subsides, but the appearance

of a petechial prodromal rash in the groins may lead to earlier recognition. It is more common for small-pox to be mistaken for influenza than for the converse to occur. Lumbar puncture is diagnostic in cerebrospinal fever. In pneumonia sooner or later lung signs appear. Precipitate certification of a supposed case of small-pox, even in a contact, is unwise; it is better to isolate and await the appearance of the rash, remembering this should appear first on the forehead, near the roots of the hair, the cheek bones, sides of the nose, wrists, hands and forearms. The interior of the mouth should be inspected and also parts of the skin which have been subjected to special irritation.

The prodromal rashes, if purpuric, may be confused with different varieties of purpura or leukæmia; if erythematous, with scarlet fever, measles, rubella, urticaria or other forms of erythema.

The characteristic groin or "bathing drawers" incidence of the purpuric rash of small-pox is of great assistance in early diagnosis. More widespread purpuric rashes, however, are at times misdiagnosed as febrile purpura until the occurrence of small-pox in contacts reveals their true nature. Conversely, febrile purpura and purpuric rashes occurring in bacterial endocarditis, cerebrospinal fever and other conditions may be mistakenly thought to indicate small-pox. The distribution of the rash and the character of accompanying symptoms should be noted. Physical examination of the organs may reveal signs which help to clear up the diagnosis, which may be very difficult.

A scarlatiniform prodromal rash is distinguished from scarlet fever by its explosive outbreak with the absence of tonsillitis and of punctate redness of the soft palate. The rash, too, on the skin is not definitely punctate and the area of circumoral pallor is wanting. The tongue is not typical nor are the tonsillar lymph glands enlarged. The Schultz-Charlton test is negative.

Morbilliform prodromal rashes are less common and bear only a very superficial resemblance to measles. The diagnosis is discussed below. Nor should rubella be confused if its characters are borne in mind. The prodromal erythematata may resemble those induced by antitoxin serum, by soap enemas and by drugs. The characters of these rashes are given in the article on scarlet fever (p. 45).

The focal eruption of small-pox in its various stages may be confused with measles, chicken-pox, herpes zoster and even herpes febrilis or perhaps typhoid or typhus, also with various forms of papular erythema, urticaria, acne, papular or pustular syphilides, and glanders. Sometimes drug rashes, particularly bullous eruptions due to iodides, lead to mistakes. Confluent or hæmorrhagic small-pox in the papular stage is often mistaken for measles. The 3-day prodromal fever and lesions in the mucous membrane of the mouth favour this error. But there is no real catarrh in small-pox, and the buccal infiltrations only superficially resemble Koplik's spots. The distribution of the rash, and the fact the temperature tends to fall as the eruption increases instead of rising as it does in measles are distinctive.

The differentiation of chicken-pox is important. Chicken-pox is a disease of childhood whilst small-pox now chiefly affects adults, but cases of chicken-pox in the adult are not infrequent, and in them prodromal symptoms may be sharp and the rash not appear until the second or third day. Chicken-pox presents the following distinctive characters:

1. The rash of chicken-pox appears first on the trunk, and is thickest on the trunk, face, perhaps the scalp, upper arms and thighs. It is centripetal and tends to avoid the extremities of the limbs. It does not so markedly select irritated areas, nor does it avoid the axillæ and groins. The presence of many lesions on the palms and soles is greatly against chicken-pox.

2. The eruption comes out in distinct crops for 3 to 5 days or more.

3. The vesicles develop much more rapidly and are mature in 24 hours. Vesicles are not seen at this period in small-pox.

4. The lesions are superficial and unilocular, rarely umbilicated. Their bases are not indurated. Near flexures they may assume oval outlines, sometimes becoming irregular or crenated.

5. The outbreak of fresh vesicles on a given area of skin over a period from the 24th to the 72nd hour, *i.e.* on the second and third days, is characteristic. Hence by the third day the lesions of chicken-pox are in various stages of development from vesicles to crusts.

6. The lesions are smaller. Pustules and scabs half an inch across are almost certainly due to small-pox.

7. Efficient vaccination within 5 years or revaccination within 10 years is generally but not invariably evidence against the disease being small-pox.

8. Chicken-pox does not protect against successful vaccination in an unprotected individual: in small-pox vaccination will not take after the rash has appeared. This rule, however, is not absolute. Vaccination may prove successful in anomalous forms of small-pox, and has been alleged to take in ordinary small-pox on rare occasions.

9. Apathy and muscular relaxation are not features of chicken-pox. A copious rash with complete absence of prostration suggests chicken-pox rather than small-pox.

In distinguishing skin eruptions it should be remembered that zoster is rarely bilateral. Erythemas are often polymorphic; they may show occasional vesiculation which is quite superficial and are sometimes febrile. Acne affects the face, shoulders, back and chest, but not the forearms or hands; it is chronic, afebrile and often associated with comedones and scars. The lesions may be pustular but are never vesicular.

If syphilis is borne in mind its eruptions are not likely to be mistaken. Glanders is rare, but when the nodules on the face suppurate and are accompanied by fever, small-pox may be suggested. There is usually a nasal discharge and a history of close contact with horses. Bacteriological examination will show the *Pfeifferella mallei*.

**Laboratory diagnosis.**—Certain laboratory tests are valuable:

1. Detection of variola antigens in the vesicular fluid or in the crusts by a precipitation test or by complement deviation, making use of anti-vaccinal rabbit serum.

2. Paul's test which depends on the production of Guarnieri bodies by scarification of the cornea of a rabbit with vesicular fluid from small-pox or vaccinia.

3. The intradermal injection of vesicular fluid produces in the rabbit a characteristic inflammation which is prevented by previous admixture with hyperimmune rabbit serum.

4. The procedure recommended by van Rooyen and Illingworth who have shown that even in the early papular as well as in the vesicular stage of small-pox the elementary bodies can be demonstrated in great profusion by the application of Paschen's method of staining to films of scrapings from the bases of the buccal lesions, the skin papules and the vesicles, but not the pustules of small-pox. This facilitates early diagnosis. Moreover, since the elementary bodies of chicken-pox, herpes zoster and also of herpes febrilis are smaller, scantier and extremely difficult to stain, the important differentiation of these diseases is possible.

5. Inoculation of the chorio-allantoic membranes of a growing chick embryo with the virus of small-pox or vaccinia produces discrete plaques. These do not appear when the virus is that of chicken-pox. Febrile herpes and herpes zoster also produce visible lesions, which can be identified serologically.

Procedures 1 and 5 are the most valuable differential tests.

**Prognosis.**—Variola major has a mortality which varies from 25 to even 50 per cent. The prognosis may be considered under the following heads: (1) The vaccinal condition of the patient; (2) the age; (3) the nature of the attack; and (4) the character of the prevailing epidemic.

1. When a vaccinated person takes small-pox the nature of the attack usually



indicates some residual immunity, the severity of the disease being less and the mortality much lower than in the unvaccinated. The presence of large, well-foveated vaccination scars renders the prognosis very favourable. After the age of 15 or even 3 years earlier, the protective influence of infantile vaccination will to a large extent have disappeared, but revaccination at puberty, properly performed, confers a high degree of immunity for the rest of life.

2. In the unvaccinated the death-rate from variola major in the first 5 years of life is very high and may exceed 40 per cent. After that there is a fall, at first gradual, then considerable, up to the age of 15 or 20, which is the most favourable period. Subsequently the mortality rises steadily and may even exceed the figures given for the first quinquennium. In the vaccinated, however, the younger the patient the more certain is recovery. If revaccination has not been performed, as age increases the mortality does so also, and may reach 15 per cent. in persons over 30 years of age.

3. The nature of the symptoms is important. Mild invasion presages a mild attack. Severe invasive symptoms usually, but not invariably, mean a severe infection, but they may precede mild attacks in the vaccinated and sometimes in others. Prodromal rashes of a vivid lobster hue, especially if petechiæ are present, are the heralds of grave, often hæmorrhagic infections. Very intense backache is also an ominous invasive symptom. The more profuse the pustular rash the worse the prognosis, but the intensity of the suppurative stage is much modified by previous vaccination. Confluent eruptions mean a bad outlook, whilst patients in whom the rash remains discrete usually recover. Recovery from the vesicular or pustular form of hæmorrhagic small-pox is occasional, but in the pre-eruptive *purpura variolosa* death is usually inevitable. Bleeding from mucous membranes is of very bad augury.

Other unfavourable symptoms are incomplete remission between the primary and secondary fever, sleeplessness, active delirium, especially in drinkers, considerable implication of the larynx and broncho-pneumonia. The influence of pregnancy in inducing abortion and miscarriage has already been mentioned (p. 159).

4. Epidemics vary much in their severity and mortality. In some the disease is so slight and the mortality so low, that doubts arise whether the epidemic is really small-pox.

**Treatment.**—**PROPHYLACTIC.**—Vaccination and revaccination are the most powerful safeguards. The chief measures to be taken when the disease is recognised are the following: (1) Prompt removal of the patient to an isolation hospital. (2) Thorough disinfection of infected rooms and clothing. (3) Immediate and efficient vaccination or revaccination of all other members of the household and of contacts. Four or even more days after exposure vaccination may prove effectual in preventing the disease, at all events will modify it (see p. 163). (4) Quarantining of contacts for 16 days, or a daily inspection so that initial symptoms may be detected at once. (5) Notification of schools or institutions attended by inmates of the same house.

Inoculation with small-pox, which confers more complete immunity than vaccination and which prior to vaccination was a method of prophylaxis, is said in some instances to have a mortality of 2 or 3 per cent.; but even this compares favourably with a mortality of 40 or 50 per cent. as seen in some epidemics of ordinary small-pox. Inoculation, however, was found to spread the disease, and so has, in England, been made a penal offence.

**SYMPTOMATIC.**—Fresh air, cool surroundings, light bedclothes, free fluid intake, regulation of the bowels and tepid sponging night and morning form the regular routine. The mouth should be cleansed regularly, and the nose gently douched or liquid paraffin instilled. Pain in the head and back may be mitigated by the ice-bag to the scalp and use of fomentations to the loins. Aspirin, phenacetin or chloral and bromide may give relief; but the drug most generally useful, both in this stage and in the sleeplessness, delirium and discomfort of the secondary fever, is opium in the form of gr. 10 of Dover's powder. Sometimes paraldehyde is effectual. Delirious

patients should never be left alone. The vomiting of the early stage is allayed by citrating the milk or substituting ice and champagne. Liquor iodi mitis in 5-minim doses is also useful. When fever continues high and is accompanied by toxæmia and delirium, tepid sponging may be replaced by hot or cold packs with advantage.

Many methods have been tried in the hope of aborting the eruption and preventing the subsequent sepsis and pitting. Sulphonamides have no influence on the toxic stage, but both they and the antibiotics are said to influence favourably the focal eruption in the vesicular stage and to be of value in the septic complications. Some advocate painting the face with liquor iodi mitis, diluted if painful, twice a day for the first 8 or 10 days, and then applying soft paraffin; or, better, commencing in the papular stage, a saturated (5 per cent.) solution of potassium permanganate may be painted over the whole body three times a day until scabbing begins, and afterwards less frequently. In confluent cases the patient may be immersed daily in a 3 per cent. permanganate bath for 15 minutes at body temperature. The application of a lint mask soaked in glycerin is useful, and glycerin may also be applied to the hands. It may be necessary to cut the hair short. To mitigate the offensive odour, dilute carbolic lotions may be applied (they also relieve the itching), or creosote may be vaporised in the sick-room. Starch poultices and alkaline washes are used for the removal of crusts and zinc ointment or a 5 per cent. sulphathiazole ointment with 1 per cent. of phenol applied.

The eyes should be bathed with boric acid lotion at frequent intervals, and dilute nitrate of mercury ointment smeared on the edges of the lids. Should keratitis threaten, silver protein is instilled or an ointment of atropine with yellow oxide of mercury applied.

Laryngitis is relieved by a steam tent and inhalations of benzoin or lysol.

Patients are to be regarded as infectious until the scabs are all separated and the skin and mucous membranes quite healed. Deep-seated crusts in thick skin should be extracted and destroyed.

## VACCINIA

Vaccinia or cow-pox, a disease at one time very prevalent among cows, but now rare, is characterised by a vesicular eruption on the udders and teats. The vesicles, which are surrounded by inflammatory areolæ, may by rupture form extensive ulcers. Abrasions on the hands of milkers may be accidentally inoculated from these lesions and they, in turn, may inoculate other cows in the herd. The hands of the infected milkers show vesicles with surrounding induration, the axillary glands become swollen and there is some fever.

Individuals accidentally inoculated with cow-pox are protected from small-pox, and Edward Jenner made practical use of this fact by inculcating the practice of deliberate vaccination and transference of the virus from arm to arm. In addition he demonstrated that those thus vaccinated were refractory to subsequent inoculation with the virus from small-pox lesions, and that milkers who had had small-pox did not catch vaccinia from the cows. But it appears that although vaccinia protects against small-pox, an attack of small-pox does not invariably protect against vaccinia.

After long dispute, the question of the identity of cow-pox and small-pox has been settled by animal experiment in favour of Jenner's view that the two diseases are one and the same, small-pox virus being so modified by its transmission through the cow that its inoculation results only in a local lesion, a lesion which, however, affords a high degree of protection against small-pox. Vaccinia differs from small-pox, whether the latter is natural or deliberately inoculated, in that it has lost its infective character, and so can be used for purposes of vaccination without risk of propagating small-pox.

The histology of the vaccine vesicle is similar to that of the lesion of small-pox. It goes through the stages of papule, vesicle and pustule; and loculation is produced by persistence of the remnants of vacuolated epithelial cells in the form of septa.

Professor Paschen has described minute "elementary bodies" as constant accompaniments of vaccinal lesions, and Ledingham has shown that these "Paschen bodies" are agglutinated by the sera of rabbits which have recovered from vaccinia. It is believed that these bodies are the filtrable virus of the disease.

For the purpose of vaccination vaccine lymph is prepared by the inoculation of healthy calves, the contents of the vesicles being collected and freed from pyogenic and other extraneous organisms by admixture with glycerin. This process of glycerinisation kills most of the adventitious germs, but leaves the virus of vaccinia uninjured. The lymph thus prepared, if stored in capillary tubes at low temperature, will remain efficacious for at least 8 months. Vaccinia virus may be cultivated on the chorio-allantoic membrane of chick embryos and this product has been used for vaccination. Continuous passage deprives the virus of some of its virulence, and there is good evidence that it affords less enduring protection against small-pox than calf lymph.

Vaccination is carried out as follows: An area of skin over the insertion of the left deltoid muscle or on the outer side of the thigh or leg is cleaned with soap and water, and afterwards with ether or acetone and allowed to dry thoroughly. A drop of lymph is ejected from the capillary tube on to the area of cleaned skin and, with a sterile needle, a scratch is made through it one-quarter of an inch long and just deep enough to penetrate the epidermis without drawing blood. The arm should be left uncovered until the lymph has dried and a wheal appeared when a sterile dry dressing should be applied.

Until 1929 it was customary to make four insertions of lymph, but, following an increase in post-vaccinal encephalitis, a Vaccination Order of that date recommended a single linear insertion of the type described. In 1947 the Ministry of Health advised a single insertion for primary vaccination in infants and two insertions an inch apart for others. Revaccination should be effected by one insertion. It is probable that this method does not provide immunity for more than 1 or 2 years and it should be repeated yearly in those especially exposed to infection.

If the operation is successful, inflamed areas appear at the sites of inoculation, and by the third day become distinctly papular and itchy. By the fifth day, small clear vesicles have formed which slowly increase in size and become depressed at their centres. By the eighth day the vesicles are large, sharply defined and their inflammatory areolæ are confluent. From this time the contents become increasingly cloudy. The vesicles attain their full size by the twelfth day and collapse. By the tenth or twelfth day a brownish scab is forming. This separates later, leaving a depressed and pitted or foveated scar which at first is livid, but in course of time becomes dull white.

An alternative method which is very effective is vaccination by multiple pressure. A flat-sided needle held between thumb and forefinger is laid tangentially on the skin, its point in a drop of lymph. By finger pressure on its shaft it is rapidly depressed and released 20 times or more. By this means the epidermis is pierced superficially by the side of the needle-point without drawing blood.

In vaccination the virus is distributed by the blood throughout the body. Headache, malaise and fever accompany maturation of the vesicles at the beginning of the second week; the axillary glands may become enlarged and tender and the spleen palpable. Sometimes febrile disturbance is noticed as early as the fourth day.

In revaccination the events are similar, but both the local and constitutional disturbances are accelerated and less pronounced or may fail to appear. The lesions may run a very rapid course, aborting at the papular or early vesicular stage. Vaccination should only be recorded as successful when a vesicle appears. A fleeting papule 3 to 72 hours after vaccination is often a sensitivity reaction to some alien constituent

of the lymph. The Ministry of Health (1947) has recommended that the results of vaccination should be recorded as follows: negative—"No local reaction to vaccination (repeated)"; erythema only—"Maximum local reaction (non-vesicular) on second to third day"; vesicular (maximum 3 to 7 days)—"Accelerated or vaccinoid reaction"; marked vesicular (maximum after seventh day)—"Typical vaccinia, primary or equivalent".

Natural insusceptibility to primary vaccination is excessively rare, and at least three successive attempts should be made before insusceptibility is assumed.

Although infants can be vaccinated successfully in the first few weeks of life, under ordinary circumstances the best period is from the second to the sixth month. Revaccination is advisable after the second year and when small-pox is epidemic. Vaccination is no longer obligatory in Great Britain.

The degree of protection afforded is in some degree proportional to the extent of the vaccinal lesion. The test of a successful scar is its depression and foveation, the latter indicating that vesiculation has occurred. The period of immunity may be regarded as not less than 2 years.

**RISKS OF VACCINATION.**—Fugitive erythemata, which are sometimes scarlatiniform, measly or urticarial, may appear about a week after vaccination; they are akin to serum rashes. Erysipelas, septic infection and cellulitis sometimes result from the use of contaminated lymph or the lack of proper cleanliness at the operation or after. Under modern methods of glycerinisation and asepsis, these should not occur. There is no doubt, too, that syphilis has on rare occasions been conveyed by arm-to-arm vaccination. In such cases, the chancre does not appear before the fifteenth day, and is usually later. The calf being insusceptible to syphilis, the use of calf lymph has abolished this danger. Tetanus is another infection which has occasionally resulted, especially in hot climates. Tuberculosis and leprosy have also been cited as possible sequels, but with little or no proof. The appearance of eczema and impetigo has been attributed to vaccination.

A rare sequel, to which special attention has been drawn, is a form of encephalomyelitis. Its greatest incidence has been in Holland, Great Britain and Germany, and has varied from 1 in 5000 to 1 in 100,000 vaccinations. The characteristic lesion is a focal, perivascular demyelination of nerve fibres, often associated with perivascular cuffing. It very rarely follows vaccination during the first year of life. Its chief incidence is where infantile vaccination is not the rule, *i.e.* after primary vaccination of children of school age or of adolescents. Very similar to the encephalomyelitis of small-pox and of measles, it sets in 7 to 12 days after vaccination, with headache, vomiting and paresis. These symptoms become aggravated, and delirium may pass into coma and death. In other cases the symptoms are more suggestive of meningitis, myelitis, lethargic encephalitis, with ocular palsies or of tetanus. The mortality may reach 50 per cent., but when recovery occurs it is usually complete. Human serum, from a healthy donor who has been successfully vaccinated recently, or anti-vaccinal horse-serum, is the best antidote. The serum is given intravenously. The dose is 8 to 30 ml., repeated if necessary. Repeated lumbar puncture is a valuable adjuvant.

Latent infection may be brought into activity and prominence by vaccination; this is the case with congenital syphilis and tuberculosis. Hence the advisability of postponing vaccination until the age of 2 or 3 months or should the infant show skin eruptions or signs of ill-health. Acute specific fevers are no bar to vaccination if necessary.

Very rarely the course of vaccinia is complicated by the appearance of a generalised vesicular eruption, the lesions appearing on the trunk and perhaps in successive crops. They pass through the stages of papule, umbilicated vesicle and crust. Generalised vaccinia of this type is usually febrile and occurs from 7 to 11 days after vaccination.

*Accidental vaccinia* is the term applied to fortuitous inoculation from a vaccinal

lesion. Mothers are sometimes thus inoculated from their infants, the common site being the face, lip or eye. The mouth, throat or a skin lesion may at times be involved. When occurring on the face, there is much œdema with swelling of the lymph glands, so that anthrax or syphilis has been suspected. The vaccinated baby may also, by scratching, inoculate its own nose, cheeks, fingers or other parts of its body.

**PROTECTION AFFORDED BY VACCINATION.**—The immunity to small-pox which vaccination confers is not necessarily permanent. Ten years is considered an average duration. A child vaccinated in infancy should be revaccinated at the age of 7 years and again in adult life. In areas where small-pox is endemic revaccination every 10 or 12 months has been recommended. Whatever their vaccinal condition, persons coming into contact with small-pox should be revaccinated at once.

Since vaccinia has a shorter incubation period than small-pox, a person efficiently vaccinated or revaccinated within 3 days of exposure to the latter disease will, in all probability, escape it, but vaccination does not fully protect during the first week of the vaccinal period should exposure continue. Ricketts made the following statement: "The period of incubation of small-pox, counting to the outcrop of the rash, may be taken as 14 days. If this period be divided into three intervals comprising 7 days, 3 days and 4 days, it will be accurate, in the main, to say that a successful vaccination done in the first period will wholly prevent the attack, done in the second will have more or less effect in modifying the eruption, and done in the third will merely add to the patient's troubles."

## CHICKEN-POX

**Synonyms.**—Varicella; Glass-pock; Water-pock.

**Definition.**—An acute infective disease, characterised by a rash which tends to appear in successive crops, each lesion passing rapidly through a papular stage to one of superficial vesiculation and subsequent partial pustulation. The lesions then desiccate and scab.

**Ætiology.**—Chicken-pox is universally prevalent and highly infectious. One attack usually affords complete protection, second attacks being extremely rare. It is mainly an affection of middle childhood, being uncommon after 10 years of age, but adults even of advanced years may contract it, and infants are not completely immune. Season and climate are not known to exert any influence on its incidence. It affects both sexes equally. Infection is in most cases direct by droplet spray, but articles of clothing may remain infectious for a considerable time, and the disease is sometimes carried by a healthy intermediary. The dried scabs can communicate the disease, probably by powdering and ingestion or inhalation. Like small-pox, chicken-pox is inoculable from the vesicles—but not easily. Convalescents from acute diseases, particularly from measles, diphtheria and scarlet fever, are believed to be peculiarly susceptible to chicken-pox. The disease occurs sporadically or in the form of limited outbreaks. The infective agent is a virus, and the association with herpes zoster lends support to the view that it may be a filtrable virus, identical with the neurotropic virus of that disease.

**Pathology.**—Micro-organisms occur in the pocks, and particulate bodies have been described similar to those seen in vaccinia and small-pox. Pure suspensions of these particulate or elementary bodies are agglutinated by the serum of convalescents from varicella or herpes zoster. The inflammatory lesions are more superficially situated in the skin than those of small-pox; but the process of vesiculation is similar. Loculation is indistinct, and umbilication exceptional. When the clear vesicles become clouded, but rarely before this, polynuclear and mononuclear cells are found in their contents. An occasional leucocytosis and a shift to the left occurs in the first week. Later eosinophils, plasma cells and Turk cells also appear.

**Symptoms.**—*Incubation period.*—This is usually a fortnight or a little more; but extremes of 11 to 23 days are mentioned.

In childhood the appearance of the eruption usually constitutes the first sign, and is taken to indicate the first day of the disease. In adults slight pyrexia and sometimes headache, shivering and even pain in the back may precede the eruption for 48 hours. In exceptional cases, mostly in children, vomiting and convulsions have occurred at the onset.

Prodromal rashes are not very uncommon. An erythema, either patchy or uniform, which may be punctate, sometimes precedes the eruption for some hours and may be mistaken for scarlet fever; it avoids the face, does not blanch by the Schultz-Charlton test and does not desquamate. The incipient papules of chicken-pox can sometimes be recognised in the erythema or in the mouth. Less frequently the prodromal rashes are measly or urticarial.

The eruption of chicken-pox appears first on the trunk, but soon spreads to the face, the scalp and the proximal parts of the limbs. Sometimes it is on the face that it is first noticed. Occasionally, and it may be primarily, the eruption invades the mucous membranes, especially the fauces, soft palate and the pharynx. The lesions have been seen in the alimentary canal, the bladder and the renal pelvis, also on the peritoneum. The spread of the rash does not conform to the orderly progress of small-pox, it appears in several crops on successive days; these may come out for 2 or 3 days in mild cases, for a week or more in those which are severe. The total number of lesions may be anything from a few to some hundreds. They are thickest on the trunk, especially on the back, and next to this on the face and in the scalp. They tend to invade the limbs from above downwards, but are characteristically sparse and often small on the distal portions; a few vesicles are occasionally seen on the palms and soles. The axillæ do not escape as in small-pox, and it is unusual for the rash to show an especial incidence over ridges or pressure points. Various forms of skin irritation may, however, at times determine a local profusion of the rash.

The lesions are in turn macular, papular, vesicular and mildly pustular. The macules are very transitory, soon becoming rounded or ovoid papules of a pinkish colour and slightly salient, something like the rose spots of typhoid, or larger. Vesiculation rapidly ensues, and is complete in 24 hours or a little more. The vesicles seldom exceed a third of an inch in diameter. They look like translucent droplets, lying on rather than in the skin. An areola may or may not be present. On the scalp, forearms, hands and feet they may be set deeper, and show some hardness. Some assume oval or irregular outlines, especially when lying near creases or folds of the skin. On maturity the vesicles take on a pearly hue. When punctured, most of them collapse entirely, and umbilication is rare. Confluence of adjacent vesicles hardly ever occurs. Owing to its itchiness, the rash is often infected by scratching or rubbing, and then the lesions become larger and more inflamed. Otherwise the vesicles dry up into superficial brown scabs in a day or two, which on separating leave slight pink stains, but no appreciable pitting.

The appearance of the eruption in successive crops, as the disease progresses, leads, after the lapse of a day or two, to the presence at the same time on the same area of skin of lesions in all stages of development, *i.e.* papules, vesicles, small pustules and scabs.

On mucous membranes the vesicles soon rupture and leave shallow grey ulcers, often with red areolæ.

Slight pyrexia usually accompanies the appearance of the rash. Some cases are apyrexial throughout. Rarely the temperature rises as high as 103° or 104° F. Successive crops of spots may be accompanied by successive recurrences of fever. Constitutional symptoms, as a rule, are absent.

**Varieties.**—Chicken-pox varies much in intensity. It may be so mild that only one or two pocks are recognised. Sharp invasive symptoms may mark its advent in

the adult. There are three special but uncommon varieties of the disease: (1) *Varicella bullosa*; (2) *Varicella gangrenosa* and (3) *Varicella hæmorrhagica*. In *V. bullosa* the vesicles rapidly form large blebs, which on rupture leave painful raw surfaces. *V. gangrenosa* is seen in debilitated children and those recovering from scarlet fever; large dark crusts form and on separation reveal ulcers which may spread on the surface and in depth with great rapidity. Constitutional disturbance is severe, and pulmonary complications often supervene. Infection of the lesions with yellow staphylococci, hæmolytic streptococci or virulent strains of the diphtheria bacillus should be suspected. *V. hæmorrhagica* is rare; hæmorrhages occur into the vesicles and intervening skin, and bleeding sets in from the mucous membranes. It has a very high fatality rate. Bleeding confined to the vesicles is not so serious.

**Complications.**—Laryngitis or slight bronchitis is present in some cases. Pocks on the conjunctivæ, vulva or prepuce may give rise to troublesome symptoms. Accidental septic infections sometimes occur in the eruptive stage. Acute nephritis and arthritis are exceptional results of these.

Nervous complications are very rare and usually benign. They are attributed to encephalomyelitis, and chiefly affect children, usually occurring during the second week of the infection. Rarely they precede the eruption. The onset is acute and febrile; it may be accompanied by vomiting, vertigo and convulsion. Ataxia and tremor are more common than motor paralysis. With spinal lesions the picture may be that of a transverse myelitis. Optic neuritis, ophthalmoplegia and, very rarely, peripheral neuritis have also been recorded. In most cases recovery has ensued.

*Herpes zoster* is closely akin to chicken-pox. A scattered vesicular rash indistinguishable from chicken-pox may precede, accompany or follow the zoster eruption. Herpes zoster may also give rise in contacts, mostly children, to typical chicken-pox after an incubation period of from 12 to 21 days, and chicken-pox may follow inoculations from zoster vesicles. The converse, for chicken-pox to give rise to herpes zoster, is a much less common event, which usually occurs in adults. It is a curious fact that there is no clinical evidence of any cross-protection between the two diseases.

**Diagnosis.**—A mild or modified case of small-pox may erroneously be supposed to be chicken-pox, or chicken-pox with a profuse eruption and constitutional, or the rare hæmorrhagic, symptoms may be supposed to be small-pox. The differential diagnosis, in which the distribution of the rash is of primary importance, is considered in the article on small-pox. Here it may be stated that in a patient under 10 years of age, with well-foveated vaccination scars, a profuse eruption is generally chicken-pox, whilst a scanty eruption with well-marked invasive symptoms is more likely in these circumstances to be modified small-pox.

The erythematous prodromal rash may simulate scarlet fever, but other signs of this disease are wanting, and the chicken-pox eruption appears within 24 hours in the mouth or on the skin (see also p. 45).

Certain skin diseases characterised by vesicles or bullæ may be mistaken for chicken-pox. These include insect bites, scabies, acne, impetigo, papular urticaria, pemphigus and erythema multiforme. Differential criteria are prolonged duration, recurrences, distribution, absence of fever and usually no lesions in the mouth.

A varicella-like type of syphilide is known. It usually affects the trunk, is much more persistent and is accompanied by other evidence of its nature.

**Prognosis.**—Death is very rare. The gangrenous form may prove fatal to debilitated children, and the rare hæmorrhagic form is said by most authorities to have a very bad prognosis.

**Treatment.**—Although most infectious in the pre-eruptive and early eruptive stages, patients should be isolated until every scab has separated—usually a period of 2 or 3 weeks. They should be confined to bed during the eruptive period. Skin irritation may be allayed by mild dusting powders, and it is sometimes advisable to fix the arms in light splints. It is rarely necessary to cut off the hair. Inflamed

pocks may need fomentation with boric acid. Crusts which re-form may be removed by starch poultices and zinc or mercurial ointment applied. Septic or gangrenous varicella is an indication for the use of an appropriate antibiotic, perhaps combined with a sulphonamide.

When discharging patients, particular attention should be paid to the scalp, as scabs may remain entangled in the hair. It is doubtful if lesions which have crusted several times are still infectious. The quarantine period for contacts is 3 weeks, but it is quite safe for it to commence 10 days after exposure to infection and be maintained for 12 days.

Attempts at prophylaxis with convalescent serum and gamma globulin have not proved very successful.

## MUMPS

**Synonyms.**—Epidemic Parotitis; Infectious Parotitis.

**Definition.**—An acute infectious disease, characterised by swelling of the parotid, and sometimes of the other salivary glands, accompanied by constitutional disturbance which is usually mild. With the exception of orchitis, complications are infrequent, and a fatal termination is exceedingly rare.

**Ætiology.**—Mumps is endemic in most large centres of population throughout the civilised world. No climate is adverse and no race is immune. Children and young adults of both sexes are those usually attacked; but no age is entirely exempt, although the disease is rare in infants and in the aged. The mother has transmitted the disease to the foetus *in utero*. There is also some evidence that congenital malformations may result. Dogs and cats have been known to contract the infection from their owners.

The malady usually appears during the winter or spring months. Outbreaks are generally localised, and often limited to particular schools, business houses or barracks. Infection is direct from patient to patient and close contact is necessary; but is sometimes conveyed by an apparently healthy intermediary, or by fomites.

**Pathology.**—Mumps is due to infection by a neurotropic filtrable virus. Invasion of the nervous system is thought by some to occur prior to invasion of the salivary glands. An alternative view is that a primary septicaemia is followed by localisation of the virus in certain susceptible organs. The infection can be passed to monkeys by bacteria-free filtrates of saliva on the first or second day of the disease, or by puncture fluid from the swollen glands, and has been re-transferred from monkey to man. The virus can be cultivated in chick embryos and the antigen from this source used in complement-deviation tests.

A round-celled inflammatory exudate with much œdema and small hæmorrhages involves the interstitial tissue of the affected organs. Their acini and ducts may show a patchy epithelial degeneration. The interstitial inflammatory œdema may spread to surrounding tissues and sometimes to adjacent lymph-glands. The secreted saliva contains a few polymorph and mononuclear cells with cells shed from the acini and ducts.

**Symptoms.**—The incubation period is 3 weeks; but extremes of 14 and 35 days, or even 37 days, are admitted. A swelling of the parotid gland is usually the first indication of the malady, but this may be preceded for a day or two by pain and stiffness in the region of the masseter muscle, or by tenderness on deep pressure below and behind the angle of the jaw and by such prodromal symptoms as feverishness, shivering and sore throat. Sometimes a meningeal reaction marks the onset (*Cerebral Mumps*).

The parotid swelling is at first unilateral, and commonly appears on the left side. It may increase for 2 or 3 days, forming an ill-defined, elastic swelling, which obliter-



ates the sulcus between the mandible and the mastoid process, lifts the lobe of the ear away from the head in a characteristic manner and extends forwards on the surface of the masseter. Only rarely is the skin over and around the gland either reddened or œdematous. The swelling subsides after a few days, sometimes very quickly, but a distinctive and, when present, highly diagnostic feature is the occurrence, 24 or 36 hours after onset, of swelling in the other parotid region, sometimes with fresh febrile disturbance; or the submandibular and sublingual glands may now be attacked. The interval between the invasion of the two parotid glands may extend to 4 or 5 days, or even longer; sometimes they are attacked simultaneously. Sometimes, too, the submandibular or sublingual glands become swollen first, in which case palpation with one finger in the mouth and another below the jaw will reveal the acorn-like swelling, and movement of the tongue may become painful. The parotid may escape, or may swell in its turn. The lacrimal gland is rarely attacked. When multiple bilateral glandular swellings are present the features become much distorted.

Moderate pyrexia ( $101^{\circ}$  or  $102^{\circ}$  F.) may accompany the onset and persist for a day or two; but the attack is often afebrile and the pulse-rate hardly quickened. On rare occasions constitutional disturbance is severe, the temperature rising to  $104^{\circ}$  or  $105^{\circ}$  F., with delirium and circulatory depression. It is said that the spleen usually becomes palpable.

The glandular swellings are accompanied by a feeling of tension rather than acute pain, but the inflamed parotid gland may cause great pain on attempts to separate the teeth, to chew or to swallow. The secretion of saliva is often defective, but in some excessive salivation is noticeable and food may increase the swelling of the gland. Injection of the orifices of the salivary ducts, pharyngitis and even tonsillitis are sometimes observed at the height of the attack. Enlargement of the cervical lymph glands may occur.

Mumps may appear in so mild a form as to be hardly noticeable. At times the only gland affected is the submandibular (*Submaxillary Mumps*). Occasionally orchitis, pancreatitis or lymphocytic meningitis is the sole manifestation of the disease.

With rare exceptions the swellings caused by mumps neither suppurate nor persist, although, occasionally, the parotid gland is said to be several months in resolving. Relapse sometimes occurs.

During the period of glandular swelling the blood usually shows a moderate leucocytosis, a characteristic feature being a relative and absolute increase in the number of lymphocytes. The supervention of orchitis does not invariably alter the blood picture, although, according to some authorities, it may give rise to an increase in the number of polymorphonuclear cells.

**Complications.**—*Orchitis* occurs in 15 to 30 per cent. of the males. It affects boys about the age of puberty and young adults; in childhood it is rare. Sexual activity is held to be a definite predisposing factor. The seventh or eighth day of illness is the usual time of onset; but it may occur 2 or 3 weeks later. In some instances orchitis precedes the inflammation of the salivary glands. The condition is really an epididymo-orchitis. Where surgical attempts have been made to relieve tension by decapsulation or incision of the tunica albuginea, effusion has been found in the tunica vaginalis, the testis engorged and the epididymis deep red. The onset is characterised by pain in the testis, which soon becomes swollen. Delirium, vomiting, collapse and considerable fever may accompany the testicular inflammation. The temperature may rise abruptly to  $103^{\circ}$  or  $104^{\circ}$  F. Fortunately the complication is usually one-sided, but in 10 to 20 per cent. of cases the other testicle is attacked in turn. Orchitis may be accompanied by œdema of the scrotum, swelling of the spermatic cord and enlargement of the inguinal glands. The pain may radiate to the lower abdomen. Exceptionally urethritis accompanies the testicular swelling. Subsidence of orchitis within a week is the rule, the temperature falling rather abruptly. Suppuration is very rare; but relapse sometimes occurs. Less than half the cases

show some appreciable testicular atrophy. When bilateral orchitis occurs before puberty the development of the individual is usually checked; rarely feminism has been reported. In the adult, even when as a sequel both testes appear atrophic, spermatogenesis may return after many months.

In the female, oöphoritis, inflammation and oedema of the vulva and mastitis are occasional complications.

*Pancreatitis* is a much less common complication than orchitis, but like the latter on rare occasions is the only manifestation of mumps. It should be suspected when acute abdominal pain, fever, vomiting and epigastric tenderness occur as sequels to the parotid swelling, which under these circumstances may show a rapid subsidence. Sometimes the swollen pancreas may be felt, but often its presence is masked by abdominal rigidity. The bowels are constipated, the stools may be fatty, or even contain blood. The serum and the urinary diastase is increased, as also is the lipase. The blood sugar may be raised, and glycosuria may occur. Jaundice is rare. The onset may be accompanied by alarming collapse. Fortunately recovery has occurred in most cases. Diabetes as a sequel to mumps is very exceptional, but undoubtedly may occur, sometimes even when the abdominal symptoms have been quite trivial. When mumps attacks a diabetic dangerous ketosis may occur. It should be noted that in mumps a raised diastatic index may occur without clinical evidence of pancreatitis, and is then attributed to infection of salivary glands.

*Nervous complications* are exceptional. Meningismus may signalise the onset and meningo-encephalitis may set in towards the end of the first or during the second week, it has even been known to precede the appearance of the glandular swellings. Later and rarely, an ascending paralysis or a general paralysis of the limbs and of certain cranial nerves, attributed to peripheral neuritis, occurs. As a general rule, however, a parotid swelling which causes unilateral facial paralysis is not due to mumps.

An excess of lymphocytes or of protein may be found in the cerebrospinal fluid, and is not uncommon during the first 15 days of mumps, even in the absence of definite meningeal symptoms.

Certain affections of the *organs of special sense*, although uncommon, deserve mention on account of their importance. Quite apart from deafness, due to the occasional occurrence of otitis media, true nerve deafness may occur unaccompanied by signs of middle ear disease. The deafness is of sudden onset, and when accompanied by nausea, vomiting, tinnitus and inco-ordination it is attributed to hæmorrhage or exudation within the labyrinth; but it may occur without any labyrinthine symptoms. Fortunately the deafness is usually unilateral, for it is incurable. A few cases of deaf-mutism have been attributed to mumps.

Papilloedema or retro-bulbar neuritis and optic atrophy are other rare but important sequels. Iridocyclitis, paralysis of certain extra-ocular muscles and loss of power of accommodation may also at times ensue; these mainly terminate in recovery after a variable time.

Among other possible complications may be mentioned epistaxis, bronchitis, pneumonia, pericarditis and arthritis. Electrocardiographic evidence of myocarditis has been reported in as high a proportion as 15 per cent. in some series. Transient albuminuria is not uncommon and nephritis sometimes occurs as late as 4 or 5 weeks after the onset of the salivary swellings; uræmia has been responsible for death in rare instances.

Suppuration in the parotid gland, gangrene of the gland, cellulitis of the neck and floor of the mouth and suppuration of the cervical lymph glands are very rare events, which are generally attributed to superadded septic infection. The inflammatory oedema of submaxillary mumps has on occasions spread to the glottis and necessitated tracheotomy. It has been noted, too, to affect the tissues overlying the manubrium sterni.

Relapses, characterised by a recurrence of the glandular swelling after a distinct interval, are not very uncommon. Although one attack of mumps usually protects the individual for life, second attacks are not unknown.

**Diagnosis.**—In the presence of an epidemic this presents little difficulty; but the true nature of the infection may be overlooked in sporadic cases or when the parotid swelling is insignificant, and when the disease primarily affects the submandibular or sublingual glands, or again when orchitis, pancreatitis or even meningo-encephalitis constitutes the first, and perhaps the only, manifestation.

Parotitis, usually unilateral, and attributed to ascending duct infection, is a well-known complication of certain fevers, and of some abdominal diseases. This is not contagious. It generally ends in suppuration, and is accompanied by a polynuclear leucocytosis. Swellings of the salivary glands, distinguished from mumps by their recurrent nature, are attributed by some to a mild chronic infection of the ducts, which may be dilated; others believe them to be allergic in nature (see p. 532). Swelling of the salivary glands may also follow the administration of certain drugs, such as iodide of potassium and pilocarpine, or be caused by salivary calculi.

A painless enlargement of the parotid and lacrimal glands, of great chronicity, occurs in Mikulicz's disease. In uveo-parotid fever irido-cyclitis accompanies the parotid swelling (see p. 532).

Inflammatory swelling of the higher cervical glands, especially when accompanied by *peri-adenitis* and *œdema*, may be mistaken for mumps. Swelling of this character occurs in certain cases of malignant diphtheria, and also in scarlet fever. Careful attention to the history, proper examination of the fauces and search for rashes should eliminate this serious error. Enlargement of the pre-auricular lymph gland due to lesions about the nostrils and angle of the mouth, and the swelling caused by *periostritis* of the lower jaw, or otitic infection of a zygomatic air-cell, may superficially resemble inflammation of the parotid, as also in some cases may subcutaneous *emphysema*.

When the submandibular and sublingual glands alone are swollen the distinction from *lymphadenitis* may be difficult. In such cases extension to the opposite side indicates mumps, as also does the transitory character of the swelling. In all forms of septic adenitis a polynuclear leucocytosis is likely to be present.

In glandular fever, which is an acute infective adenitis of the cervical and other lymphatic glands, the salivary glands are not involved.

**Prognosis.**—The mortality from mumps is remarkably low. Most deaths occur in children under 5, especially in infants, usually from some complication. Attacks of mumps in pregnancy have been known to prove fatal, and on rare occasions congenital malformations have been attributed to them.

**Treatment.**—Mumps is infectious for 2 or 3 days before the swelling appears; after that infectivity rapidly becomes negligible. Isolation for not less than 2 weeks from the onset is advisable, provided that 1 clear week has elapsed since the subsidence of the glandular enlargement. Some would reduce the week to 3 days. Contacts should be removed from exposure and isolated for 28 days, or better, supervised from the fourteenth to the twenty-eighth day, unless they have already had the disease. Thirty ml. of whole blood, or 15 ml. of serum of recent convalescents, if given on first exposure, seems to prevent infection, but its protective effect only lasts about 14 days. A fractionated globulin has also been prepared. Attenuated attacks are difficult to produce, but see also remarks under measles (p. 154). On account of the liability to orchitis, it is better to have mumps before puberty than after. Gamma globulin from recent convalescents has given the best results in preventing this complication. In fulminant and bilateral attacks incision of the tunica albuginea has been found to relieve pain and fever, and thought to avert subsequent atrophy. For the after-results substitution therapy with testosterone may be considered.

The patient should be isolated and confined to bed. The incidence and severity of orchitis are said to be less in those who are not allowed to get up until the time at which this complication usually appears is past. Foods which need no mastication are indicated during the acute stage. The mouth should be kept clean. Pain may be relieved by local applications and acetylsalicylic acid. The inflamed testicle should be enveloped in cotton-wool and suspended or supported by a small pillow. If pancreatitis is suspected, fomentations may be applied to the abdomen, small doses of opium administered and the diet strictly restricted to fluids. Delirium and pyrexia are met by sponging, wet-packs or the ice-cap. Hyoscine may become necessary. Repeated lumbar puncture is beneficial in meningo-encephalitis.

## INFLUENZA

**Definition.**—An acute infectious disease of short duration, existing in pandemic and epidemic form, with sporadic outbreaks. It is characterised by sudden onset, pyrexia, headache, pains in the back and limbs, and a tendency to inflammatory complications in the respiratory system.

**Ætiology.**—There are influenzas rather than influenza, but there are questions which have baffled epidemiologists and bacteriologists for many years, nor did the exceptional opportunities for observation and research afforded by the pandemic of 1918-1919 serve entirely to answer them. Are the protean features of disease which are at present included in our conception of influenza all manifestations of the same *materies morbi*? What causative factors determine the pandemics of the disease during which the case-incidences rises so rapidly and so enormously? What is the association between benign influenzal catarrhs of endemic and sporadic occurrence and the pandemics which decimate whole races of mankind?

We are ignorant of the reasons why a state of relative quiescence in regard to the incidence of the disease—scattered sporadic cases and mild epidemics—suddenly blazes up into a devastating pandemic. We know that when this conflagration arrives the disease becomes very highly infectious in character, that its virulence is enormously increased and that the usual close association with catarrhs and seasons and latitudes and lowered general resistance is no longer observed. Age gives no security at such times; witness both the high case-incidence and high case-mortality in young adults during the pandemic of 1918-1919.

A previous attack of the disease gives little or no protection; according to some authorities the reverse is the case; yet promising results from prophylactic virus vaccine inoculation have been reported.

In the matter of its relation to other catarrhal states the absence of definite criteria makes it impossible to be precise in diagnosis. It is only in the presence of a severe and widespread outbreak that the guide of probability is of assistance in this respect.

Andrewes and his co-workers at the National Institute for Medical Research in 1933 isolated from the naso-pharyngeal discharge of influenza patients a virus which is capable of infecting ferrets. When human influenzal garglugs are dropped into the noses of ferrets they become ill in 48 hours and the disease has been transferred from the experimental animals to the experimenter. Further, they have shown that patients who have had influenza recently develop antibodies in their blood which kill, or inactivate, the virus. Neutralisation tests with antisera prepared from human strains prove that different serological varieties of the virus exists. So far virus A and virus B have been identified, each with different epidemiological behaviour, but there are cases which, though clinically influenza, are not due to either of these, and in which no recognised virus or antibody can be demonstrated. Such cases have provisionally been designated "influenza Y".

Virus A appears to be associated with most of the more widespread and virulent epidemics, but no hard-and-fast distinction is possible. Virus B influenza is commonly sporadic, mild and of insidious onset, but it may become epidemic, while virus A may give rise to sporadic cases. There is usually an admixture in any epidemic, although one virus commonly predominates.

Secondary infection undoubtedly plays a very important part in the complicated symptomatology of the disease. It is unfortunate that in bacteriological nomenclatures the term "influenza" is still linked with Pfeiffer's bacillus. For though *Hæmophilus influenzae* is one of the organisms most frequently responsible for secondary infection, it occurs as the causal microbe in cases of disease quite other than clinical influenza—septic endocarditis, sinusitis and meningitis. A special feature seen in regard to it is the fact that, when present in acute cases of influenza, it usually occurs in enormous numbers in the infected tissues and their secretions. Next to *H. influenzae*, the micro-organisms most commonly found in association with the disease are streptococci of the hæmolytic kind, pneumococci, *N. catarrhalis* and *Staphylococcus pyogenes*. It seems certain that many of the most serious and fatal cases owe their lethal character to streptococcal or staphylococcal pneumonia.

**Symptoms.**—So far as can be judged the incubation period is, with considerable constancy, something from 24 to 48 hours. A marked feature of the disease is the abruptness of the onset. So abrupt is it at times that the victim is stricken down, as it were, in the street, and, from being quite well he is, within a few hours, prostrated and already suffering the maximum discomforts of the disease. The temperature rises rapidly; there is often a rigor. The chief symptoms are racking headache, intolerable aching pains in the loins and limbs, dryness and irritable redness of the mouth and fauces, and a distressing dry cough. An erythematous rash is not uncommon.

Although the symptoms are protean, it is customary to describe certain types of case that are frequently met with, dependent largely upon the particular tissues and functions which suffer the chief results of the infection. It is to be noted that different outbreaks of the disease are prone to be characterised by different clinical types, as also by differing degrees of severity.

1. *The febrile type.*—In this variety of the disease the chief features are pyrexia, with associated malaise, headache, pains in the back and limbs, and a moderate degree of catarrh of the upper air-passages. In many cases this type differs only from the "common cold" in its more abrupt onset, its higher degree of pyrexia, its disproportionately severe prostration and its relatively "dry" form of catarrh. The eyeballs are often painful, with some conjunctivitis, and the fauces are often red and slightly œdematous and the tongue "dove coloured". Cough is often present, with few or no associated pulmonary signs. The pyrexia lasts for a variable time, usually 4 to 6 days; the temperature chart may show two peaks in the 24 hours. It is unusual to see the fever prolonged past the fifth day without some focal complication, generally pulmonary. Defervescence is quite frequently by crisis, but this is by no means the rule.

2. *The respiratory type.*—This is the form of the disease which is most prevalent in pandemics, and, when severe, it is the form to which the mortality is chiefly due. Somewhere about the fourth day of the disease it becomes obvious that the catarrhal process is growing troublesome, with more definite involvement of the larynx, trachea and bronchial tract. A dry catarrh of the larynx and trachea, with pain and distressing cough, may constitute the main feature of the disease. In many cases the temperature falls about the third or fourth day, to rise again concurrently with a definite exacerbation and extension of the catarrh. The respiratory involvement does not tend to remain localised as a bronchitis, but involves the lung tissue, leading to a bronchiolitis and, in many cases, an alveolitis also. Then ensue the signs of acute pulmonary congestion which are so characteristic of the disease, and cause so much anxiety for

fear of untoward developments. The respiratory manifestations of influenza infection extend from laryngitis and tracheitis through bronchitis to lobular and lobar pneumonia and pleurisy, both "dry" and with serous or purulent effusion. But the dominant feature, rarely absent in any really severe case, is a condition of capillary bronchitis with intense pulmonary congestion. This may be unilateral or bilateral, is more often basal than apical, but is not seldom universal. The physical signs are copious fine râles (crepitation), with impaired vesicular sound, and, less often, impaired percussion tone. This condition may well be termed the essential lesion of the disease, for even when actual consolidation of the lung is present, this is quite often an incident by comparison, and if the patient dies, he dies with the consolidation rather than of it.

Cough is usually a very troublesome symptom in this type of the disease, and is often quite independent of the need to expectorate. The sputa vary considerably. They may be quite absent, even in cases where there is widespread lung congestion. When present they are generally of a kind that corresponds with the nature of the chief lesion, whether tracheitis, bronchitis or pneumonia. Two special kinds of sputa are very typical of influenza, and they are seen frequently during epidemics. (a) Bright, pink, frothy mucus, sometimes produced in large amount, it may be as much as a pint in 24 hours. This rose-red mucus results from acute inflammatory œdema of the lung. It may be expelled involuntarily during cough and sometimes it spurts from the nostrils. (b) Tenacious mucus, less viscid than in lobar pneumonia, and more copious, differing also in colour which is of several hues—red, brown, saffron and various shades of green, all of these being occasionally present at the same time. Seen in a white earthenware vessel these sputa are very striking and in a high degree diagnostic.

3. *The malignant type.*—This severe and very fatal form is almost confined to pandemic or to epidemic periods. The patient is gravely ill from the onset, or soon after, with intensely toxic symptoms, cyanosis of a peculiar character ("heliotrope cyanosis") and rapid development of heart failure before focal manifestations have time to show themselves—unless it be the presence of copious fine râles of the kind referred to in (2). The duration of this type of case varies from 48 hours up to a week, and no measures of treatment, however prompt, serve to avert the almost certain issue. It is asserted by reliable observers that death may occur even within the first 24 hours from the onset.

There is no evidence that the influenza viruses give rise to an epidemic illness in which abdominal symptoms dominate the picture. "Gastric influenza" is a term which should not be retained. Epidemic nausea and vomiting has been noted in small outbreaks and a "virus diarrhoea" is thought to occur. The causal agents of these diseases have not been identified, but there is no reason to inculcate the influenza viruses.

**Complications and Sequelæ.**—These are both numerous and important. Indeed, if we except the malignant cases and the very severe respiratory cases occurring during pan- and epi-demic periods, it may be said that the importance of the disease lies more in its complications, and perhaps still more in its sequelæ, than in the stage of infection proper. For convenience these disabilities may be grouped as follows:

1. *Respiratory.*—The main extensions of the catarrhal process have been already referred to, as also has the occurrence of pleurisy. Sinusitis may be mentioned here; it is both common and troublesome. Otitis media also occurs. Asthma sometimes appears for the first time in a patient's life after influenza, and the age of the sufferer may be much more advanced than is usual with asthma generally. Pulmonary tuberculosis not seldom shows itself also for the first time in the same association. The associated pneumonia may be followed by bronchiectasis.

2. *Circulatory.*—Perhaps the most serious complication and sequel is referable to the heart. Some degree of cardiac enlargement is common during a severe attack

of the respiratory type, and this condition is apt to prolong convalescence in a very tedious fashion. In some cases a bradycardia due to heart block has been observed: the prognosis in this condition is good.

Vasomotor troubles are not uncommon and often complicate the heart condition. Phlebitis may occur.

**Diagnosis.**—During pan- and epi-demics the diagnosis is, as a rule, not difficult, especially when the case is very severe. If the highly characteristic condition of bronchiolitis with copious fine râles referred to on p. 179 be present in a febrile illness with nerve prostration and general toxæmia, the diagnosis is fairly certain. A leucopenia is present in influenza until secondary bacterial infection is established.

The diagnosis of milder cases of influenza, if occurring in sporadic fashion, is frequently a frank admission that it is well to give the patient and his friends a label to his disease. There are so many causes of an acute febrile illness with malaise and slight catarrh that exact clinical diagnosis may not be possible.

Precise diagnosis requires laboratory evidence that the infection is due to one of the influenza viruses. The influenza viruses agglutinate fowl erythrocytes, but this agglutination is inhibited if serum containing antibodies is first added to the virus suspension. These observations have provided a relatively simple method of demonstrating the presence of circulating antibody and the "agglutination-inhibition" test has proved a valuable weapon to the epidemiologist. It remains impracticable and unnecessary to seek this laboratory confirmation in routine clinical practice.

A word of warning is perhaps necessary in respect of diseases known to be prevalent coincidentally with outbreaks of influenza. Thus, true pneumococcus pneumonia, whether lobular or lobar, is not infrequently called influenzal when this latter disease is epidemic. Of greater importance is the fact that waves of incidence of influenza and poliomyelitis and encephalitis sometimes concur. If the practitioner's attention is bent only upon the former disease he is apt to put down to it certain serious nerve lesions that really belong to the latter.

**Treatment.**—**PROPHYLACTIC.**—As we do not know the factors leading to the production of influenza epidemics we do not know how to prevent them. When they arrive we can, to some extent, control them by efficient quarantine, by early diagnosis and notification, and by a proper system of hospitalisation, adequate to the peculiar features presented by the disease. In regard to individual prophylaxis it was formerly held that to keep generally "fit" was a good protection against infection. But recent experience does not confirm this view: influenza attacked the strong as well as the weak; indeed, the robust young adult fell a victim by preference, though this may have been partly because he was more open to infection by virtue of the conditions of his life. The age-mortality as well as the age-morbidity during the 1918-1919 pandemic seemed to make it clear that some method of specific immunisation is essential before we can hope to protect against infection. The protection given by vaccines prepared from the viruses is curiously variable, apparently because of the changes in antigenic characters of the prevalent strains. For instance, a mixed virus A and B vaccine which gave good protection against influenza in 1946 was almost ineffective in 1947. Protection is established, experiments with induced influenza have shown, within 8 days, but endures for only  $4\frac{1}{2}$  months for virus A and about a year for virus B. These vaccines have not yet emerged from the experimental stage.

**CURATIVE.**—1. *General measures.*—With the onset of symptoms the patient is put to bed and is kept there until the temperature has reached normal and has remained there for 48 hours. Isolation is desirable. He is only allowed up if examination of the heart and lungs, and a review of his general condition, reveal nothing abnormal.

A light, easily digestible diet should be given in quantities determined by the patient's appetite. There is no need to press a well-nourished patient to take more

food than he desires during a short-lived illness, but he should be encouraged to drink liberally. The patient is sponged all over with warm water twice daily.

2. *Drugs*.—There is no drug which acts as a specific. Aspirin and Dover's powder in gr. 10 doses may be given together as early as possible and may be repeated once or twice every 6 or 8 hours. This may be followed by a simple diaphoretic mixture. The sulphonamides and penicillin are only of service when secondary infections are present, and especially when these are of a pulmonary nature.

3. *Treatment of symptoms*.—If the headache is severe, phenacetin gr. 10 with caffeine gr. 2 may be given 4-hourly for four doses. If the stomach gives trouble, and the tongue is foul, sod. bicarb. and sod. sulphocarb., of each gr. 10, with glyc. acid. carbol. min. 10, may be given 6-hourly with the feeds, well diluted.

Distressing and persistent cough is often the most difficult problem. Local applications to the chest, including dry cupping, are often of service. If the origin of the cough is irritability of the upper-air passages inhalations of tinct. benzoini co. 4 parts, with menthol or eucalyptus 1 part, are useful. Failing this, a spray containing chlorbutol (Chloretone) and menthol, 2 per cent. of each in liquid paraffin, may be used to the nose and throat. In the "essential cough" of the disease, syr. cocillanæ co., syr. codeinæ and linct. terp-heroin. co. are of some value. In intractable cases relief may follow syr. chloral min. 30, ammon. brom. gr. 10, with ext. glycyrrhiz. liq. min. 20, etc., in 4-hourly doses for 4 doses.

Insomnia calls for a general review of the whole programme—ventilation, control of pyrexia, posture, food, stimulants, etc. Failing attention to these things, a sedative draught of ammon. brom. gr. 20 and tinct. valern. min. 20 may be tried; if not successful, min. 120 doses of paraldehyde, with tinct. quillaizæ and tinct. aurantii to cover its unpleasant taste. Failing this, again, chloral and bromide may be given, since drugs of the barbitone group are better avoided.

4. *Treatment of more severe cases and of complications*.—(a) *Intensely toxic cases, with hyperpyrexia*.—Attention to good ventilation should be redoubled. The thermometer and not the patient's sensations must be the guide to the amount of bed-clothes. "Cradling" is often very useful, as also is tepid or spirit sponging. In cases in which the temperature is even then resistant, the cold pack should be used and repeated if necessary. Febrifuge drugs are to be avoided in such cases.

(b) *Pulmonary cases*.—In most instances a secondary infection is responsible for pulmonary symptoms. A bacteriological examination of the sputa is desirable, with investigation of the sensitivity of any pathogenic organisms to the antibiotics and the sulphonamides. Penicillin or chlortetracycline should be administered while the results of these tests are awaited. Oxygen delivered through a nasal catheter or B.L.B. mask is useful in all severe cases with cyanosis.

(c) *Heart failure*, to be estimated more by the general state of the patient (facies, cyanosis, dyspnœa, delirium, posture) than by pulse-frequency or physical signs, is met by alcohol, strychnine injections, nikethamide (Coramine) subcutaneously, and, as a measure supplementary to these, strophanthin gr.  $\frac{1}{100}$  in 20 min. of sterile saline solution, injected slowly into a vein of the arm and repeated, if indications are still present, in 8 or 12 hours.

## FOOT-AND-MOUTH DISEASE

**Synonyms**.—Aphtha Epizootica; Epidemic Stomatitis.

**Definition**.—A contagious disease, due to a virus, communicated from animals to man, characterised by mild pyrexia, swelling and vesiculation of the tongue and buccal mucosa, accompanied, sometimes, by a vesicular eruption on the hands and fingers.

**Ætiology**.—Man is relatively insusceptible to infection which, however, is of



almost world-wide distribution amongst cattle, pigs and sheep. Up to 1872 there were but few reported cases of supposed foot-and-mouth disease in man. In that year a more virulent form appeared in cattle, and human cases were more frequently described. Bussenius and Siegel in 1897 analysed the reports of more than 1,500 cases; the majority are sporadic or occur in small groups.

Three types of virus have been recognised by immunological tests: anti-serum of types O and A (Vallée and Carré) and C (Waldman) has no protective influence against infection by either of the other two types. In cattle the virus enters through the mucosa of the alimentary tract, a septicæmia ensues during which all the secretions and excretions of the body become infective, with subsequent localisation in the specific lesions. The virus can remain active on hair or in soil for a month.

Foot-and-mouth disease is communicated to man: (1) By the consumption of unboiled milk from a cow suffering from the disease. (2) By direct inoculation: from (a) the saliva of infected animals, or (b) milking cows suffering from the specific eruption on the teats or udders. Those affected are for the most part either children, milkers or cowmen.

**Symptoms and Course.**—The incubation period of foot-and-mouth disease in man appears to be the same as in cattle, namely, 2 to 5 days. Whatever the route of infection the disease sets in with slight headache, a mild grade pyrexia and dryness of the mouth. This state continues for a few days, and is then succeeded by a period of salivation and the development of the characteristic lesions—vesicles upon the lips and tongue, which contain yellowish-white turbid fluid. In 48 hours or so the vesicles rupture with the formation of superficial ulcers having a smooth purplish base. There may be considerable swelling of the tongue and mouth, which, with the pain, renders mastication and swallowing difficult. At the same time a crop of small vesicles may appear around the nails and on the hands; they increase rapidly in size, become pustules and then scabs, which fall off early in the second week. In adults the disease runs a mild course with recovery in from 7 to 10 days. Occasionally the infection spreads to the eyes, where it may cause a severe keratoconjunctivitis. In young children, fed on infected unboiled milk, the condition is prone to be more severe because of the liability to anorexia, gastro-enteritis and diarrhœa.

**Treatment.**—This is entirely dietetic and symptomatic. A weak solution of permanganate of potash is perhaps the best local application; strong antiseptics, whether to the mouth or to the hands, must not be employed.

## PSITTACOSIS

**Definition.**—An acute infective disease derived from birds, including parrots, budgerigars, canaries, pigeons and fulmar petrels, resembling typhoid fever in its mode of onset and general features, but presenting signs of an atypical pneumonia.

**Ætiology.**—The first recognised cases of this disease were derived from parrots (hence its name), the green Amazonian parrot being usually the source. It is now known that many species of bird are affected and may transmit the infection to man; it has been suggested that a more suitable name for the disease would be ornithosis. Infection is usually conveyed direct from a sick parrot to a human being who has been in close contact with the bird, but a parrot dead of the disease is also infectious. It is probable that a healthy parrot can act as a carrier. Infection from one human being to another, although it seems to occur occasionally, is very rare. Bedson proved that the causal organism was a filtrable virus and complement-fixation and neutralisation tests have been devised which are of assistance in establishing the diagnosis.

**Pathology.**—The post-mortem appearances are those of a severe septicæmia, with characteristic changes in the lungs. The latter do not present the picture of classical lobar pneumonia or broncho-pneumonia, but of a "peculiar hæmorrhagic

vesicular pneumonia, complicated by pulmonary thrombosis and free from bacteria" (Turnbull). In addition, areas of mucopurulent bronchitis and broncho-pneumonia may occur from secondary infection. The gastro-intestinal tract is usually free from severe inflammation.

**Symptoms.**—The disease usually sets in rather suddenly after an incubation period of 7 to 14, and sometimes as long as 30, days. The rise of temperature is commonly abrupt, and headache is pronounced. Epistaxis sometimes occurs. The patient is generally dull and apathetic, and passes into a condition suggesting a typhoid infection. The abdomen may be slightly distended, and there may be a little sickness and diarrhoea at the outset. The spleen is not palpable, but in some cases a few rose-spots have been observed which are of a smaller size than the spots in typhoid fever. Pulmonary symptoms may be present from the outset, or appear after the disease has lasted some days. Cough is often frequent and troublesome, but, as a rule, there is little expectoration. Respiration may be rapid, but the pulse-rate remains low. The signs in the lung range from those of a bronchial catarrh up to massive, sometimes very dense, consolidation. Pleuritic signs are very rare. The disease usually lasts from 2 to 3 weeks, and the temperature may fall abruptly. Temporary rises of temperature during convalescence are often observed, and there may even be a complete relapse.

**Diagnosis.**—Clinically the disease can be suspected on circumstantial evidence. If one has a patient who presents a general resemblance to a case of typhoid or paratyphoid fever, but whose blood does not give the agglutination reactions, who presents also pulmonary symptoms and signs of an atypical sort, and who has also been brought into close contact with a sick parrot or love-bird, then the diagnosis is justified. A deceptive feature in the diagnosis from typhoid, however, is that sometimes the agglutination reaction to *Salm. typhi* is positive. It may be impossible at the outset to distinguish psittacosis from influenza, but the supervention of pulmonary complications *within the first few days* is in favour of the latter. Bacteriologically the existence of the disease is proved by the presence of a positive complement fixation reaction in the patient's serum.

**Prognosis.**—The mortality varies considerably in different epidemics, but may perhaps be put at about 1 in 6. Young people usually recover. Severe involvement of the lungs and failure to maintain a relatively slow pulse are unfavourable factors.

**Treatment.**—Penicillin has proved of value in some cases, but chlortetracycline is the drug of choice and reports of its action are most encouraging. Patients should be nursed with the usual precautions adopted in a typhoid case, but need not be further isolated. Special signs and symptoms must be treated as they arise.

**PROPHYLAXIS** consists in forbidding the importation of infected birds; cages should be kept clean, and the birds should not be fondled. A bird which falls sick should be immediately isolated or destroyed.

R. BODLEY SCOTT.

## YELLOW FEVER

**Synonyms.**—Febris Flava; Typhus Icteroides; Yellow Jack; Black Vomit; Kendal's Fever; Fièvre Jaune; Fièvre Amarilla.

**Definition.**—An acute infectious disease of sudden onset, endemic in parts of tropical America and West Africa, characterised typically by pyrexia, vomiting, a slow pulse relative to the temperature, early albuminuria and a tendency to hæmorrhages and jaundice. It is caused by a filtrable virus and is transmitted to man by the common domestic mosquito, *Aedes ægypti* (*Stegomyia fasciata*).

**Ætiology.**—The endemic haunts of yellow fever have been curtailed in recent years by the destruction of its intermediary host. A circle with its centre in the

Isthmus of Panama, and embracing the northern parts of South America, the West Indian Islands and the southern parts of North America includes most of the area of its late prevalence in the Western Hemisphere. Unsuspected reservoirs of infection have been found in the Amazon basin and in parts of Colombia, Venezuela and Brazil. The endemic area in Africa is regarded as including West, Central and East Africa extending north to the Anglo-Egyptian Sudan and Eritrea and south to the Uganda Protectorate and Belgian Congo. Stokes, Noguchi and Young died when investigating yellow fever, the infection being probably acquired by direct contact with infective blood rather than by the mosquito vector, *Aedes aegypti*. Carroll in 1900 showed that this mosquito would transmit the disease after a period of 12 days, provided it was fed on the blood of a yellow-fever patient during the first 3 days of fever. Reed and Carroll also found that the injection of 0.1 ml. of blood from a yellow-fever patient collected during the first 3 or 4 days of fever produced the disease, and that the serum after filtration remained infective. *Aedes aegypti* bites in the daytime, and is most aggressive in the early morning. Its domestic habits make it an efficient vector, as the larval stages develop mainly in artificial containers in or near human habitations. Males and females are equally susceptible, and infection in childhood is common. This type of urban and rural yellow fever differs from jungle yellow fever, which is found in or near tropical forests in Brazil, where *Aedes aegypti* is absent. Adult males who work in the jungle are mainly infected. Wild jungle mosquitoes have been found to harbour the virus, but the common vector is not yet known. Monkeys and possibly the hedgehog or other susceptible animals may play an important rôle as reservoir hosts. In 1927 the West African Yellow Fever Commission found that the Rhesus monkey (*Macaca mulatta*) was susceptible, only 1 out of 30 monkeys surviving. One attack confers lifelong immunity, and 0.1 ml. of convalescent human serum protects monkeys. The virus, if dried, will keep for months; it penetrates the intact skin of both man and monkeys, but is no longer demonstrable in the blood and viscera after the fourth day.

The diameter of the virus as determined by filtration through collodion membranes lies between 17 to 28 millimicrons. It possesses two qualities, viscerotropism and neurotropism; when both are present it is known as "pantropic" virus. In 1930 Theiler found that if pantropic virus was inoculated intracerebrally into susceptible mice they developed encephalitis, unless immune serum was simultaneously injected. After repeated passage through the brain of mice the virus lost its viscerotropism or capacity to attack the abdominal and thoracic organs, and was converted into a neurotropic virus with fixed characters. Injection of this virus or of pantropic virus attenuated by tissue culture immunises against yellow fever and is the basis of prophylactic immunisation.

The fact that immune bodies are demonstrable in the blood of yellow fever cases shortly after infection, and persist permanently in recovered cases has been utilised to determine the endemic incidence of the disease. Mice are employed for the purpose. The protection test, as developed by Sawyer and Lloyd, consists of an intracerebral inoculation of starch solution, followed by the intraperitoneal injection of virus and the serum to be tested. In the absence of immune bodies in the serum the virus produces encephalitis and death within a fortnight; if immune bodies are present the animal remains unaffected. This test has been of great value in affording an index to past epidemics, and in accurately determining the past and present geographical distribution of the disease. Examination of liver specimens obtained by means of the viscerotome from persons dying of illness of not over 10 days' duration has also led to the detection of unsuspected reservoirs of infection.

**Pathology.**—Death generally occurs between the fifth and ninth day of the disease. Rigor mortis comes on early. The skin may show ecchymoses and is an intense yellow colour, which becomes accentuated after death. The liver is of approximately normal size, reddish yellow, brownish yellow or "chamois leather" colour,

and may show hæmorrhages. Microscopically a midzonal fatty degeneration is characteristic on the fourth or fifth day, but later all zones undergo necrosis, and the nuclei may contain acidophile inclusion bodies. The gall-bladder contains tenacious, dark bile. The kidneys are congested, and show cloudy swelling and fatty degeneration. Petechial hæmorrhages, casts and degeneration of the convoluted tubules are seen on section. The adrenals may show cortical fatty degeneration. The left ventricle is often dilated, and its muscle pale and flabby. Bradycardia is due to damage to the auriculo-ventricular bundle, and fatty degeneration of muscle cell-elements are common. Erosions and petechial hæmorrhage in the stomach and proximal duodenum occur, hence the coffee-ground vomit and the tarry blood in the entero-colon. The spleen is almost normal in size and appearance. The pleura and meninges may show hæmorrhages, the brain is congested, and the lungs congested and apt to show hæmorrhages.

*Clinical pathology.*—The outstanding pathological features are cloudy swelling and necrosis of the parenchymatous cells, especially of the liver and kidneys, and degeneration of the capillary endothelium, resulting in hæmorrhages. Jaundice and albuminuria with casts are thus produced. Hypoglycæmia related to liver inefficiency may occur from the fourth day onwards, while the van den Bergh may show a biphasic direct positive reaction and a positive indirect reaction of from 2 to 20 units. In the later stages the blood urea may be increased, and in monkeys Findlay found an increase in guanidine bodies. Though the leucocytes may vary from 3000 to 15,000 per c.mm., leucopenia is the rule, the lowest counts occurring about the fifth to sixth day; the neutrophils are decreased, the lymphocytes increased and the eosinophiles tend to disappear. The clotting time is markedly increased. The cerebrospinal fluid is under increased pressure and may contain increased quantities of albumin and chlorides.

*Symptoms.*—The incubation period is from 3 to 5 days, but may be 10. Clinically, the disease is divided into: (1) Larval and mild forms; (2) Severe; (3) Malignant. In well-established severe cases the clinical features vary according as the liver, kidneys or heart bear the brunt of the attack, acute hepatitis and cholæmia, uræmia and anuria, and cardiac insufficiency being respectively manifest. Most cases show evidence of both renal and hepatic involvement.

1. *The larval and mild types.*—During epidemics, as well as where the disease is endemic, aberrant and irregular types are not infrequent; transient fever of 1 to 4 days' duration, perhaps associated with albuminuria, occurs with rapid return to health. Where the pyrexia persists over 48 hours, headache, vomiting, eye pain and mild jaundice may ensue. Diagnosis in the larval forms is dependent on showing that convalescent serum is protective.

2. *Severe or ordinary types.*—The typical case presents three stages: (a) the sthenic; (b) the stage of remission on the third or fourth day; (c) the asthenic stage. In the *sthenic stage* the onset, which often occurs at night, is sudden with chilly sensations or a rigor, the temperature rapidly rising to 102° F. or 104° F. There is severe pain in the back and limbs, frontal headache with flushed face, injected conjunctivæ (ferrety eye) and photophobia. Prostration is severe, often disproportionately so to the temperature (Carter). The tongue is pointed and red; anorexia, nausea and vomiting, which may be bilious, appear. Epigastric discomfort and tenderness are characteristic, and insomnia is frequent. Albuminuria generally occurs on the second day and steadily increases. The pulse is at first rapid (90 to 110 per minute) and of high tension with raised blood pressure, but later slows until by the third day it may be 60 to 70 per minute despite the fact that the temperature remains elevated. This is known as *Faget's sign*, the pulse actually falling away from the temperature. It also remains slow when the temperature rises again in the relapse. Constipation is the rule.

*Stage of remission.*—About the third or fourth day the temperature may fall to

100° F. or lower with amelioration of symptoms. Recovery may result or fever be re-established. Frequently this stage is absent altogether.

*The asthenic stage.*—The temperature rises again if it has remitted, turgidity of the face decreases, and jaundice now appears; it is first seen in the conjunctivæ and is not obvious in the skin until the fourth day of fever as a rule; sometimes, however, it is demonstrable on the third day. The gums are swollen and bleed on pressure, while the tongue is coated and later becomes dry and brown. The liver is tender and only slightly, if at all, enlarged, while the spleen is not palpable. Hiccough may be very distressing, and black or "coffee ground" vomit, tarry stools and skin petechiæ may occur. Bradycardia is marked (40 to 60 per minute) and the blood pressure low. The urine is acid and decreased in quantity; it contains urobilin and much albumin, granular casts and possibly bile salts, bile pigments, bile-stained epithelial cells and red blood corpuscles. Anuria is frequent in fatal cases. After the intermission, the fever does not last as a rule more than 3 days.

*Malignant forms.*—In this type the temperature may reach 106° F. and profuse hæmorrhages, melæna, black vomit, epistaxis, hæmaturia, purpura, jaundice and anuria may develop by the third day. Symptoms referable to the nervous system such as hiccough, tremor, subsultus tendinum and delirium are also encountered, death from overwhelming toxæmia rapidly ensuing.

*Complications.*—Complications are uncommon, but boils, abscesses and troublesome jaundice, appearing for the first time in convalescence, may occur.

*Diagnosis.*—Difficulties in diagnosis are mainly encountered in atypical cases, especially early in an epidemic. In the average case fever associated with undue prostration and early and increasing albuminuria should at once arouse suspicion, while later, the tender liver, absence of splenic enlargement, Faget's sign, hæmorrhages and jaundice appearing about the fourth day will be confirmatory. In black-water fever, jaundice appears in the first 24 hours; in bilious remittent fever on or about the second day; while in Weil's disease it is generally found on the fourth or fifth day. Dengue, malignant tertian malaria and relapsing fever also occasionally give rise to difficulty in diagnosis. Malaria, bilious remittent fever and relapsing fever are generally associated with an enlarged spleen, while blood smears should reveal malaria parasites or spirochætes. Special laboratory investigations may be necessary to differentiate Weil's disease. In the larval forms of yellow fever intracerebral inoculation of susceptible mice with 0.03 ml. of blood collected during the first 3 days of fever may reveal the virus. More frequently it will be necessary to take two specimens of blood at a fortnight's interval and establish a rise in the titre of protective antibody by the mouse protection test in order to establish the diagnosis.

*Course.*—If the patient survives, the acute disease rarely lasts longer than 10 days, and convalescence generally progresses slowly but surely once a normal temperature is established. Relapses are rare and generally fatal.

*Prognosis.*—The prognosis differs in various epidemics, the mortality rate varying from 10 to 70 per cent., the average being 20 to 30 per cent. Anuria, deep jaundice, black vomit, hæmorrhages and severe nervous disturbances are of grave significance.

*Treatment.*—*PROPHYLACTIC.*—The segregation of infected individuals in mosquito-protected wards, and the destruction of the adult and larval stages of mosquitoes (*Aedes*) have done much to stamp out the disease. Rubber gloves should be worn in collecting blood from all pyrexial cases in endemic areas. Convalescent serum affords temporary protection. All persons visiting or living in a yellow-fever area should be vaccinated with virus modified by tissue culture. A single subcutaneous injection of 0.5 to 1.0 ml. produces protective antibodies and confers an immunity which probably lasts 4 years. No local reaction follows inoculation, but headache and general aching may develop about the fifth day. Jaundice has frequently followed some 3 months after inoculation, but this is not due to the yellow-fever virus, but to the use of human serum containing the icterogenic factor.

**CURATIVE.**—Careful nursing of the patient in the recumbent position is essential, and as much fluid as can be taken is given during the acute illness, but food is contra-indicated. The juice of citrus fruits and dextrose and lactose are given in water; citrates should be added to the drinks to combat acidosis. Only when the temperature has been normal after the second paroxysm can a gradual increase in food be permitted—rice water, chicken soup, Benger's, custard, etc.—and even in convalescence it is only gradually increased. In severe cases with vomiting, 2 pints of 5 per cent. dextrose, given intravenously every 24 hours, may be helpful; also tap water may be administered per rectum. Calcium lactate, gr. 60 daily, is advocated to neutralise the effects of guanidine intoxication. Unfortunately, though protective to monkeys when given in the incubation period, convalescent serum does not affect the course of the disease once symptoms have appeared. Symptomatic treatment includes the use of an ice bag locally for headache, a mustard plaster to the epigastrium for hic-cough, hot fomentations and catheterisation for retention and sedatives for insomnia. Champagne may help the vomiting. On admission a mild purgative is administered and constipation is subsequently treated by a daily enema. A cold sponge is indicated when the temperature exceeds 103° F.

## PHLEBOTOMUS FEVER

**Synonyms.**—Papataci Fever; Three-day Fever; Sand-fly Fever; Pym's Fever; Dog's Disease.

**Definition.**—An acute specific fever lasting about 3 days due to a filterable virus and spread by *Phlebotomus papatasi*.

**Ætiology.**—The disease occurs in parts of Africa, Asia, Northern Argentina and is common in the Mediterranean basin, in India, Mesopotamia, Persia, etc., where it affects especially white races, though natives also suffer. Many thousands of troops were affected in the Middle East during 1940-1944. The virus is present in the peripheral blood for the first 24 to 48 hours, and female sand-flies sucking up such blood become infective 6 or 7 days later, and remain so for life (Doerr). The virus may also be transmitted by the female *Phlebotomus* to the egg and larva (Moshkovsky). Blood taken on the first and second days may produce the disease on experimental inoculation, and volunteers bitten by infective sand-flies develop fever in 2 to 7 days. One attack generally confers relative immunity, but second attacks are not uncommon.

The disease occurs in the summer and early autumn in the subtropics, as *Phlebotomus papatasi* passes the winter months in its larval stage. It breeds in cracks and crevices affording moisture, darkness and organic matter, and is found in stone and rubble walls, dug-outs, trenches and surface soil. The adults shelter in similar situations. The females bite just after sunset and at dawn. Numerous bites occur over the wrists and ankles, where they produce itchy papules, which may vesiculate and give rise to localised swelling. The itching is severe, and may persist for 48 hours or longer or recur after an interval of several days in a sensitised individual who is rebitten.

**Pathology.**—This has been inadequately studied, as the disease is not fatal.

**Symptoms.**—The incubation period is 2 to 7 days. Prodromata, such as malaise, vague pains, headache and weariness, may usher in the disease. Generally the attacks commence suddenly with chilliness, shivering, lumbar pain and malaise. Rigors occasionally occur. The fever is short and sharp, reaching 101° F. to 104° F. by the evening of the first day. Severe frontal headache, increased by coughing, retro-ocular pain, accentuated by movement of the eyes or pressure on the globes, and toxic pains and stiffness in the muscles of the back, neck and legs are characteristic. The face is flushed and perhaps swollen, the conjunctivæ are injected (Dog's Disease), the skin is hot and dry, the tongue has a central fur, the throat is congested, and

the fauces and palate are sometimes studded with small vesicles. Bradycardia is a feature of the disease. Sleeplessness and irritability are common. The cerebrospinal fluid may sometimes show increased pressure, some lymphocytes (10 to 30 per c.mm.), an increase in albumin, and a decrease in chloride. The blood picture shows a leucopenia with a relative lymphocytosis. Epigastric discomfort, nausea, vomiting and constipation may occur; occasionally diarrhœa is encountered.

After about 36 hours, the temperature begins to fall and reaches normal in 3 or 4 days. There may be concomitant sweating, vomiting, diarrhœa and epistaxis. Occasionally the fever only lasts for 2 days, and rarely it exceeds 4 days.

**Diagnosis.**—In the early stages it may be impossible to make a diagnosis with certainty. Influenza, dengue, paratyphoid, malaria, relapsing fever, typhus, infective hepatitis and other fevers may need differentiation. In influenza the upper respiratory tract involvement, and in dengue the secondary rash and the more prolonged or saddle-back type of temperature, may assist diagnosis.

**Prognosis.**—Recrudescences are exceptional. The disease is never fatal. Convalescence is generally rapid, but extreme depression, malaise, asthenia and digestive disturbances may persist for 1 or 2 weeks.

**Treatment.**—**PROPHYLACTIC.**—Combined outdoor and indoor spraying with D.D.T. has revolutionised the control of sand-flies, while the use of the repellent dimethyl-phthalate to the ankles, wrists and exposed parts at sunset has proved most effective. At night sand-fly nets or mosquito nets impregnated with D.D.T. should be used.

**CURATIVE.**—Cases are treated by light diet, rest in bed during the febrile period, cold sponging when the temperature exceeds 103° F., and a mixture of aspirin, phenacetin and caffeine citrate.

## DENGUE

**Synonyms.**—Dandy Fever; Break-Bone Fever.

**Definition.**—A specific fever, lasting 5 to 7 days, caused by a filtrable virus which is transmitted by *Aedes ægypti* or certain other species of this genus. A saddle-back temperature chart, severe rheumatic-like pains in the limbs, backache, bradycardia, leucopenia and a measles-like eruption appearing about the third-fourth day are characteristic. Many atypical clinical forms occur.

**Ætiology.**—The disease occurs universally throughout the tropics and sub-tropics, where it is often endemic; from time to time explosive epidemics or pandemics arise. All ages and both sexes are liable to infection. The virus is filterable, and exists in the blood for some 18 hours before onset and for the first 3 days of fever. It is communicable to man by direct blood inoculation during this period, or by the bites of certain species of *Aedes* mosquitoes. The mosquito takes 11 to 14 days to become infective, and remains so for life. The common vector is the domestic mosquito, *Aedes ægypti*, and owing to its habits the disease is especially common in towns on the sea coast. *Aedes albopictus* also transmits dengue in the Philippines, while *Aedes scutellaris* has recently been proved to transmit dengue to troops in New Guinea in areas in which *Aedes ægypti* is absent. The same virus transmitted experimentally to volunteers by the same batch of mosquitoes can give rise to a very variable clinical picture. Some volunteers fail to develop fever, though their blood contains the virus; others may have a two-day fever; others a saddle-back type of temperature chart; and others continued fever of 5 to 7 days' duration. Demonstrable immunity follows experimental infection. Immunity also develops following natural infection, and when individuals suffer second or third attacks of dengue these tend to be of lessened intensity. The fact that large epidemics are separated by intervals of many years appears to depend on acquired immunity in the local population. Newcomers

are always most prone to the disease. Dengue has now been transmitted to mice and an attenuated strain obtained which seems promising for immunisation.

**Pathology.**—Nothing definite is known of this, as the disease is only fatal in the presence of complications or intercurrent disease.

**Symptoms.**—In epidemics, the severity and clinical picture vary considerably at different times and in different areas, and though typical cases are always recognisable many atypical ones are encountered which do not conform to the classical picture.

The incubation period is generally 5 to 10 days. In the typical case, three phases are recognised: (1) the stage of invasion, (2) the stage of remission and (3) the stage of secondary rash and terminal fever. Prodromata include general malaise and pains in the limbs. Generally the onset is absolutely sudden, with a rapidly rising temperature of 102° F. to 105° F., associated with headache and aching eyeballs, more marked on movement. The skin, especially of the face, is congested and shows a general flushing—the so-called primary rash. Backache is very severe, and much pain occurs at the muscular insertion about the joints. Insomnia, initial depression, anorexia, vomiting and constipation are not infrequent. The pulse, at first rapid, soon begins to slow, and after 3 to 4 days the temperature falls by crisis; this may be accompanied by diarrhoea, sweating and epistaxis. Symptoms now improve, but after 12 hours to 3 days the temperature rises again, producing the saddle-back chart. Pains and depression recur, and a roseolar rash, fading on pressure, appears; it is best seen on the dorsal surface of the hands and feet but also involves the face, neck and trunk. The rash simulates measles but lacks its dusky-red appearance. Occasionally it is punctiform, and then somewhat resembles the eruption of scarlet fever. A rose-red flush of the palms of the hands and soles of the feet is not infrequent. Occasionally dengue rashes become petechial. The desquamation is furfuraceous in type, may be associated with marked itching and may persist for 2 weeks. A leucopenia with lymphocytosis is characteristic. Glandular enlargements may occur, and in some epidemics adenitis is present in at least 50 per cent. of cases. Two or 3 days after the secondary fever and rash appear, the temperature falls and convalescence begins.

Other clinical types are frequently encountered. One type presents a one-phase fever like sand-fly lasting 2 to 3 days; another is characterised by continued fever of 5 to 7 days' duration, with a terminal crisis; the rash is by no means invariable.

**Complications and Sequelæ.**—General debility, asthenia, anorexia, insomnia and mental depression may persist well into convalescence, and persistent rheumatic-like muscular pains in the vicinity of the joints may prove very troublesome.

**Diagnosis.**—Influenza, sand-fly fever, yellow fever, rheumatic fever, measles, German measles, scarlet fever, secondary syphilis, leptospirosis, malaria, paratyphoid and typhus may be confused with dengue. The respiratory involvement in influenza; the early albuminuria and jaundice in yellow fever; the swollen joints in rheumatic fever; Koplik's spots and early coryza of measles; the rapid pulse, adenitis and leucocytosis in scarlet fever—these will often enable a diagnosis to be made. Specific laboratory tests, the clinical features and the course of the disease will assist in differentiating the other maladies mentioned.

**Prognosis.**—Different epidemics vary in virulence, but the death-rate is extremely small.

**Treatment.**—**PROPHYLACTIC.**—Prevention of breeding and destruction of the larvæ and adult mosquito vectors will prevent the disease. As *Aedes* is a day-biting mosquito, it is important to treat all dengue patients under mosquito nets for the first 3 days of their fever, and for hospital staffs to use anti-mosquito repellent lotions and take other appropriate precautions in daylight hours as well as at night.

**CURATIVE.**—No specific treatment is available. The patient should be kept in bed on a light diet for at least 3 days after the fever has terminated. An aspirin,



phenacetin and caffeine citrate mixture is helpful for toxic pains; and sedatives and cold sponging may be necessary to induce sleep.

During convalescence, tonics, good food and a change of climate may be necessary to restore health in asthenic and depressed dengue patients.

## LYMPHOGRANULOMA INGUINALE

**Synonyms.**—Climatic Bubo; Tropical Bubo; Lymphopathia Venereum; Lymphogranuloma venereum; Poradenitis.

**Definition.**—A venereal disease, due to a filterable virus, characterised by a herpetiform chancre on the genitalia or peri-anal region, inflammation of the corresponding regional lymphatic glands, and fever. In males the inguino-cruro-iliac glands and in females the pararectal and pelvic glands are chiefly involved. Chronic ulceration and elephantiasis of the pudenda are not uncommon in females, and inflammatory stricture of the rectum may occur in both sexes.

**Ætiology.**—The disease has a world-wide distribution, but is especially common in China, Japan, Malaya, East and West Africa, and in North and South America. Though more common amongst coloured races, especially negroes, it is being recognised with increasing frequency in Europe. The disease occurs mainly in adults, is essentially venereal in origin and is commonly acquired in the tropics and sub-tropics following coitus with native women. Sailors often acquire the disease in Eastern ports. The virus particle has a diameter of 0.125 to 0.175 $\mu$ , is filtrable and was first successfully transmitted to monkeys by intracerebral inoculation of bubo pus by Hellerström and Wassén. Mice are similarly susceptible. Serologically the virus is closely related to that of psittacosis. In guinea-pigs large buboes may follow the subcutaneous injection of sterile bubo pus. Surgeons have developed axillary buboes from lesions on the fingers when operating on infected patients, and children have acquired infection from simple contact.

**Pathology.**—The extirpated glands show marked periadenitis, and form conglomerated masses. The cut section often presents a reddish or violet tinge. Foci of purulent softening may occur, and sometimes cavities, containing thick viscid pus of a grey to light green colour, are produced by their coalescence. Microscopical sections of the bubo reveal granulomatous tissue, epithelioid cells, fibroblasts, occasional giant cells and polymorphonuclear leucocytes; epithelioid cells with palisade arrangement are very characteristic. Chromatin staining inclusion bodies, known as Gamma bodies, are found within lymphocytes and plasmocytes in the infected glands.

**Symptoms.**—In males, the primary lesion is as a rule overlooked. It occurs as a small herpetiform ulcer, generally situated in the coronal sulcus on the penis, and appears a few days to 3 weeks after coitus. Swelling of the median group of inguinal glands draining the ano-genital region follows in about 2 or 3 weeks, the limits being 1 to 6 weeks. Bilateral glandular involvement occurs in 35 per cent. of the cases. The onset is generally insidious, with slight stiffness or tenderness in the groin, and fever. Often pain is absent; rarely it may be severe. The skin is at first red, but as swelling of the glands with periadenitis and hard brawny infiltration proceeds, it changes to a bluish-violet tint. The conglomerated glands are hard to the touch, generally only slightly tender, and show no fluctuation unless suppuration is advanced. Fistulæ form in about half the cases. Though the iliac glands are frequently enlarged and palpable, they never present clinical evidence of suppuration. Healing with scarring may occur within 2 months or be delayed 1½ years. The general symptoms include fever, anorexia, weakness and loss of weight. Although the fever is usually remittent in type no characteristic temperature chart is present, and not infrequently the temperature becomes normal in 7 to 10 days, but sometimes it is prolonged and a typhoid-like state supervenes. Recurrent fever is occasionally

associated with extension of the adenitis. Rheumatic and allergic skin manifestations are not uncommon, and include painful red swollen joints, erythema nodosum, erythema multiforme, scarlatiniform and urticarial eruptions.

In females, primary lesions may occur on the genitalia or peri-anal region, and the para-rectal glands are commonly involved; these glands often suppurate and form fistulae which may open into the vagina, the rectum or the skin near the anus. The disease runs a chronic course; fibrous stricture of the urethra, vagina and rectum may develop, or elephantiasis of the vulva (esthiomene) follow lymphatic obstruction. Polypoid swellings may occur about the anus, while the lower portion of the rectum may ulcerate and become converted into a narrow indurated ulcerated tube, with widespread fistulae below the stricture. According to Stannus this is generally situated some 3 to 8 cm. above the anus. Rectal stricture is more common in females—especially in prostitutes—and is associated with the passage of blood, mucus and pus from the bowel, and increasing constipation.

**Diagnosis.**—Climatic bubo has been called the sixth venereal disease, and the history and clinical features are most important in making a correct diagnosis. Where periadenitis and induration are extreme, actinomycosis may be simulated. Herpes genitalis, filarial adenitis, septic and tuberculous adenitis, venereal bubo the result of chancroid, gonorrhoea and syphilis, as well as other buboes, such as result from plague, rat-bite fever and tularemia, may need differentiation. Histological section of material obtained at biopsy and Frei's intradermal test, using a 1 in 10 dilution of virus-containing pus sterilised at 60° C., may be of assistance; in 0.1 ml. of this antigen is injected intradermally, readings being made at the end of 48 hours. A positive reaction is characterised by the appearance of a reddish, infiltrated papule, measuring from 7.5 to 20 mm. in diameter. It is regarded as a manifestation of cutaneous allergy, and is said to be specific for climatic bubo. Animal inoculation and the mouse protection test may be resorted to in doubtful cases.

Lesions in the ano-genital region must be differentiated from filarial elephantiasis and ulcerative granuloma pudenda. Polypoid swellings should be distinguished from piles, simple polyposis and bilharzia polyps. Rectal stricture which is not due to surgical or other trauma or new growth is almost certainly caused by this virus; in the past it has generally been erroneously attributed to gonorrhoea, chancroid, syphilis or tuberculosis.

**Prognosis.**—The disease runs a different course in different individuals. In males, unless the rectum be involved, the outlook is good though the disease may last many months. In females, with extensive ano-genital manifestations, such as fibrous strictures and multiple fistulae, permanent invalidism may result.

**Treatment.**—The patient should be put to bed, have a nutritious high vitamin diet and given a course of sulphadiazine or some similar sulphonamide, as some patients appear to be cured by this treatment. Chlorotetracycline, in doses of 500 mg 6-hourly for 10 days, associated with complete rest in bed, is successful in many cases in causing a rapid improvement of the clinical condition. Chloramphenicol is also effective. If the glands are small and have not suppurated they are best left alone. If suppuration has taken place, aseptic aspiration of the pus may be undertaken to prevent rupture and secondary infection.

N. HAMILTON FAIRLEY.

HERPES SIMPLEX (see p. 1246).

HERPES PREPUTIALIS (see p. 1247).

VERRUCA VULGARIS (see p. 1301).

MOLLUSCUM CONTAGIOSUM (see p. 1302).

ACUTE ANTERIOR POLIOMYELITIS (see p. 1423).

ENCEPHALITIS LETHARGICA (see p. 1414).

HERPES ZOSTER (see p. 1247).

RABIES (see p. 1420).

## EPIDEMIC MYALGIA

**Synonyms.**—Epidemic or Infectious Pleurodynia; Bornholm Disease; Epidemic Diaphragmatic Spasm; Devil's Grip.

**Definition.**—An acute infectious epidemic disease of short duration characterised by sudden onset of pain in the upper abdomen and lower thorax, pyrexia, sweating and a tendency to relapse.

**Ætiology.**—The disease occurs usually in the late summer and autumn; it mainly affects children under 15 years of age. The incubation period being 2 to 5 days; the patient remains infective so long as the pain persists. One attack may not confer lasting immunity. Although proof is not absolute, it is probable that infection with one of the Cocksackie group of viruses is responsible.

**Pathology.**—Nothing is known of the pathology. No abnormality has been detected in those cases in which an exploratory laparotomy has been performed owing to mistaken diagnosis.

**Clinical Features.**—The onset is sudden, with acute spasmodic pain in the region of the xiphisternum and the attachment of the diaphragm, perhaps more on one side than the other. The pain leads to shallow rapid respiration, and is intensified by deep breathing, by yawning, sneezing or cough; a spasm during a period of quiescence may be induced by laughing. In adults, pain may also be complained of in the neck and extremities, and there may be some frontal headache. The temperature rises rapidly, perhaps to 104° F., and subsides within 24 hours. There is a marked tendency to a return of pain and pyrexia during 3 or 4 days, and the second attack may be the more severe. Profuse sweats are common, anorexia the rule, while vomiting and diarrhoea are seldom met with.

There are usually no physical signs, other than in the character of the respiration, of involvement of the pleura, lung or peritoneum, but occasionally coarse pleural friction makes its appearance. There may be some cutaneous hyperæsthesia and tenderness on pressure in the painful area, especially in the epigastrium. In some cases a leucocytosis occurs, and eosinophilia has been reported during convalescence. No abnormality has been detected on radiographic examination.

Complications are infrequent. Conjunctivitis, catarrh of the upper respiratory tract, orchitis and, rarely, meningo-encephalitis have been reported in certain epidemics. There are no sequelæ. Prognosis is good.

**Treatment.**—The patient should be isolated, and remain in bed until 48 hours after the pyrexia and pain have subsided. Ordinary methods for the relief of pain are indicated.

## C. THE MYCOSES

Numerous fungi are pathogenic to man, and the lesions caused thereby are conveniently described as the mycoses.

Some of the diseases, for example the ringworms, are described in other sections. Nine of them will be described here—actinomycosis, sporotrichosis, aspergillosis, mycetoma, torulosis, North American blastomycosis, South American blastomycosis, coccidioidosis and rhinosporidiosis, the lesions of which are of the nature of infective granulomata.

### ACTINOMYCOSIS

**Synonym.**—Ray-fungus Disease.

**Definition.**—A local infection, tending to become general, due to *Actinomyces israeli* or other of several species of the genus *Nocardia*, producing granulomatous lesions chiefly in the jaw, skin, lung and digestive tract.

**Ætiology.**—*A. bovis* was first described by Bollinger in 1877 as the micro-organism producing large, hard, sarcomatous-like masses occurring about the jaw-bones of cattle, and in the following year Wolff and Israel found a similar organism, now known as *A. israeli*, in human cases. There are two groups of organisms which may cause actinomycosis, *A. israeli*, which is anaerobic, and several species of aerobic *Nocardia*. The second have been isolated from soil, but the first, although frequently present in the healthy mouth, have not been found in soil or in vegetable matter. The two varieties are each responsible for about half the human infections. There is reason to believe that *A. israeli*, normally saprophytic, may become invasive when tissue is injured; the aerobic actinomycetes of soil are conveyed by inhalation or ingestion.

**Pathology.**—The characteristic of the disease is a suppurative lesion, the pus from which contains visible granules which, examined microscopically, are seen to have a centre of a closely meshed filamentous network, with a border of radially arranged striations, often ending in club-shaped bodies. Formerly these club-shaped bodies were thought to be spores, but they are now regarded as hyaline thickenings of the sheaths of the threads. The clubs are only found in preparations made from pus from active lesions, or in cultures on media in which serum or blood is employed.

It is essential in examining suspected pus to isolate a granule. If granules be not readily detected in the wound or in the pus, Colebrook has pointed out that if pus be vigorously shaken in a tube of water the granules, not being emulsified, will sink to the bottom and may be removed by a pipette. Microscopical examination is very much facilitated by crushing the granules between two slides. The mycelial filaments retain Gram's stain, while the clubs lose it and take the counter-stain. Culture is in any case difficult, depending to a large extent on the amount of secondary infection. To eliminate this as far as possible the granules should be well shaken in a sterile saline solution, and then after crushing between sterile slides should be sown on to glucose agar plates which are incubated anaerobically, or crushed granules may be shaken up into melted glucose agar which is aspirated into long sterile tubes according to the method of Vignal. Numerous subcultures may be necessary to complete the isolation of the organism.

**Symptoms.**—These depend upon the anatomical distribution of the granulomata.

1. **THE JAW AND ADJACENT STRUCTURES.**—When the infection occurs in these parts the patient presents a swelling very like a sarcoma, generally about the angle or ramus of the mandible. The swelling may, however, affect the submandibular tissues and lymph glands rather more than the jaw itself, or even be confined to the glands. The swelling is tender, somewhat painful and not generally so hard as in sarcoma. It may show one or more spots of softer consistency than the rest of the lump. With progress of the disease abscesses form and point externally to give rise to multiple sinuses. In most cases there is no obvious source of infection inside the mouth; the assumption is—in the light of observations quoted above—that the avenue of invasion is a carious tooth, or the gums and peri-odontal membrane.

2. **THE INTESTINES; APPENDICITIS.**—The favourite site of infection is the cæcum and appendix region. The disease manifests itself either as an attack of appendicitis, most often acute, in which case the diagnosis is made only at the time of laparotomy; or as a slowly growing mass in the right iliac fossa, with some pain, tenderness and constitutional disturbance, in which case suspicion may be aroused as to its nature, if it be remembered that this region is a site of election for the ray fungus. Distinction must be made from a swelling due to regional ileitis (see p. 631), to tuberculosis or new growth. There is a tendency for the infection to spread from the ileo-cæcal region—(a) to the adjacent peritoneum; (b) to the abdominal wall; (c) to the liver. For this reason it is rare to find the lesion confined to the appendix by the time operation takes place. For this reason, too, the first evidence of cæcal infection may be the involvement of the parietes in the lower right quadrant of the abdomen, in which

case there is always a probability that the infection has spread from the bowel. The *liver* is sometimes involved alone, that is, without obvious intestinal infection. The disease is only to be distinguished from abscess by puncture or by free incision.

3. THE PLEURA AND LUNG.—Actinomycosis in these tissues is by no means rare (see p. 1038), and the disease should constantly be borne in mind by the practitioner when faced with an obscure case in which indefinite physical signs appear at one base, with cough, fever and (not seldom) hæmoptysis. In some cases a fairly frank pleuritic effusion appears, and the bacteriological examination of the exudate reveals the nature of the disease. In other cases the clinical picture resembles a basal tuberculosis. As the disease progresses the differential diagnosis lies between ray fungus, bronchiectasis and new growth. Hæmoptysis which recurs in the absence of any evidence of tuberculosis in an obscure case of pulmonary disease, should raise the suspicion of actinomycosis of the lung. The later stages of the disease still resemble pulmonary tuberculosis; wasting, intermittent fever, purulent expectoration, cough and physical signs of progressive lung infiltration with destruction.

4. THE SKIN.—Granulomata sometimes appear in the skin and subcutaneous tissues (a) alone, or (b) complicating the disease in deeper structures.

(a) The neck and scalp are the parts most often affected. The initial lesion is a rounded swelling, resembling a tuberculoma rather than the result of a pyogenic infection, but usually firmer in texture and larger than the lesion seen in tuberculosis of the skin. It has therefore to be distinguished from sarcoma and from gumma. As the lesion progresses it involves the subcutaneous tissue and tends to ulcerate, after the appearance of one or more soft and dusky-red areas on it. When ulceration occurs at these points, pus escapes, and this contains the tell-tale granules characteristic of the infection. At this stage the appearance is not unlike that of a chronic carbuncle or a suppurating gumma. Ultimately the skin "breaks down" over a considerable area of the swelling, and a chronic ulcer forms, which discharges freely.

(b) Similar skin lesions appear not seldom in association with primary infections of deeper structures, these superficial deposits having the significance of metastatic pyæmic deposits.

5. THE BRAIN.—The brain, like the skin, may be infected by direct spread from an adjacent lesion, or it may suffer by way of a general pyæmic process.

**Diagnosis.**—Hints have been given in the preceding account relative to the differential diagnosis from tuberculoma, sarcoma, pyogenic infection and gumma. The chief reason why actinomycosis goes unrecognised is that the possibility of its existence is overlooked. All materials from a suspected case (pus, pleural exudate, sputa, material from liver puncture, excised lymph glands, etc.) should be carefully examined for mycelium, and the bacteriologist should have his attention drawn to the possibility of its presence. Sputa from a case of recurring hæmoptysis, in which a negative report in respect of tubercle bacilli has been returned on several occasions, have been found to contain threads of actinomyces when the necessary investigation has been specially asked for.

**Course and Prognosis.**—Although these vary much, there is, as may be inferred from remarks already made, a tendency for ray-fungus infection to become pyæmic in character. It is this feature which gives the serious note to prognosis in all cases. In lesions about the jaw and in skin infections, that are primary and not associated with visceral infection, the outlook is not nearly so bad as when the lungs, liver or intestinal tract are involved and when the skin lesions are multiple and secondary. Early diagnosis, if possible before secondary infection (usually staphylococcus) has taken place, adds greatly to the chance of recovery. One of the most important points in connection with prognosis is the uncertainty as to the complete extirpation of the fungus after treatment has been apparently successful. Relapses are common, and must be allowed for in any thorough programme of treatment.

**Treatment.**—So soon as the diagnosis is made, penicillin should be given in combination with one of the sulphonamides and the question should be raised whether or not radical surgical measures are practicable. If they are, they should be pursued without delay; any abscess or infected area should be drained, or incised and freely curetted; infected lymph glands should be excised; doubtful teeth should be sacrificed.

Radiotherapy has also been advocated as a supplementary measure.

## SPOROTRICHOSIS

In this disease, which is much less common than actinomycosis, lesions (granulomata) appear in the skin, and rarely in the muscles and bones.

**Ætiology.**—The causative microbe was first described by Schenk in 1898. Two varieties, *Sporotrichum schenki* and *S. beurmanni*, were originally described, but are now generally regarded as identical. The organisms occur in pus as oval or fusiform spores, and grow in culture as a colourless branching septate mycelium, with clusters of brown fusiform spores on the ends of the filaments. Occasionally the spores are arranged round the filaments. They stain well with the aniline dyes, but irregularly with Gram's stain. Growth occurs under aerobic conditions only, and on ordinary laboratory media. Cultures are best made from closed lesions, which should be punctured with a wide-bore needle, and the material aspirated should be thickly sown on glucose agar plates, which should be kept at laboratory temperature. The colonies, which appear in from 4 to 10 days, are very characteristic. At first white, thick and leathery, they later become convoluted and coffee-coloured, and still later may become black. Laboratory animals, especially mice and rats, are susceptible, the lesions resembling those in man; but the disease is seldom fatal. The serum of infected individuals agglutinates the spores of the organism, and specific immune bodies can be demonstrated by complement-fixation tests.

**Symptoms and Diagnosis and Treatment.**—See p. 1239.

## ASPERGILLOSIS

Infections with aspergillus, usually *A. niger* or *A. fumigatus*, have been observed in the middle ear, on abraded corneæ and in the lung. These organisms grow on ordinary laboratory media, and related species frequently occur as contaminants.

Cases of lung infection are not very rare (see p. 1039). They resemble cases of chronic pulmonary tuberculosis very closely; indeed, they are generally mistaken for this disease until investigation of the sputa reveals their true character.

R. BODLEY SCOTT.

## MYCETOMA

**Synonyms.**—Madura Foot; Maduramycosis.

**Definition.**—A chronic granulomatous condition affecting especially the feet, characterised by marked swelling and the appearance of external nodules connected with deeper sinuses which exude oily, purulent fluid containing various coloured fungoid granules.

**Ætiology.**—The disease is endemic in certain parts of India, especially in the Madras Presidency (Madura), but it also occurs in Ceylon, Madagascar, parts of Northern Africa, Cochin-China, Senegambia, the United States, West Indies, South America, New Guinea and elsewhere. It is found in country districts, and generally attacks those who go barefooted, the mycetoma fungus probably gaining access through thorn punctures, small cuts or abrasions. Males are more commonly affected than

females. The disease is especially prevalent in the third and fourth decades of life, being generally confined to natives. Many different fungi which have the capacity to produce grains composed of hyphæ in animal tissues have been described as causing mycetoma. Laveran divided them into two groups: (1) the Actinomycoses, caused by fungi of the genera Actinomyces and Nocardia, (2) the Maduramycoses, caused by true fungi, the most important of which is the genus *Madurella*. White, red and black varieties of mycetoma occur clinically.

**Pathology.**—On section through the softened, jelly-like tissue, sinuses and cystic dilatations communicate with external nodules and internal granulomatous infiltrations which ultimately implicate muscle, fascia and bones, forming a honeycombed cheesy mass. Both the cysts and sinuses are filled with whitish-yellow, red or black granules like fish's roe, which microscopically show thin Gram-positive branching mycelium and peripheral, club-like swellings. Section shows fungoid granules surrounded by mononuclear and leucocytic infiltrations and by fibrous-tissue cells. Sometimes giant cells are evident.

**Symptoms.**—The incubation period is not definitely known, but in about 50 per cent. of cases there is a history of trauma; many weeks or months may elapse before local lesions develop. The first signs are the presence of one or more hard, painless, subcutaneous nodules, which are about 0.5 to 1 cm. in diameter and generally involve the sole of the foot, and more rarely the hands, face and limbs. Unlike actinomycosis the glands and viscera are never affected, adenitis if present, being due to secondary bacterial infection. After several months swelling increases, the nodules break down and ulcerate, sinuses are formed and discharge their characteristic contents. Finally, the parts become riddled with sinuses, exuding foul-smelling, semi-purulent fluid. The foot becomes more and more swollen and distorted, but it shows little tendency to pain or hæmorrhage. In the early stages the general health is not adversely affected, but later anæmia and cachexia develop if secondary bacterial infection supervenes. Radiograms reveal involvement of the small bones of the feet or hands; both destructive and proliferative reactions are present.

**Diagnosis.**—This is readily made by finding the characteristic fungi in the pus, but the identification of the actual species of mycetoma requires detailed laboratory investigation.

**Prognosis.**—There is no tendency to natural cure, and if untreated the prognosis is bad, the patient generally dying from intercurrent disease or secondary infection within 15 years of onset.

**Treatment.**—PROPHYLACTIC.—Protection of exposed parts, like the feet, from thorns and similar trauma appears to lessen the tendency to this disease. Walking barefooted is to be avoided.

**CURATIVE.**—Sulphonamide therapy combined with surgery is the only satisfactory treatment. In the early stages curettage, or local excision of the nodules with the electric cautery may prove successful. In sinus-riddled feet amputation is almost always necessary but this should not be done until sulphonamides have been well tried.

## TORULOSIS

**Synonyms.**—Cryptococcosis; European blastomycosis.

**Definition.**—A subacute or chronic infection produced by a yeast-like organism, *Torula histolytica* (*Cryptococcus neoformans*), possessing a special affinity for the cerebrospinal system and lungs.

**Ætiology.**—The disease affects both men and women and has a widespread geographical distribution. Species of the genus *Torula* reproduce only by budding without mycelial or endospore formations; in pus and cerebrospinal fluid they appear as ovoid or spherical structures, measuring  $3\mu$  to  $15\mu$ , with definite cell walls

(Jacobson). This infection is a true blastomycosis, since it shows budding in the tissues, but it is not limited to Europe.

**Pathology.**—Chronic leptomenigitis may be present, while the brain shows tubercles and gelatinous cyst-like structures in which torulæ abound. Clear spaces containing gelatinous material are found round the parasites in the tissues, and this constant finding led Stoddard and Cutler to name the parasites *Torula histolytica*. Similar lesions may occur in the lung, which may be honeycombed, the interstices being filled with gelatinous material.

**Symptoms.**—Occasionally localised torulosis involves the skin or mucous membranes, lymph glands, etc., but much more commonly the central nervous system or lungs are implicated. Pulmonary torulosis may involve one or both lungs and gives rise to mild fever, and cough with or without sputum which is mucoid and rarely blood tinged. Dullness and altered breath sounds are generally demonstrable and radiograms often reveal dense shadows resembling neoplasm or massive tubercular infiltration. Meningitic torulosis may have a gradual or sudden onset, early symptoms being headache, vomiting and pain and stiffness in the muscles of the neck. Apathy, depression, irritability and delirium follow. The signs are those of a subacute or chronic meningitis with papillædema. Death occurs with coma and respiratory failure.

**Diagnosis.**—The skin and gland lesions are diagnosed by biopsy or culture on blood agar or Sabouraud's medium at room temperature. The pulmonary lesions have to be differentiated from tuberculosis, other mycotic infections and new growth. Torulosis involving the central nervous system may simulate tuberculous meningitis, brain tumour or abscess, encephalitis and other mycoses involving the meninges. The cerebrospinal fluid which may be clear, xanthochromic or turbid, is under increased pressure and contains an excess of lymphocytes and globulin and a normal or decreased quantity of sugar. The diagnosis is made by culture or finding *Torula histolytica* in the sputum or cerebrospinal fluid where the torulæ appear as ovoid or spherical structures measuring  $3\mu$  to  $15\mu$  with definite cell walls.

**Prognosis.**—The course of the disease is subacute or chronic, lasting a few weeks to 2 years, with an average duration of  $4\frac{1}{2}$  months. In localised infections the outlook is fairly good, but systemic torulosis is practically always fatal.

**Treatment.**—Surgical resection with the cautery followed by radiotherapy is the treatment for local lesions. In generalised infections sulphonamide therapy is worthy of trial combined with repeated lumbar puncture to decrease cerebrospinal fluid pressure where the central nervous system is involved.

## NORTH AMERICAN BLASTOMYCOSIS

**Synonyms.**—Gilchrist's Disease; Chicago Disease.

**Definition.**—A term applied to certain chronic granulomatous lesions of the skin or viscera, caused by yeast-like blastomyces.

**Ætiology.**—People of any age are susceptible, but males in the industrial classes are most often affected. The disease was especially prevalent in Chicago, but is now known to occur in Canada, England and elsewhere. It is caused by *Blastomyces dermatitidis*, which occurs in the tissues as a round, budding, yeast-like fungus, but which produces aerial hyphæ on culture. In this respect it differs from torulosis, which retains its yeast-like characteristics on culture.

**Pathology.**—Nodules, gummata, papillomata and ulcerations may be produced in the skin, and tumour-like granulomata and abscesses in the viscera. The pathological lesions resemble the tissue reactions induced by the tubercle bacillus, but central necrosis is less, and yeast-like organisms are present.

**Symptoms.**—The clinical manifestations are very variable. Jacobson divides



the primary cutaneous manifestations into papulo-ulcerative, papillomatous and gummatous types: cutaneous lesions secondary to systemic blastomycosis consist of superficial ulcers with granulating bases which exude pus or form crusts. Local pain and discomfort are produced.

In systemic blastomycosis the clinical picture resembles a subacute or chronic pyæmia, and almost any organ may be involved; the lung (95 per cent.) and kidneys (30 per cent.) are most frequently implicated, producing localising features resembling pleurisy or pneumonia on the one hand and nephritis on the other. Osseous involvement and blastomycotic meningitis may also occur.

**Diagnosis.**—This depends on the demonstration of blastomyces in pus, sputum or cerebrospinal fluid; moist specimens are prepared by mixing with a drop of sodium hydroxide (10 to 30 per cent.) and examined microscopically, when the round or oval, highly refractile bodies ( $5\mu$  to  $20\mu$ ) surrounded by a hyaline capsule, may be observed. They may also be cultured on glucose agar.

**Prognosis.**—Cases with localised cutaneous lesions as a rule ultimately recover if properly treated, but in systemic blastomycosis 90 per cent. of cases end fatally in a few weeks to 3 years. Cerebrospinal cases invariably die.

**Treatment.**—Skin lesions should be radically treated by complete resection with the cautery, or curetted and cauterised. Radium and radiotherapy combined with full doses of iodide, *i.e.* grains 20 to 60 three times a day, are sometimes successful. Patients with systemic blastomycosis should receive large amounts of iodide. A skin test should be made with 0.1 ml. of a standardised heat-killed blastomyces vaccine before starting either potassium iodide or radiation in order to determine hypersensitivity. If at 24 and 48 hours the erythematous reaction is less than 1 cm. in diameter it is safe to give iodides or radiation. If the reaction exceeds 1 cm. the patient should be desensitised by the subcutaneous injection with gradually increasing amounts of vaccine.

## SOUTH AMERICAN BLASTOMYCOSIS

**Synonyms.**—Paracoccidioidal granuloma.

**Definition.**—A chronic granulomatous disease of the skin, lymphatic glands, mucous membranes and viscera which occurs in South America and is produced by *Blastomyces brasiliensis*.

**Ætiology.**—The fungus, *B. brasiliensis*, differs from *B. dermatitidis*, the cause of North American blastomycosis, in that it produces multiple budding forms in the tissues instead of single budding forms. Some authorities say there are three different species which can cause blastomycosis in South America, but as only minor differences have been found it is reasonable to regard them as varieties of the same species. The infection is more prevalent in the third decade of life and is much more frequent in males than females. The method of infection is unknown.

**Pathology.**—Abscesses may occur in which polymorphonuclear reaction is predominant, while elsewhere lesions with caseous centres are encountered; the peripheral zone is composed of giant cells, macrophages, lymphocytes and fibroblasts. There is frequently extensive intestinal ulceration involving lymphoid tissue as well as nodules in the liver, spleen and kidneys.

**Symptoms.**—The cutaneous and systemic clinical manifestations are similar to those encountered in North American blastomycosis. South American workers recognise the (1) cutaneous type characterised by skin and mucosal lesions which are common in the region of the mouth and nose, (2) lymphatic type involving the cervical and axillary glands, (3) visceral type with lesions of the abdominal viscera and intestine and (4) mixed type in which a variety or all of these lesions may be found.

**Diagnosis.**—The cutaneous lymphatic and visceral types may simulate a variety

of infections, particularly those caused by tuberculosis, syphilis, yaws, leishmaniasis and certain other mycoses. The diagnosis is made in the laboratory by the isolation of *B. brasiliensis*.

**Prognosis.**—This disease is almost invariably fatal.

**Treatment.**—Iodides have been reported as causing improvement in early cases, but as in North American blastomycosis harmful effects may result in hypersensitive patients before iodides are given. Certain of the sulphonamides have been reported on favourably but their value needs confirmation.

## COCCIDIOIDOSIS

**Synonyms.**—California Disease; Coccidioidal Granuloma; Coccidioidomycosis.

**Definition.**—An acute, subacute or chronic disease, characterised by granuloma formation in the skin or viscera, caused by *Coccidioides immitis*.

**Ætiology.**—The disease is endemic in certain parts of North America and affects persons of any age. Males of the working class are particularly prone. The causative agent is *C. immitis*, which is inhaled in dust in endemic areas, and appears in the tissues or pus as a spherical, double-contoured body measuring  $20\mu$  to  $80\mu$ , which is filled with small endospores ( $2\mu$  to  $5\mu$ ). The fungus is readily cultured and laboratory animals are susceptible.

**Pathology.**—The lesions are those of an infectious granuloma, and the tissue changes include tubercles, caseation, necrosis, abscess formation, cavitation, fibrosis and even calcification.

**Symptoms.**—Primary pulmonary coccidioidosis is often subclinical as proved later by positive coccidioidosis skin tests, and the symptoms are generally those of a mild upper respiratory tract infection with dry cough and slight temperature. Others have rigors, night sweats, backache, headache and mucopurulent sputum. About 80 per cent. of patients show radiological changes in the lungs. Only 1 in 500 cases of primary pulmonary infection is said to develop the fatal form of the disease. Primary cutaneous coccidioidosis frequently occurs on exposed surfaces manifesting itself as nodular lesions which ulcerate and later become papillomatous. Gummatous-like ulcers and abscesses containing thick mucoid pus may be found in the subcutaneous tissues. A scrofulodermic type of lesion involving the superficial lymph glands, especially of the neck, is also recognised. The progressive type of coccidioidosis terminates within a few months to a year or more. Fever continues, dyspnoea and cyanosis develop and the pulmonary physical signs increase. Later progressive involvement of the skin, bones, joints, internal organs, brain and meninges may follow and death ensues within a few weeks. Meningitis is found in 25 per cent. of the fatal cases.

**Diagnosis.**—Numerous diseases, including tuberculosis, syphilis, blastomycosis, sporotrichosis, mycetoma and bacterial osteomyelitis may be simulated. Diagnosis essentially depends on isolating *C. immitis* from pathological exudates. Radiograms are of assistance where bone lesions supervene or pulmonary involvement is progressive.

**Prognosis.**—The prognosis is good in primary pulmonary coccidioidosis resolving within 1 month, as well as in the cutaneous and glandular types of primary infection. If the pulmonary infection persists 5 or 6 weeks or longer the acute progressive form of the disease should be suspected. In the meningitic type or where the internal organs are involved, the prognosis is grave.

**Treatment.**—Patients with primary pulmonary coccidioidosis should be kept in bed until they are afebrile, the sedimentation and leucocyte counts are normal and physical and radiological examination of the lungs satisfactory. Occasionally artificial pneumothorax may be necessary. Radiotherapy may be useful in the treatment of the local lesions. Every effort should be made to build up the resistance of the

patient by good nursing, bed rest and a well-balanced diet reinforced with vitamins, while in acute progressive coccidioidosis desensitisation with progressively increasing doses of coccidioidal vaccine should be attempted and intramuscular injection of colloidal copper (5 ml.) given every 8 to 14 days, the interval being determined by the local and constitutional reaction (Jacobson).

## RHINOSPORIDIOSIS

**Definition.**—A chronic disease due to *Rhinosporidium seeberi* (Wernicke, 1903), which produces friable pedunculated polyps; mucous membranes of the nose, eyes, ears and larynx may be implicated and occasionally the penis, rectum and vagina.

**Ætiology.**—The disease is most common in children and young adult males. It is especially common in India and Ceylon, where the disease is endemic, but it also occurs in Cochin-China, Malaya, North and South America and England. The infecting spore which has not been cultured is a round body of  $6\mu$  to  $7\mu$  in diameter, with a chitinous wall, a nucleus and a karyosome. Multiplication by fission occurs, and sporangia or large cysts ultimately lined by cellulose with a diameter of up to  $300\mu$  are formed. It is believed that these spores which may number up to 16,000, escape by rupture of the sporangium at the "pore", invade the tissues and repeat the life cycle there; the disease, however, has never been transmitted directly to animals or man. Rhinosporidiosis also occurs in horses, mules and cows, but it is thought to be primarily a disease of fish. In India sand divers are reported to be frequently infected, and it occurs in individuals who dive and swim in stagnant water.

**Pathology.**—The polyps are soft and nodular and under the surface opaque greyish-white areas occur, which are found on microscopic examination to be large sporangia containing innumerable spores. Chronic inflammation, with plasma cells and lymphocytes, is commonly found but when the spores escape into the tissues, tissue necrosis and acute inflammatory reaction, with the formation of pus sometimes may result; secondary bacterial infection should be suspected under such circumstances.

**Symptoms.**—A history of nasal symptoms over years may be obtained. Painless itching sensations and profuse mucoid discharge may be the first symptoms. Bleeding is rare unless produced by trauma. The polyps are soft and vascular, sessile at first and later pedunculated; as they enlarge they may protrude through the nares anteriorly or into the pharynx posteriorly. Nasal obstruction, dyspnoea and dysphagia may follow. Polypi may also involve the cheeks, conjunctiva, lacrimal sac or ear. The early lesions on the penis resemble venereal warts and infections of the vagina and rectum may produce lesions resembling rectal polypi, hæmorrhoids or condylomata.

**Diagnosis.**—The presence of papillomatous polyps composed of granulomatous tissue on the mucous surfaces should suggest the possibility of rhinosporidiosis in doubtful cases. The diagnosis is established by biopsy, microscopic examination revealing the characteristic sporangia.

**Prognosis.**—The disease is rarely fatal and only causes serious symptoms when the polyps become so large as to result in obstruction of the nose, larynx or œsophagus, or are secondarily infected with bacteria. Smaller lesions sometimes disappear spontaneously after 10 years.

**Treatment.**—The old practice of removing polyps by a wire snare has been discontinued because of the danger of spreading the infection locally and bacterial complications (Wright). The early lesions may be removed by careful dissection and in advanced cases extensive excision may be necessary, followed by cauterisation. Favourable results have been reported with Neostibosan given intravenously in doses of 0.3 g. for 10 days, especially when combined with surgical treatment.

N. HAMILTON FAIRLEY.

## D. SPIROCHÆTAL INFECTIONS

## SYPHILIS

**Definition.**—A specific disease due to entry of a micro-organism (*Spirochæta pallida* or *Treponema pallidum*) into the tissues, either by inoculation into the skin or mucous membrane, or by needle puncture into veins or other deeper tissues (acquired syphilis) or by transmission *in utero* (congenital syphilis).

Acquired syphilis, unless conveyed by transfusion, or other needle puncture, commonly presents as a primary sore or so-called syphilitic chancre developing at each site of inoculation, which may be followed after a few weeks by a succession of lesions of the skin, mucous membranes, subcutaneous tissues, arteries, muscles, bones, viscera and central nervous system. These may recur again and again at varying intervals throughout the patient's life. Degeneration of the parenchyma of the brain (general paralysis) or of the spinal cord (tabes dorsalis) may develop as late manifestations. From an early stage changes in the blood serum can be detected by various serological tests. Any or all manifestations, including the primary, may be omitted or go unrecognised. With congenital syphilis and syphilis acquired by transfusion the systemic disease is the first manifestation.

**Ætiology.**—The specific micro-organism was discovered by Schaudinn and Hoffmann in 1905 and called by them *Spirochæta pallida*. Subsequently the organism was renamed *Treponema pallidum*, but many prefer to use the original name. *T. pallidum* is a minute organism which in fresh specimens under dark-ground illumination appears as a bluish-white, very delicate corkscrew. Its length varies from 5 to 24  $\mu$  (average 8 to 10  $\mu$ ); the distance between individual coils is 1  $\mu$ , and the depth of each coil is 1  $\mu$ . It is very active in its own ground but slow in moving through the microscopic field. It alternately contracts and expands its coils, bends into loops or forms itself into a right angle. It has been demonstrated in every affected tissue, including the brains of general paralytics. It has a life of only a few hours under natural conditions outside the body, but in blood obtained for purposes of transfusion it can remain alive for 72 hours. It is killed at once by drying, by comparatively low degrees of heat and by much weaker antiseptics than suffice to destroy ordinary pathogenic organisms.

The usual methods of transmission are by sexual intercourse and by way of the placenta to the fetus *in utero*. It does not seem necessary for a person transmitting the disease by intercourse to be suffering at the time from syphilitic lesions of the external genitals, but whether the semen contains the micro-organism in the absence of infectious lesions of the genital mucosæ is a matter of dispute. The period during which a person suffering from syphilis is liable to convey the disease by sexual intercourse varies; after the second year infectivity diminishes, and it is unusual for infection to be transmitted sexually after the fifth year. In the case of the fetus, however, although the mother is most dangerous in the first 5 years of her infection, transmission may occur much later, and there is, possibly, no limit to the duration of potential infectiousness. Transmission occurs most often in the second half of pregnancy. Accidental infection usually results from contamination of a minute abrasion with secretion from infectious syphilitic lesions, of which the most dangerous are the primary sore, the moist secondary lesions and some of the early lesions of congenital syphilis. The dangers of accidental infection from later or tertiary syphilides are extremely slight, but it is possible to infect susceptible animals with material from these lesions. Even in the earlier stages the risks of accidental infection appear to be slight, presumably because the organism is so susceptible to external agencies. This is shown by the fact that, even when the disease has been highly

prevalent, the proportion of extragenital syphilitic chancres has been low in countries where the standards of personal hygiene are equal to those of Western Europe. A number of instances of infection by transfusion of blood have been recorded, and they have included cases in which the donor was still in the incubation stage of the disease. On the other hand, tertiary syphilitics have been used as donors in cases of emergency in a number of instances without harm to the recipients, and it is clear that the older the infection the less likely is the micro-organism to be in the blood stream.

**Pathology.**—Kolle and Evers showed that, after inoculation by scarification, the micro-organism reached the nearest lymphatic glands of a rabbit in half an hour. The syphilitic lesion of every stage is histologically the same—a granuloma composed of a collection of epithelioid cells, plasma cells, very numerous small lymphocytes and some giant cells, with obliterative endarteritis of the vessels. The pathology of syphilis as it affects the nervous and cardiovascular systems is discussed in the sections dealing with those parts of the body. Here it may suffice to sketch the main general effects of syphilis on the vessels, since they cause a large proportion of the serious results of syphilitic infection. A common result of syphilitic arteritis of smaller vessels is obliteration of the vessel, with important effects resulting from limitation or loss of blood supply. In the primary stage the effect is to produce necrosis of the surface tissue of the sore with "erosion" or ulceration. The epithelium covering the secondary papule is likely to become necrotic and remain adherent as a fine scale, giving the so-called "papulo-squamous" lesion. The vascular supply is most affected in the gumma or tertiary lesion, leading to necrosis and considerable destruction of tissue. Gummata of bones destroy bony tissue but at the same time provoke a reaction by the periosteum whereby new bone is deposited on the surface of the cortex in irregular fashion and destroyed bone is replaced by densely sclerotic new bone. In the long bones, formation of new bone usually keeps pace with destruction but in the flat bones and particularly those of the skull, destruction is likely to predominate, giving, in neglected cases, the appearance of rounded areas of erosion of bone of which the classical example is the *worm-eaten skull*. At all stages of syphilis healing is by scar tissue. If the inflammatory infiltrate is small, as in some primary and most secondary lesions, the amount of scar tissue is also small. If there is much infiltration, as in some primary lesions and most tertiary lesions, the scarring may be considerable. Scar formation and subsequent contraction occasionally has important effects on viscera, interfering seriously with their functions.

It is well known that syphilis is a milder disease in females than in males, and experimental evidence suggests that the difference is due to the action of female sex hormones.

**Symptoms and Signs.**—For convenience of description, syphilis is divided into three stages, of which the primary consists of the lesions occurring at the sites of inoculation, the secondary of the early generalised lesions and the tertiary of the gummatous and late destructive lesions, usually occurring much later after a period of quiescence. Some prefer to classify the lesions affecting primarily the parenchyma of the central nervous system as a fourth or quaternary stage. The division at all stages is only empirical, and it is common experience that one stage may merge into or overlap another.

**PRIMARY STAGE.**—The incubation period varies from a minimum of 10 days to a maximum of about 90, with an average of 2 to 4 weeks. A small papule, the *primary chancre*, then appears at each site of inoculation; most commonly there is only one lesion, but there may be two or more. The papule quickly enlarges to a round or oval lesion of varying size; the surface usually becomes eroded, or perhaps more deeply ulcerated; the eroded area is clean and granular and surrounded by a dull-red areola varying in width from half to 2 or 3 mm. Beyond the confines of the eroded area the tissues are infiltrated, giving a feeling of thickening or induration

when the base of the lesion is palpated between finger and thumb. This induration, on account of which the name of *hard chancre* has been given to the lesion, may become more and more pronounced until in some cases it feels as though there were a button embedded in the tissues. The sore does not bleed easily when scraped but serum oozes freely from it, and this serum usually teems with syphilitic organisms. The sore is comparatively painless.

Individual features vary with the site. Thus, the most indurated primary chancres are those on the mucous surface and edge of the prepuce in males, and on the labia posterior commissure and *portio uteri* in females. In the case of a sore at the reflection of the prepuce on to the *corona glandis*, when the prepuce is retracted the lesion may flick over like the tarsal plate when the upper eyelid is everted. A sore at the edge of the prepuce may convert the preputial orifice into a fibrous ring. Induration is easily felt in a sore affecting one wall of the *fossa navicularis*, which then feels as though a solid object were embedded in it. With primary sores of the *glans penis* induration is difficult to appreciate because of tightness of the tissues, but the sore is easy to recognise by its dull-red areola, even contour, eroded centre and indolent progress. Rarely, a primary sore has been found deep in the urethra, and the diagnosis has been made by urethroscopic examination together with the discovery of *T. pallidum* in the scanty urethral discharge. Primary chancres of the skin are dusky red and indurated. They may be covered with a reddish-black scab due to dried secretion containing altered blood. Ulceration is usually more marked in sores affecting the under-surface of the prepuce, the skin at the peno-scrotal angle, the perionychial tissues, the lips and the tonsils. Almost all primary sores are comparatively painless, but when related to a nail of finger or thumb they may be exquisitely painful, and thus may be mistaken for whitlows. The primary sore affecting the prepuce, the skin of the penis or, especially, the female labia may be accompanied by an indurated œdema of the affected parts, which may become rather livid in appearance; the same condition may affect the uterine cervix. This is sometimes called cold œdema.

The course of the primary syphilitic sore varies greatly. In some cases the lesion is fleeting, and its apparent triviality may lead to failure to seek advice; the history of a substantial proportion of cases of late syphilis is that the initial lesion was either unnoticed or was very trivial. Ordinarily, the primary sore which remains untreated lasts for a month or longer, and, after the erosion has healed over, a button of indurated tissue may remain to mark the site. Weeks or months after healing, the sore may break down again; syphilitic organisms have been found by histological examination of the scars of such lesions many years later. When a syphilitic chancre is infected by secondary organisms, ulceration may be more severe, and in rare instances the area becomes phagedenic. In such cases the surrounding tissues very rapidly become black and necrotic, and large parts of the external genitalia may be destroyed.

Shortly after the appearance of the primary sore the nearest lymphatic glands often become painlessly enlarged, the *indolent bubo*, and the lymphatics running from a sore on the penis can sometimes be felt beneath the skin. The affected glands may reach a large size, bulging under the overlying skin which, however, does not become reddened. The glands are of firm, rubbery consistency and remain discrete, or distinguishable one from another. The character of the swelling and the absence of signs of acute inflammation often give the clue to the nature of the causative lesion. In females the inguinal lymphatic glands remain unaffected if the sore is deeply situated. Syphilitic buboes do not usually suppurate, but may do so if the sore has become contaminated by secondary organisms, so that the presence of suppuration should not weigh heavily against a diagnosis of syphilis. Some time after the local lymphatic glands have begun to enlarge and before other signs of secondary syphilis can be found, there may be widespread adenitis, which can be appreciated by palpation, particularly of the cervical, axillary and epitrochlear glands.

When the sore is about 15 days old, the blood serum commonly gives positive

Wassermann and other serological reactions, such as the Kahn, Kline, Meinicke and Price. These tests employ antigens made from crude alcoholic extracts of heart muscle. Recently, the purified active principle of these extracts, *cardiolipin*, has been isolated and is employed in conjunction with lecithin and cholesterol for various complement fixation tests or for flocculation tests such as the V.D.R.L. reaction (Venereal Disease Research Laboratory). The percentage of cases in which positive results to the serological tests are given increases with the duration of the disease until the outbreak of lesions of the skin characteristic of the next or secondary stage. Practically 100 per cent. of patients in the secondary stage have positive serological tests.

**SECONDARY STAGE.**—In general the skin eruptions of secondary syphilis tend to be widespread, non-irritant, discrete, polymorphic, symmetrically distributed, dull red in colour, rounded in outline and infiltrative to touch.

Commonly, a generalised pink macular rash, the *macular* or *roseolar rash*, appears 4 to 8 weeks after the sore. It usually appears on the sides of the trunk as pinkish spots, varying in size from a split-pea to a finger-nail, which with age may deepen in colour to a dull red. At first they may be difficult to see, but they become more obvious after the patient has been stripped for a few minutes. The eruption spreads gradually over the trunk and limbs, missing the face except perhaps for slight mottling of the chin, and fades in a few weeks, leaving little or no staining.

After the fading of the first roseola, a patchy loss of pigment may occur, especially in the pigmented zone of the necks of brunettes. The depigmented areas are circular and each about the area of a finger-tip. The condition has been called *syphilitic leucoderma* or *collar of Venus*. It is a residual effect which may persist indefinitely.

The papular eruption follows closely after the roseolar, and takes a number of different forms, the commonest and usually the earliest being dome-shaped, rounded, dull-red papules distributed over the trunk, limbs and face. Most are about the size of a lentil, but amongst the smaller papules may be larger ones, sometimes even the size of a silver threepence. The papules are discrete and symmetrically distributed. On palpation with the tips of the fingers they feel indurated. Variations of the ordinary, papular eruption are the papulo-squamous, squamous, papulo-pustular and pustular. In the *papulo-squamous* a large proportion of the papules are covered at their centres by loose scales. The *squamous* syphilide is a papular eruption in which scaling is a still more prominent feature. In the *papulo-pustular* syphilide the centre of the papule becomes necrotic, and looks rather like an acne spot. When the whole papule breaks down, a *pustular* syphilide results and in the aggregate may resemble a varicellar or a variolar eruption. A more severe form is the *ecthymatous* type in which the papule breaks down quickly, and the underlying tissues become eroded or ulcerated. As the destruction of tissue extends, the secretion dries to a crust. This may become heaped up by a deposit of successive layers with the formation of limpet-like crusts, blackish or greenish in colour due to altered blood, a condition which is called *rupia*.

*Variations of the papular syphilide in different situations.*—Round the anus, between the buttocks, on the lateral surfaces of the scrotum, on the labia, on the inner aspects of the upper thighs and in other warm moist areas of the body, the papular syphilide often becomes large and prominent, forming fleshy-looking masses, rounded in outline, with broad base and flat top. The surface may become greyish white, due to necrosis, and exude serum packed with *T. pallidum*. These are the *broad condylomata*, *condylomata lata* or *moist papules*, the most infectious lesions of syphilis. They tend to become confluent and, after necrotic tissue is shed from the surface, to present a moist, dull-red, eroded surface fringed with loose epithelium. They are occasionally found between the toes, under pendulant mammae and in other unexpected situations.

On the palms and soles the papules appear as flat or slightly raised spots, varying in size from a split-pea to a sixpence. They scale easily, leaving collars of loosened

epithelium surrounding shining papules. The finger-nails may show characteristic changes, more especially in the later secondary stage. The ends of the fingers become pinkish red and bulbous, and at the reflection of the skin on the nail are weeping granulations. The nail becomes brittle and lustreless and is shed. The papular syphilide may be well marked on the forehead following the margin of the hair, the so-called *corona veneris*, and it is often possible to find many papules in the hairy scalp. On other parts of the face, especially about the naso-labial folds and the chin, the papules are sometimes set in rings, *annular syphilides*. In some cases the facial lesions may be hypertrophic, especially at muco-cutaneous junctions, appearing like condylomata lata; on account of a resemblance to surface lesions of yaws, the condition has been called a *frambsiform syphilide*.

The small *follicular* syphilide usually appears later than the early papular eruption. Each lesion is related to a hair follicle and they are found in small clusters of minute dusky-red papules on the trunk, particularly the back. Only in pigmented skins are these lesions found in considerable numbers. The *lichenoid* syphilide, also a late secondary manifestation, occurs as a small, flat, dull-red elevation, a few millimetres wide and often polyhedral.

*Recurrent papular eruptions.*—Recurrences of the papular eruption tend to be much more limited in distribution. A common form, the *corymbose* syphilide, appears as one or only a few rather densely packed groups of papules, the diameter of each group covering 1 to 3 inches or more. In some cases there is a large papule in the centre of the group and around it, separated by a zone of healthy skin, is a crowd of smaller papules. The chief sites are the extensor surfaces of the arms, the shoulders, back and abdominal wall.

The *hair* is shed to a varying degree in the secondary stage. In most cases the thinning is not particularly noticeable; in others there is patchy loss, giving the sides and back of the head a moth-eaten appearance; exceptionally the patient may become temporarily bald. The beard and eyebrows may participate in these changes.

*Lesions of the mouth and throat.*—Before the rash appears on the body the soft palate may become erythematous. Other lesions of the mouth usually make their first appearance with the papular syphilide of the skin. On the mucous surfaces of the lips and the pillars of the fauces the early syphilide is a rounded greyish-white patch—the so-called *mucous patch*—edged with a dull-red areola, which marks it off from the surrounding mucous surface. The greyish-white appearance is due to necrotic tissue. On the pillars of the fauces the lesions may become confluent and, on separation of the slough, form a serpiginous erosion, sometimes known as the *snail track ulcer*. On the tonsil the lesion tends to ulcerate rather deeply. If a mucous patch on the lip crosses the angle of the mouth it becomes fissured. On the sides of the tongue there may be fissuring and ulceration, and on the under-surface there may be condylomata lata. On the dorsum of the tongue the mucous lesions appear as pink, bald spots after the papillæ of the tongue have been shed in the necrotic process. The discharge from these lesions teems with syphilitic organisms and is very contagious. Mucous patches can also be found in the nose, on the septum and the floor. In the larynx, by suitable examination, they can be seen chiefly on the epiglottis and aryepiglottidean folds; they are apt to become eroded and ulcerated, causing the husky voice which is common with patients suffering from secondary syphilis. These lesions of the mouth and throat are more apt to recur in uncured cases than are those of the skin, and it is therefore very important to examine the mucous membranes thoroughly in a possible case of relapsing syphilis.

*Other mucous membranes.*—Mucous patches also occur on other mucous membranes, such as those of the vulva, at the vaginal outlet, at the posterior commissure, on the cervix, just within the anal canal, and on the glans penis and the mucous surface of the prepuce. Usually these lesions are eroded and appear sharply defined against the background of normal-looking mucous membrane. At these sites they



are usually called *mucoous erosions*. On the genitalia, especially on the glans, they may be mistaken for primary lesions, especially if other signs of secondary syphilis are absent or inconspicuous.

*Lymphadenitis*.—Rubbery, discrete, non-tender enlargement of accessible lymphatic glands, especially those of the neck, is very common in the secondary stages of the disease.

*Joints and bursæ* are not often affected in secondary syphilis, but occasionally effusion occurs. The result is likely to be swelling without pain or great limitation of movement, but in rare instances such effusions are painful, especially at night. The tendon-sheaths may be affected similarly. Aching pains in the long bones—so-called *osteocopic pains*—may result from mild periostitis. The pain may be severe and tends to be worse at night. It is rare to find the objective signs of periostitis at this stage of the disease.

*The eye*.—Acute *iridocyclitis* of one or both eyes occasionally occurs late in the course of secondary syphilis, but is more common in association with infectious relapse. It may be differentiated from iridocyclitis due to other causes by presence of other evidence of secondary syphilis and by prompt and satisfactory response to antisyphilitic treatment.

*Hepatitis*, with jaundice and enlargement of the liver, is occasionally found in the secondary stages of syphilis and responds promptly to antisyphilitic treatment.

*Epididymitis* occurs in a very small percentage of cases, usually in the form of small nodules, varying in size from a pea to a small marble, in the globus major.

From about the sixth month, or even earlier, the patient may develop symptoms and signs pointing to syphilitic disease of the *central nervous system*, which are described elsewhere in this volume. It is well to remember that in over 30 per cent. of cases of secondary syphilis changes in the cerebrospinal fluid indicate invasion of the central nervous system, though only a small proportion of these patients show clinical signs of nervous disease; this fact should be borne in mind in testing for cure.

**Constitutional Symptoms.**—Even in the incubation period, there may be a rigor followed by some degree of fever and pains in the limbs. In some cases, towards the end of the primary stage or on the appearance of the rash, the patient may develop pyrexia which is intermittent, continuous or remittent, and accompanied by some constitutional disturbances, such as headache, malaise, anorexia and loss of weight. In rare cases the fever and constitutional symptoms may be prolonged and severe, and if no rash appears the condition may be very puzzling. The presence of generalised adenopathy should arouse suspicion. Headache may be severe and persistent and may be due to meningeal involvement.

*Anæmia*.—Moderate degrees of secondary anæmia are common. The red cell count may be slightly reduced, to between 4,000,000 and 5,000,000 with hæmoglobin content as low as 70 per cent. In rare cases the anæmia may be much more severe. In the early stages the total white cells may reach 20,000 per c.mm. but levels of 10,000 to 12,000 are more common. Lymphocytes predominate and may constitute 65 per cent. of the total; this lymphocytosis may persist for months.

**TERTIARY STAGE.**—There is no sharply dividing line between the secondary and tertiary stages, and late in the secondary or early in the tertiary stage lesions may appear which have features common to both stages. In general the tertiary or gummatous lesions tend to be localised and asymmetrical in distribution and destructive in character.

The gummatous lesions which involve the skin are of three kinds:

(1) *The nodular cutaneous syphilide*.—This appears as a group of small gummata arising in the true skin of one or more isolated areas of the body. The individual nodules are each about the size of a pea, rounded, dull red in colour and firm and elastic on palpation. They often become confluent to form a more or less continuous ridge, arranged in roughly concentric circles, or arcs of circles, or as a snake-like line

of varying length. The affected area is very often one that is exposed to injury or constant friction; it may be as small as a finger-nail or larger than a hand. The individual gummata may degenerate only so slightly as to produce some scaling, or may ulcerate more deeply and become crusted. The lesion extends centrifugally by the development of more gummata, and leaves in its wake an area of skin which may appear normal, or may be pigmented or, if the nodules have ulcerated, may show supple, papery scars, following the concentric distribution of the lesion. In some cases with ulceration, extension is more rapid than healing, and a large patch of small ulcers of the skin may be left behind the advancing line of involvement. Sometimes the nodules do not resolve as the lesion extends and dull-red rounded or polycyclic plaques of indurated tissue are formed. These become covered with greyish waxy-looking crusts and the condition has therefore been named:

(2) *The squamous tertiary syphilide*.—The lesions often resemble those of psoriasis and have been called on that account *psoriasiform tertiary syphilides*. The commonest tertiary lesion to involve the skin is

(3) *The subcutaneous gumma* which commences in the subcutaneous or deeper tissue, such as muscle or periosteum of bone, and presents as an indolent rounded subcutaneous swelling of rubbery consistency. The swelling is painless and, at first, the skin over it is not discoloured; when first noticed it may be no more than a small nodule but may slowly increase in size to that of an orange. In due course the expanding swelling is likely to become attached to the overlying skin which then shows dull-red discoloration. The central area of skin then becomes involved in the necrotic process and breaks down with the formation of a sinus which develops into a gummatous ulcer. This is highly typical in appearance. It is circular in outline, following the contour of the original swelling, or polycyclic if confluence of two or more gummata has occurred. The ulcer is sharply punched out with vertical walls leading down to a granular floor covered with clean dull-red granulations. A tough yellowish-white slough, the so-called *wash leather slough*, may remain adherent to walls and floor. The skin surrounding the margin of the ulcer shows dull-red discoloration and squamous change. If the gummatous process commences in or subsequently involves the periosteum of bone, the floor of the ulcer consists of necrotic bone. The regional lymphatic glands are not involved. On healing, the non-contractile "tissue paper" scars show the rounded outline of the original lesion.

The mucous membranes of the *mouth and throat* are often involved in the tertiary stage of syphilis. The process usually commences in submucous tissue or in deeper structures, such as the periosteum of the hard palate or the musculature of the tongue. The soft palate and uvula are particularly common sites and ulceration is likely to cause perforation and subsequent deformity. Sometimes the soft palate becomes adherent to the posterior pharyngeal wall. Perforation of the hard palate may result from gummata commencing in the roof of the mouth or in the floor of the nose. Ulceration of the tonsil may be deeply destructive. These conditions are remarkable for their chronicity and for the fact that they produce discomfort rather than pain.

In the *tongue* discrete gummata may reach the surface and cause deeply punched-out ulcers, but more commonly the process is a diffuse gummatous infiltration following the distribution of the vascular supply. In the initial stages the tongue is swollen, but on healing diffuse fibrosis occurs with subsequent contracture and the tongue may become smaller than normal. At the same time characteristic changes may appear on the surface of the tongue, giving the appearance known as *chronic superficial glossitis*. The changes are three in number, and one or any combination of them may be present. Firstly, contraction of fibrous tissue may produce deep irregular fissuring of the surface of the tongue. Secondly, interference with the blood supply of the mucous membrane renders it abnormally vulnerable to minor injury which causes patchy necrosis of superficial epithelium with irregular white areas of adherent

dead epithelium, particularly at the margins of the tongue, the condition known as *leucoplakia*. Similar patches may be found on the mucous surfaces of the cheeks at the angles of the mouth. Thirdly, the patches of leucoplakia are apt to separate at the margin of the tongue carrying away the papillæ and leaving smooth glazed areas. The patient may complain of pain in the tongue and may be sensitive to acids, spices and hot foods. The condition may, however, be symptomless. Discomfort and pain are usually relieved by antisyphilitic treatment but the changes in the tongue are permanent. Carcinomatous change is common.

In the *larynx* submucous gummata are common and, on laryngoscopy, may be seen as small rounded swellings above the vocal cords. Deeply destructive ulceration may follow and there may be actual sloughing of laryngeal cartilages. In the early stages there are alterations of voice and later, in neglected cases, stenosis may follow.

Tertiary syphilis of *bones* causes variable symptoms and signs, and may be difficult to diagnose unless the possibility of such infection is remembered. The bones most commonly affected are the tibia, the bones of the skull, the clavicle, sternum and femur, but no bone is immune and trauma is frequently a predisposing cause. There may be no symptoms or the patient may complain of pain at the affected site—a gnawing, persistent pain of boring character which is worse at night. If the bone is near the surface an irregular hard swelling may have been noticed. In long bones the process is likely to involve a limited segment of the bone giving rise to an irregular hard swelling as the result of subperiosteal deposits of new bone. Radiologically the new bone formation can be seen on the surface of the original cortex and the cortical bone is seen to be sclerotic with, perhaps, some invasion of the medullary cavity. In the flat bones, and particularly those of the vault of the skull, the process is destructive, with rounded areas of osteoporosis surrounded by areas of moderate sclerosis—so-called *worm-eaten skull*. Severe deformities may result when this destructive process involves the nasal bones, the nasal septum and the palate, which are common sites of gummatous lesions. After a period of *ozæna* the bridge of the nose may be destroyed or a large perforation suddenly appear in the hard palate. From the nose, the process may spread to the skin with disfiguring ulceration of the face. Syphilitic dactylitis is very uncommon but occasionally causes an indolent painless swelling, usually of the proximal phalanx of a finger. Vertebral gummata are rare but have been known to cause retropharyngeal, lumbar or iliac abscesses.

Gummata of the *liver* are now quite uncommon. The lesions are usually multiple and may grow to a large size and be very destructive. On healing, the liver substance may be intersected by sheets of fibrous tissue which reach the surface, dividing the organ into irregular lobes, *hepar lobatum*. The condition is commonly asymptomatic but irregular enlargement of the liver may be felt and the spleen also may be enlarged. Evidence of portal obstruction is uncommon. Gross secondary *anæmia* is sometimes associated.

Tertiary syphilis of the *testis* is now quite rare. It may result in diffuse interstitial involvement, with slow painless enlargement of the organ. Testicular sensation is lost. Occasionally localised gummata are found.

The *joints, bursæ and tendon-sheaths* are not often invaded in tertiary syphilis. The parts affected are those most exposed to stress and strain, such as the knee-joint and the pre-patellar bursa. The swelling is of soft rubbery consistency and shows no signs of acute inflammation. It follows the outlines of the affected joint, bursa or tendon-sheath.

*Fever* occurs in some cases of tertiary syphilis, and the fact that it is due to the disease may be suggested by its response to antisyphilitic treatment. It has occurred particularly in association with gummatous hepatitis. Syphilis should be remembered as a possible cause in cases of persistent pyrexia of unknown origin.

**Diagnosis.**—PRIMARY STAGE.—It is axiomatic that every genital sore and every inflammatory sore elsewhere on the body of which the diagnosis is not obvious should

be examined for *S. pallida*. This should be done before any antiseptics have been applied or antibiotics administered. The sore should first be cleaned with a swab and its edge scraped, or a fairly deep puncture made in its margin with the point of a scalpel or a vaccination lancet. The sore should then be squeezed and the serum collected after it has oozed for a few minutes. When the necessary apparatus is at hand it is better to examine the specimen at once by dark-ground illumination; if it has to be sent away, the serum should be allowed to run into a capillary tube, of which both ends may be sealed with candle grease. Spiral organisms other than *T. pallidum* may be seen in specimens obtained from the genitals or the mouth, but they are largely eliminated by taking care to clean the surface of the lesion before collecting the specimen. Organisms should not be accepted as *T. pallidum* unless they are characteristic in appearance and movement. Alternatively a good method is to puncture the nearest enlarged lymphatic gland and aspirate a little of the gland fluid. A moderately stout hollow needle is inserted obliquely into the gland, and a few minims of sterile normal saline are injected into it. The gland is massaged and aspiration applied by a syringe.

Clinically, primary syphilitic sores are distinguished from others by the long incubation period, comparative painlessness, colour, indolence, surrounding infiltration, slighter tendency to bleed, indolent enlargement of neighbouring lymphatic glands, and the presence of *T. pallidum*. The length of the incubation period is a guide only when the patient has not been exposed to infection for more than 10 days.

Various conditions which are commonly found on the genitalia may give rise to difficulty in diagnosis. Several of the more important require brief mention. *Herpes genitalis* appears as grouped vesicles of pinhead size which break down to small circular erosions. They cause irritation but they are not indurated. *Chancroid* has an incubation period of only a few days; the sore is painful and destructive, and the edges are undermined. Usually there is more than one sore. There may be an accompanying bubo which tends to suppurate and to break down with the formation of a chancroidal ulcer in the groin. Infection with both syphilis and chancroid occurs sometimes and therefore to exclude the diagnosis of syphilis it is important to repeat the microscopic test at intervals until the sore heals and to test the blood serum at least monthly for 3 months.

*Scabetic runs* on the glans and skin of the penis are mound-like and not eroded or indurated.

Syphilitic chancres in parts of the body other than the genitals are often overlooked, mainly because the possibility of syphilitic infection is not considered. Unilateral tonsillitis should arouse suspicion, especially if associated with painless enlargement of lymphatic glands in the upper part of the anterior triangle of the neck on the affected side. Similarly, the clue to the nature of a syphilitic chancre on the lip may be given by enlargement of lymphatic glands of the submaxillary group. A primary sore affecting the terminal phalanx of a thumb or finger often simulates a whitlow; the syphilitic sore is more brawny and more indolent.

**SECONDARY STAGE.**—The maculo-roseolar syphilide is fairly easy to distinguish by the history of a primary sore with indolent adenitis, by the subcuticular, deeply grounded appearance of the spots, which very rarely itch and are pinkish in colour, and by the association of positive serological reactions. Other erythemata are brighter red and irritable, and often affect the backs of the hands. The ordinary dome-shaped papular syphilide is usually easy to distinguish from a non-syphilitic eruption. The indurated feel of the papule, its shining appearance when pinched, its readiness to scale, its dull-red colour and its association with lesions of the mouth and throat are all valuable diagnostic signs. The different appearances which a papular syphilide presents in different parts of the body, such as dry papules on the trunk and most areas of the limbs and moist papules in the perianal area, on the scrotum, between the toes and in other moist warm parts, contrast strongly with non-syphilitic derma-

toscs, which are true to type, wherever situated. *The microscopic test should always be applied to the exudate from the lesion in any doubtful case, and rarely fails to clinch the diagnosis, even with papulo-pustular or pustular syphilides.*

Among the eruptions which may be confused with syphilitic rashes is that of *urticaria pigmentosa*, but with this condition the spots are dark and are not raised, and on rubbing the macule a wheal is formed. The blood serum may give a doubtful or even positive reaction in such a case, but the titre of a quantitative test is considerably lower than that usually given by the blood of a patient with secondary syphilis. *Seborrhœa* is more superficial and is more scaly, the scales being greasy. *Pityriasis rosea* is often mistaken for syphilis, but the lesions are brighter in colour and more irritable; they tend to become annular, with their centres covered by branny scales. *Ringworm* is more superficial and irritable, and the fungus can be found in scrapings from its border. *Tinea cruris* or *dhobie's itch* affects a triangle at the upper and inner part of the thigh; it is brighter red, more irritable and quite superficial. *Drug rashes* are more inflammatory and irritable; they appear more suddenly, and are usually associated with a history that the patient has taken a drug which is known to cause such an eruption. *The eruptions of specific fevers* are usually accompanied by more pronounced constitutional symptoms. *Acne spots* are pustular and show more inflammatory reaction than secondary syphilides and they affect the upper part of the chest and the back between the shoulders, rather than the flanks, loins and limbs. The spots of *molluscum contagiosum* are white and umbilicated, and caseous matter can be squeezed from their centres. *Lichen ruber planus* is characterised by flatter, smaller, polygonal spots of a violet tinge and waxy appearance; it is more irritable. *Psoriasis* is usually superficial, bleeds at a number of points when slightly scraped, and affects the extensor rather than the flexor surfaces of the limbs; the scales are more silvery, and in moist situations the rash remains true to type, contrasting with the syphilide, which becomes the moist papule or broad condyloma. *Varicellar spots* are vesicular at one stage and more superficial and irritable. With *variola* there is a prodromal stage with fever and backache; the spots are of uniform character and appear first on face and wrists. *Pemphigus vegetans* may bear a superficial resemblance to condylomata lata, but no *T. pallidum* can be found in serum from the lesions, and usually typical bullæ can be found elsewhere on the body or limbs. Syphilitic condylomata have sometimes been diagnosed as hæmorrhoids, but they are usually separated from the anal ring by some normal skin. *Condylomata acuminata*, or genital warts, are granular and pedunculated. The deeper forms of pustular syphilide which show considerable crusting, such as the ecthymatous or the rupial, are distinguished from ordinary *impetigo* by the darker colour of the crusts, the circular rather than linear shape of the lesions, and the greater degree of tissue destruction below the crusts. *Scabies* is sometimes mistaken for a crusted syphilide, and the reverse is also true. The individual scabietic lesion is often easy to recognise where it has not been scratched, on the wrists, and between the fingers, but it is well to remember that scabies and syphilis often co-exist.

Secondary syphilitic lesions of the mouth can usually be diagnosed by the characteristics described. *Vincent's angina* is a possible source of error, but the condition is painful and the microscopic findings are characteristic.

**TERTIARY STAGE.**—An indolent swelling, or an ulcer preceded by a swelling, should always arouse a suspicion of syphilis. Denial of primary sore, or of secondary lesions, is of no importance, for they may never have appeared or have been forgotten long ago. The positive serological reactions may mislead, for by no means all swellings and ulcers in syphilitic patients are themselves syphilitic. On the other hand, negative serological reactions are strong but not absolute evidence against tertiary syphilis. Space does not permit enumeration of the many conditions from which the lesions of tertiary syphilis may have to be diagnosed. An occasional source of error is *epithelioma* in the mouth, which is more apt to be painful than a gumma and to

appear as a lesion with a raised rolled everted edge. The onset of the condition is frequently determined by old syphilitic glossitis and the presence of positive blood serological tests may obscure the diagnosis. *Varicose ulceration* on the legs may have to be diagnosed from gummatous ulceration. The ulcers are usually much less regular in contour, less sharply punched out, and associated with more evidence of acute inflammation and of venous stasis.

**Treatment.**—**PREVENTIVE.**—The value of any method of prevention of syphilitic infection has always been difficult to determine. Local cleansing and the use of antiseptics have been recommended and practised for many years, but with any such procedure the failures are obvious enough but the successes are never known. Clearly no method of disinfection is likely to be successful unless it is promptly applied. The genitalia should be washed well with soap and water and then steeped for some minutes in a mercurial solution such as 1 : 2000 mercuric potassium iodide, or 1 : 2000 oxycyanide of mercury. The parts should then be anointed with an ointment, such as Gauducheau's, viz., mercury cyanide, 0.10; thymol, 1.75; calomel, 25.00; lanolin, 50.00; liquid paraffin, 10.00; soft paraffin to 100.00. Some solution of mercury oxycyanide 1 : 4000 may be injected into the urethra after urination. For females washing of the external genitals, followed by inunction with ointment should be practised as for males and should be followed by a vaginal douche with mercurial solution such as 1 : 4000 oxycyanide of mercury. Any prophylactic measure may prevent only the appearance of the chancre and should therefore be followed by blood tests for at least 3 months.

Prophylaxis by ingestion or injection of antisyphilitic remedies should not be practised, because the effect may be to mask the symptoms for many months without curing the patient. Since the introduction of penicillin for the treatment of syphilis a good deal has been said and written about the desirability of abortive treatment of the patient who has taken a risk of contracting syphilis. To give such treatment is tantamount to accepting the diagnosis, and logically, should be followed by observation and testing for at least 2 years with due restrictions as regards marriage and family life. Quite apart from the prolonged anxiety involved there are obvious disadvantages to the patient, who in most cases can be pronounced free from infection with certainty after 3 months.

Accidental infection of fingers, lips and other extra-genital parts is best prevented by avoiding contamination with fresh secretions from patients in the early stages of infection. They should be warned of the risks arising from sharing table utensils, crockery and house linen with others. They should not kiss others nor talk directly into people's faces, and articles which they have used should be dipped in very hot water. A further precaution is to smear open lesions with a mercurial ointment. With modern methods of treatment the secretions cease to be infectious within 24 hours.

**CURATIVE.**—The remedies most commonly employed for the treatment of syphilis have been preparations of (1) arsenic, (2) bismuth, (3) mercury, (4) penicillin and (5) iodine. The first four destroy the parasites; the last promotes the removal of granulomatous tissue. The position of the most recent remedy, penicillin, is still a matter of some discussion. Most workers are now convinced that it alone is sufficient for the successful treatment of almost every case of syphilis, but others, though admitting the powerful anti-spirochætal properties of penicillin, prefer to supplement it with other remedies. The different remedies will be described separately before discussion of their use in the management of syphilis.

### (1) ARSENICAL PREPARATIONS

In consideration of the fact that most workers in this field no longer employ these drugs reference to their use in the treatment of syphilis will be made in the past tense.

They are organic compounds in which arsenic is trivalent or pentavalent. The trivalent preparations were the most frequently used for most forms of syphilis; the pentavalent preparations were used chiefly for syphilis of the central nervous system and for syphilis in infants.

(a) TRIVALENT ARSENICAL REMEDIES.—The first of these was "606" or the Ehrlich-Hata remedy, which was first introduced in 1910. There have been many of these compounds with different trade names which were apt to be confusing, but all except oxophenarsine have been subject to Regulations under the Therapeutic Substances Act, under which, besides the requirements of certain tests for toxicity and therapeutic potency, each must bear on its label an official name according to its chemical constitution. The following are the principal remedies in this class:

(i) Arsphenamine, or the dihydrochloride of dioxy-diamino-arsenobenzene, which is the original "606" or salvarsan; it must have an arsenical content of not less than 30 per cent. and not more than 34 per cent. (ii) The disodium salt of (i), or sodium salvarsan; it contains about 20 per cent. of arsenic. (iii) Neoarsphenamine, or the sodium salt of dioxy-diamino-arsenobenzene-methylene-sulphoxylic acid, which is the original "914", or neosalvarsan; it is sold under the trade names Evarsan, Neokharsivan, Neosalvarsan, Novarsan, Novarsenobillon and Novostab; it must contain not less than 18 per cent. and not more than 21 per cent. of arsenic. (iv) Sulpharsphenamine, or the sodium salt of dioxy-diamino-arsenobenzene-methylene-sulphurous acid; it is sold under the trade names Kharsulphan, Metarsenobillon, Myosalvarsan, Sulfarsenol and Sulphostab, and its arsenical content is the same as that of neoarsphenamine. (v) Arsphenamine glucoside or Stabilarsan; the arsenical content of the dose stated on the label equals that of the same dose of neoarsphenamine. (vi) Silver arsphenamine. (vii) Neosilver arsphenamine. (viii) Oxophenarsine.

Each of these preparations except oxophenarsine bears the name "arsphenamine" in its official designation, and these as a group will be referred to as the arsphenamine preparations. All but the diglucoside are in powdered form, sealed, in stated doses, in glass ampoules containing a neutral gas. All the powders are yellow except the silver preparations. All oxidise and become increasingly toxic on exposure to air and must consequently be made up and administered as soon as possible after the ampoule has been opened. Oxidation in an ampoule, through a flaw in the glass, makes the powder become darker and sticky. Arsphenamine diglucoside is in solution and ready for use when drawn from the ampoule. It must be used before the expiry date stated on the label.

Arsphenamine (606) is therapeutically the most active of the arsphenamine preparations, but was little used outside the United States of America because of the complexity of its preparation for administration and of its greater tendency to cause serious reactions on the day of injection.

Neoarsphenamine was much the most commonly used of all the arsphenamine preparations. In equivalent dosage it is less active than arsphenamine, but is more easily prepared for administration and causes less general reaction. It causes too much pain to be given by the subcutaneous or intramuscular route, and was, therefore, given intravenously.

Sulpharsphenamine was given by the intramuscular or deep subcutaneous route. It causes comparatively little discomfort when administered in this way. Being relatively stable, its action is inferior to that of neoarsphenamine when it is given intravenously, and even when administered subcutaneously its effect is barely equal to that of intravenous neoarsphenamine. It is more prone than the other arsphenamine preparations to cause blood dyscrasias.

Arsphenamine diglucoside is a convenient preparation in that it is ready for use when drawn from the ampoule, but its immediate effect in causing disappearance of

*T. pallidum* from the secretions of early lesions is not so great as that of neoarsphenamine in equivalent dosage. Silver arsphenamine and neosilver arsphenamine are emery-coloured powders. They are more active but also more toxic than the other arsphenamines and were therefore given in approximately half the standard dosage of the latter. They were sometimes useful as a change from neoarsphenamine.

Oxophenarsine is a comparative newcomer in this field, although it was originally tested by Ehrlich; it is commonly known as arsenoxide. It is believed to be chemically identical with the spirochæticidal substance which is formed from the arsphenamine preparations in the body. It is *m*-amino-*p*-hydroxyphenyl-arsine oxide, and is sold in this country as the hydrochloride, Mapharside (in the U.S.A. as Mapharsen) and the tartrate, Neohalarsine. It is a stable compound which, during the years before penicillin was available, acquired great popularity, especially in the United States of America, and was the arsenical compound of choice for the intensive treatment of syphilis. Its relative efficacy is a matter of some dispute. It has the advantages that it is stable and rapidly excreted and it has been claimed to be less toxic and more efficient than neoarsphenamine. It was useful for intensive forms of treatment in which 3 or more injections of an arsenical were given weekly.

*Dosage of arsphenamine compounds.*—Doses of the different preparations described varied greatly with circumstances. Some details of dosage will be given in discussing schemes of treatment (*see p. 222*). In a case of primary or secondary syphilis it was reasonable to aim to bring about rapid disappearance of *T. pallidum* from the secretions of external lesions, and in the case of an adult when there was no contra-indication it was the usual practice to start with 0.45 g. neoarsphenamine.

*Technique of administration of arsphenamine preparations.*—*Intravenous route.*—In the case of neoarsphenamine the dose was dissolved in 10 ml. of distilled water. The solution was drawn into a syringe, which was then fitted with a fairly fine needle (S.W.G. 22). The technique was that of any intravenous injection. The median basilic or other convenient vein was distended by fixing an elastic band round the upper arm and asking the patient to grasp a roller bandage. The operator looked along the vein and steadied it with the index finger of his spare hand laid on the skin below the site. The eye of the needle was made to look away from the skin and the shaft of the needle held almost parallel to it. The point of the needle was inserted into the vein and a pull on the piston caused blood to flow back into the syringe, indicating that the needle was properly within the vein. The rubber band was then released and the piston *slowly* pressed home. After the syringe had been emptied, a little blood was aspirated into it to clear the needle of any solution.

*Deep subcutaneous and intramuscular routes.*—Arsphenamine remedies are believed to have a greater therapeutic effect when administered subcutaneously or intramuscularly, but most of them cause too much pain when given in this way; almost the only one which could be employed for the purpose was sulpharsphenamine. The dose was dissolved in distilled water, or in a glucose solvent containing an analgesic prepared for the purpose. In either case as little as 1 ml. might be used, but 2 ml. of the glucose solvent seemed to be more effective in preventing local reaction. The technique of intramuscular injection is described on p. 217. Deep subcutaneous injection of sulpharsphenamine caused less pain than intramuscular injection and was usually preferable. It was given as follows: In the upper and outer quadrant of the gluteal region the skin and fat were pulled away from the underlying fascia, by grasping them with the thumb and fingers of the left hand, and a needle (S.W.G. 20) 1½ inches in length was inserted obliquely at the base of the pyramid thus produced. The needle was made to underrun the fat so that its point might scrape on the fascia overlying the gluteal muscles. The charged syringe was fitted to the needle and the injection given fairly slowly. The site was then massaged with a pad of lint.

*The toxic effects of arsphenamine preparations* are described on page 229.



Certain other reactions may follow the administration of arsenicals but these are not due to the toxicity of these preparations. The commonest of these is the *Jarisch-Herxheimer reaction* which is a focal and general reaction which may follow the use of a rapidly effective drug, such as an arsenical or penicillin, at the commencement of treatment. It occurs in about 50 per cent. of cases of primary and secondary syphilis in which the first injection may be followed within a few hours by fever, headache, malaise, pain in the joints and limbs and exacerbation of the symptoms and signs of infection. At this stage it is not harmful but the patient should be warned of the possibility that it may occur. Ordinarily the reaction occurs within 12 hours and lasts for not more than 24 hours. The cause is unknown and there is little evidence to support the theory that it results from liberation of toxins following the destruction of large numbers of spirochætes. In the late stages of syphilis the reaction is less common and usually slight. In most cases there is no more than slight fever of which the patient may be unaware. Occasionally, however, serious results have followed through exacerbation of severe involvement of the central nervous system, complete blockage of a large cerebral vessel or of the opening of a coronary artery, perforation of the aortic wall or of an aneurysm, or œdema of the glottis in cases of gummatous infiltration of the larynx. Such cases are very rare but, even so, they can and should be prevented by care in the institution of treatment in cases of late syphilis, in which nothing is to be gained by speed and intensity of treatment. Further reference will be made to this reaction in describing the effects of treatment with penicillin.

*Neuro-recurrences* are also not direct toxic effects of treatment with arsphenamines. Lesions of various cranial nerves, especially the seventh and eighth, became more common shortly after the introduction of the organic arsenical remedies and were later shown to be syphilitic recurrences due to the small amount of treatment given in the early days of "606". They became very rare when bismuth or mercury was given in conjunction with the arsenical remedies.

*Contraindications to the use of arsphenamine preparations.*—The use of arsenicals was absolutely contraindicated in cases of severe systemic disease such as chronic nephritis, Addison's disease, severe disease of the liver and hæmophilia, and also in the cases of patients who had shown intolerance to the drugs in the past. In view of the fact that an efficient non-toxic substitute is now available these drugs are certainly better avoided in cases of diabetes mellitus, alcoholism and of chronic diseases of the skin such as eczema or seborrhoea. Older patients showed poor toleration to arsenicals and it was customary not to use them for patients over the age of 55 years.

*Precautions to be observed in the use of arsphenamine preparations.*—It is essential to observe scrupulous care in the technique of injection, especially in the sterilisation of syringes and needles, and careful watch must be kept for the appearance of signs of intolerance during treatment. Patients who receive intravenous injections should fast for 2 hours beforehand. The indications for the use of arsenicals are now so few that these problems seldom arise. Nevertheless, because of the increasing number of patients who are becoming sensitised to penicillin it is still important that the method of use and the contraindications of the arsphenamines should be understood.

*Administration of oxophenarsine compounds.*—These compounds were always given intravenously dissolved in 8 to 10 ml. of distilled water, as with neoarsphenamine. Unlike neoarsphenamine, oxophenarsine may be brought into solution by shaking, and the solution may be left standing, without danger of increasing toxicity. The injection was given quickly in order to avoid pain along the vein or venous thrombosis. The standard dose for an adult is 0.04 to 0.06 g., and for the routine prolonged treatment of syphilis it seemed advisable to give this dose twice weekly instead of once, which was the usual practice with standard doses of neoarsphenamine.

(b) **PENTAVALENT ARSENICAL REMEDIES.**—The principal remedies of this class which have been used in the treatment of syphilis are: (i) Sodium N-phenylglycine-amide-p-arsenate (tryparsamide); (ii) 3-acetyl-amino-4-hydroxyphenylarsonic acid,

or acetarsol (Kharophen, Orarsan, Spirocid and Stovarsol); (iii) the sodium salt of (ii); and (iv) the diethylamine compound of (ii), Acetylarsan.

Tryparsamide was the most important of these because of its value in the treatment of syphilis of the central nervous system. It is a white powder easily soluble in water, and the dose for an adult is from 2 to 4 g. (usually 3 g.) freshly dissolved in distilled water and injected intravenously once a week. A course lasted 10 to 12 weeks, and the interval between any two courses was a month or 6 weeks.

Acetarsol was introduced in 1922 primarily as a drug to be given by mouth for the prophylaxis of syphilis. Subsequently it was used extensively for the treatment of infants with congenital syphilis. Acetarsol-sodium and Acetylarsan were given by injection; their effects were like those of acetarsol.

## (2) MERCURIAL PREPARATIONS

Mercury was formerly the main remedy for the treatment of syphilis, but it has been almost entirely superseded by bismuth. It is now used occasionally in cases where injections are impracticable. Mercury and bismuth had the advantage that small amounts of them could be kept in the circulating blood almost continuously, so that anti-spirochætal action was maintained after the arsphenamine had been excreted until it was safe to administer another arsenical injection. This method of treatment was based on the view which still prevails, that it is necessary for an anti-syphilitic remedy to be present constantly in the body fluids for a considerable period to ensure destruction of all the spirochætes of syphilis.

*Methods of administration.*—The oral method was much favoured, but was apt to cause gastro-intestinal disturbance; like other oral remedies for syphilis it had the disadvantage that regularity of treatment depended upon the memory and co-operation of the patient. Mercury by mouth is still occasionally useful when a patient cannot take injections or continue injections or remain under close observation. The following preparations have proved useful: (1) hydrargyrum cum creta, gr. 1 to 2; (2) hydrargyri iodidum viride or flavum, gr.  $\frac{1}{4}$  to  $\frac{1}{2}$ ; (3) hydrargyri perchloridum, gr.  $\frac{1}{4}$ ; (4) hydrargyri tannas, gr. 1 to 3; (5) pil. hydrargyri, gr. 1 to 3; (6) liq. hydrargyri perchloridi, min. 30 to 60. The latter is often prescribed in a mixture with potassium iodide. The first five of these were usually given in the form of pills, often combined with a little opium, e.g. pulv. ipecacuanhæ et opii gr. 1 to 2, or extractum opii gr.  $\frac{1}{2}$  to counteract the irritant effect of the metal upon the gastro-intestinal tract; but it is better to prescribe the sedative separately, and to regulate the dosage as required. It was customary to give courses of 6 weeks' duration, gradually increasing the daily intake of mercury until slight signs of stomatitis appeared, and then to reduce the dose. An adult patient could usually take from  $\frac{3}{4}$  to 1½ grains of the yellow or the green iodide given daily in this way. Rest periods between courses varied from 1 to 4 weeks.

*Inunction* was a useful method of administering mercury. It had to be done by a skilled rubber, and had the inconvenience of soiling the skin and clothes. Five to 10 g. of mercurial ointment, unguentum hydrargyri B.P., containing 30 per cent. of mercury, were rubbed for 20 minutes into the skin of thighs, calves, arms, chest and back on successive days, avoiding hairy areas because of the danger of folliculitis. A bath was taken on the sixth day and the cycle restarted on the seventh. The number of rubbings in one course varied from 60 to 200; the length of a course depended on the patient's tolerance, which was judged by the state of the gums, the maintenance of weight and general well-being.

*Intramuscular injections* of mercury are no longer used because bismuth administered in this way is more effective, less toxic and less painful. Details of intramuscular preparations of mercury are therefore omitted.

The toxic effects of mercury are considered on page 233.

## (3) PREPARATIONS OF BISMUTH

Bismuth was applied to the treatment of syphilis by Sazerac and Levaditi in 1921, and has supplanted mercury in all cases for which intramuscular or deep subcutaneous injections of heavy metal are indicated. Because bismuth is more effective and better tolerated than mercury the almost universal practice before the introduction of penicillin was to use bismuth in conjunction with arsphenamine preparations for the treatment of syphilis in all stages, except general paralysis.

Bismuth is administered almost exclusively by the intramuscular route, and many different preparations are available. They may be classified according to their solubility as follows: (a) solutions in water; (b) solutions in oil; (c) suspensions of bismuth metal or insoluble salts of bismuth in watery or oily media. Absorption and excretion are most rapid with the watery solutions and least so with the insoluble suspensions.

*Watery solutions* are now seldom used because, on account of rapid absorption and excretion, they are very apt to produce toxic effects. *Oily solutions* contain organic lipo-soluble compounds dissolved in oil. In absorbability they are intermediate between watery solutions on the one hand and insoluble suspensions on the other. The following preparations of this kind have been used in this country. They are described by their proprietary names without details of their chemical formulæ which are rather complex. The bismuth content per millilitre is stated in brackets after each preparation: Bivotol (0.035 g.); Cardyl and Neocardyl (0.05 g.); Neo-olesal (0.03 g.) and Stabismol (0.1 g.). If these preparations are used it is advisable to give two doses each week at intervals of 3 to 4 days, because of the relative rapidity of absorption and excretion. *Insoluble suspensions* of bismuth have been those most commonly used for antisyphilitic treatment. Only three of these are included in the British Pharmacopœia, namely: (1) *injectio bismuthi*, B.P., which is precipitated bismuth in a dextrose solution with cresol containing 0.2 g. of bismuth per ml. (2) *injectio bismuthi oxychloridi*, B.P., which is a watery suspension of bismuth oxychloride containing 0.13 g. of bismuth per ml. (3) *injectio bismuthi salicylatis*, B.P., which is a 10 per cent. suspension of bismuth salicylate in olive oil with camphor and phenol containing about 0.6 g. of bismuth per ml.

*Technique of injection.*—The technique of intramuscular injection is simple. By far the best site is the upper and outer quadrant of the gluteal region; the upper third of the vastus lateralis muscle and the deltoid muscle are much less satisfactory. A needle of S.W.G. 20,  $1\frac{1}{2}$  inches long, is introduced almost to its full length, perpendicularly to the skin surface. The base is examined to see that no blood is oozing from it, the syringe is applied, the piston partially withdrawn to make sure that the point of the needle is not within a vein, and the piston is then pressed home. The needle is withdrawn and the site is well massaged with a ball of cotton wool. Before an insoluble preparation is drawn into the syringe, the suspension should be well mixed, either by stirring with a glass rod or by energetic shaking of the bottle.

*Toxic effects of bismuth.*—The toxic effects are few. Care must be taken to avoid injecting preparations of bismuth into veins because they are then highly toxic and, if an insoluble preparation is used, pulmonary embolism may result.

*Stomatitis.*—A slaty-blue line commonly appears at the margin of the gums of patients receiving this treatment, especially adjoining the molar teeth. It is due to the formation and deposition of bismuth sulphide and is only found in association with infection of the gums and pocketing. The appearance of the blue line is not in itself a bar to the continuation of treatment, but if the gums become swollen, tender and spongy and bleed easily the treatment must be stopped. In some cases in which oral hygiene has been neglected, ulcerative stomatitis may supervene. Treatment is preventive by preliminary dental care. The treatment of established stomatitis is by the cleansing of gums and pockets with antiseptics such as potassium

chlorate and hydrogen peroxide or by the use of mouthwash containing these preparations. Good results have been obtained with dimercaprol (B.A.L.) in the dosage recommended for the treatment of arsenical poisoning (see page 231). The blue line is likely to persist for many months after the administration of bismuth has ceased. *Nephritis*.—Albuminuria is found occasionally, especially with the soluble preparations. It is an indication to stop bismuth, for otherwise the patient may develop acute nephritis. The urine should be tested before each injection. *Intestinal disturbance*, in the form of colicky pains with, perhaps, constipation or diarrhoea, is uncommon. Rarely patients receiving this treatment complain of *restlessness, insomnia, rheumatic pains* and *general depression*; the possible relationship of such symptoms to the administration of the drug should be remembered. Various *eruptions of the skin* have been described as due to the administration of bismuth, including exfoliative dermatitis and purpura, but these complications must be very rare.

*Choice of preparations of bismuth*.—In the treatment of syphilis the main value of preparations of bismuth has been to supplement the action of the arsenical drugs which, because of rapid excretion, produced transitory effects unless given with such frequency as greatly to increase the incidence of toxic complications. For the purpose of slow absorption and prolonged effect the insoluble preparations have been the most satisfactory, and in this respect there has been little to choose between the three preparations recognised by the British Pharmacopœia. The writer has a preference for injectio bismuthi, B.P., which, in addition to being effective, rarely causes local pain or tenderness. The oily solutions of bismuth have been recommended for use in cases where more quickly acting remedies are required, but it is difficult to see how these preparations could match penicillin or the arsenicals in this respect. On the other hand the oily solutions were of value in the treatment of those patients who were or became intolerant of the arsenicals in the years before penicillin was introduced.

#### (4) PENICILLIN

The general properties and the methods of administration of penicillin are described elsewhere in this book. Here it is necessary only to describe: (a) the effect of the drug on the different manifestations of syphilis; (b) the methods of using it for the treatment of syphilis which seem most effective in the light of knowledge available at the time of writing and (c) the toxic effects which may be encountered in the course of this treatment.

Of the various types of penicillin which have been isolated benzyl penicillin, (penicillin II or G), appears to be the most effective for the treatment of syphilis. Investigative work in the United States indicated that pure crystalline benzyl penicillin gave results which were moderately superior to those obtained with commercial penicillin. Commercial penicillin as originally distributed in this country was claimed to contain at least 85 per cent. of benzyl penicillin and therefore to be an effective drug for this purpose.

Penicillin, in appropriate doses, has an effect upon *T. pallidum* which is at least equal to that of the best arsenical compounds, and, correspondingly, its effect in producing healing of the various manifestations susceptible to the action of the arsenical compounds is at least equally satisfactory. Penicillin has, of course, the great advantage over the arsenical compounds that for most patients it is practically non-toxic, and it is possible to give large doses very frequently with impunity. A very important therapeutic advantage over the arsenical compounds is that it reaches the *fetus in utero* far more easily. It is very effective indeed in preventing fetal infection, or in curing the fetus if it is already infected. For the treatment of neurosyphilis, also, the effect of penicillin appears to be superior to older methods of treatment even though the drug appears in the cerebrospinal fluid either in very small quantity or not at all after intramuscular administration of ordinary dosage.

Whether penicillin should be used alone or in conjunction with other antisymphilitic remedies will be discussed in the appropriate section.

**Administration and Dosage.**—Continuous administration of penicillin was found to be impracticable for the treatment of syphilis, because of the necessity of confining the patient to bed and the frequency of thrombophlebitis with intravenous drip and painful local reactions with continuous intramuscular or subcutaneous administration. The method of choice was found to be that of intermittent intramuscular injections. At first, the drug was dissolved in sterile distilled water or isotonic sodium chloride solution, in concentration of 50,000 to 100,000 units per ml., and was injected deep into the upper and outer quadrants of the buttocks every 2 or 3 hours, day and night, in doses of 20,000 to 100,000 units. Some give the injections into the outer thigh muscles or the deltoids, but general experience indicates that injections into the buttocks cause far less discomfort to the patients. Subcutaneous injections are less satisfactory because they need to be given in more dilute solution and may cause painful local reactions.

Penicillin has been given intrathecally but the earlier impure preparations were apt to cause dangerous toxic reactions. In view of the evidence that good results are obtained by intramuscular administration in cases of neurosyphilis, the intrathecal route is better avoided.

Penicillin by mouth is said to require dosage five times as large as that used intramuscularly. For outpatients suffering from syphilis this method of treatment is inadvisable because of the difficulty of ensuring that the prescribed doses are taken. There is, also, considerable individual variation of absorption of the drug from the gastro-intestinal tract. For these reasons penicillin by mouth is not recommended for the treatment of syphilis.

Various preparations have been devised to delay the absorption of penicillin when given by intramuscular injection, by suspending it in media which repel moisture. The first effective preparation of this kind was a suspension of calcium penicillin in arachis oil thickened with 4.8 per cent. of beeswax. A more satisfactory preparation is procaine penicillin which is a chemical compound between procaine and penicillin and may be administered in oily or watery suspension. It is painless, non-toxic and effective. Effective blood levels of penicillin can be maintained for as long as 24 hours by an average single dose of 600,000 units of procaine penicillin contained, in the case of the oily suspension, in 2 ml. of oil. This method is therefore applicable to the treatment of outpatients. A further development is the addition of the water-repellent aluminium monostearate in 2 per cent. concentration to oily suspension of procaine penicillin of fine particle size. This still further prolongs absorption so that the effect of an average dose may extend over several days. A preparation now under trial is benethamine-penicillin (N N'-dibenzylethylenediamine dibenzyl-penicillin). It has been shown that after single injections of 2.5 mega units of this preparation therapeutically effective levels of penicillin can be found in the blood stream for 2 weeks or even more. It is hoped that by this means the treatment of syphilis with penicillin may be restricted to one or two injections.

**Toxic effects of penicillin.**—Penicillin is relatively non-toxic except when given intrathecally. Serious reactions have been rare although in recent years some deaths have been reported from anaphylactic shock of patients who have become sensitised in the course of earlier administration of the drug. Precautions which should be taken to avoid this dangerous reaction are described on pp.10, 220. Local, systemic and cutaneous reactions were common with earlier impure preparations but they have become much less so with the pure preparations now available. The more serious reactions reported include thrombophlebitis after intravenous injection or intravenous drip, and generalised exfoliative dermatitis resulting from sensitisation. Other effects are fever of varying degree, reactions like serum sickness with fever, scarlatiniform or morbilliform rash and arthralgia or serous effusions into joints,

local vesicular eruptions, urticarial and other rashes, including generalised erythematous macular and maculo-papular eruptions, resembling erythema multiforme in some cases. Patients with a pre-existing fungus infection have sometimes experienced exacerbation of that infection following injections of penicillin.

With the exception of urticaria most of these reactions have been uncommon. Some seem to have been due to impurities in the drug but some are certainly due to penicillin itself. Severe reactions immediately following upon injections of procaine penicillin in watery suspension have been described. The patients were excited and noisy, and in one case, violent; they complained of a feeling of impending death. The reaction was attributed to accidental intravenous injection of the preparation. In cases of reactions attributed to sensitisation the administration of anti-histamine drugs has given relief from symptoms in some instances.

*Jarisch-Herxheimer reaction.*—This reaction has been considered in relation to treatment with the arsenicals (see page 215). With penicillin the effects are very similar, but certain aspects of them require special consideration. The reaction is not uncommon in cases of neurosyphilis treated with penicillin. Ordinarily, the results are not serious, but severe effects have been reported, including exacerbations of psychoses, convulsions, transverse myelitis, mania, hallucinations, exacerbations of lightning pains, parietic deterioration progressing to death and optic atrophy progressing to blindness. It has been suggested that patients with late syphilis should commence treatment with very small doses of penicillin with gradual increase of dosage, but experimental work has shown this to be an ineffective precaution, indicating that the reaction is of the all or none type. It does not occur with minute doses but does occur when the trigger dose is reached and then with full force, irrespective of the size of the dose. In most cases the reaction can be prevented by a preliminary course of injections of bismuth, which, of course, acts much more slowly and seldom produces this effect. Bismuth, however, will not protect from the Jarisch-Herxheimer reaction in cases of general paralysis.

It was thought possible at first that penicillin might cause abortion in cases of pregnancy in women, but further experience indicates that it has no such effect.

Patients who are susceptible to procaine may possibly develop symptoms of procaine poisoning after receiving injections of procaine penicillin suspension. The average dose of 600,000 units of this preparation contains 240 mg. of procaine, but absorption is so slow that it must be very uncommon for a patient to develop a concentration of procaine in the blood which produces toxic effects. Susceptibility to procaine is, in any case, rare. Suspicion of undue susceptibility may be put to the test by intracutaneous injection of 0.1 ml. of a 1 per cent. solution of procaine.

*The effects of penicillin on the diagnosis of syphilis.*—Penicillin given for other diseases is sometimes a source of confusion in the diagnosis of syphilis. For instance, serious difficulties may arise in the cases of patients treated with penicillin for pneumonia, or for surgical infections, who are later found to have positive serological tests for syphilis. In such cases it is necessary to distinguish between biologically false positive results and true positives which indicate that the patient is suffering from syphilis. The decision requires careful study of the patient and, if necessary, examination and testing of contacts. The treponemal immobilisation test (Nelson's test) may help. If the result of careful investigation leaves the diagnosis in doubt and the amount of treatment has been inadequate by accepted standards, then full treatment should be given followed by the necessary observation and tests presently to be discussed.

If the patient has acquired early syphilis and gonorrhoea at the same time, penicillin given for treatment of gonorrhoea may delay or even suppress the lesions of syphilis without curing the patient. On this account it has been customary to observe the following rules when giving penicillin for the treatment of patients with gonorrhoea:

(a) All patients with gonorrhoea should have blood taken for routine tests for syphilis before treatment is given.

(b) The dosage of penicillin for gonorrhœa should be the minimum consistent with the probability of a good result. Details will be found on page 65.

(c) Penicillin should not be used for the treatment of patients with gonorrhœa who also have lesions suggestive of syphilis until those lesions have been fully investigated.

(d) All patients treated with penicillin for gonorrhœa should remain under observation with monthly serological tests for at least 3 months, and a final serological test should be performed at the end of 6 months.

(e) A sharp febrile reaction within the first 24 hours after the use of penicillin for gonorrhœa suggests the possibility of concurrent early syphilitic infection. It has been shown that the Jarisch-Herxheimer reaction may occur in the incubation period of syphilis.

### (5) IODINE PREPARATIONS

Iodides promote the absorption of syphilitic granulation tissue and may be useful in the later stages of infection. Potassium iodide is most often given by mouth in doses of gr. 5 to 30 thrice daily. It is usually prescribed with alkali to avoid gastro-intestinal disturbances. Most patients tolerate gr. 5 to 10 three times a day without difficulty, but iodism may result from higher dosage. The common manifestations are due to increased flow of secretions, causing coryza, salivation and lacrimation. There may be pain over the accessory nasal sinuses. Sometimes the drug produces an acneiform eruption. The benefit to be derived from this remedy is not now sufficient to justify perseverance with it in the face of major discomfort. Sodium iodide is probably the best preparation for intravenous injection. After testing the patient's tolerance by giving some potassium iodide by mouth, a dose of gr. 150 of sodium iodide dissolved in 100 ml. or more of sterile distilled water may be given intravenously every 24 to 48 hours up to a total of 20 to 30 injections in a course.

**The Treatment of Acquired Syphilis.**—The main principles to be observed in the treatment of syphilis are as follows: (1) treatment should begin as soon as possible. The earlier treatment is begun the better the results; (2) the amount and duration of treatment should be sufficient to ensure the probability of cure but over-treatment should be avoided; (3) due attention should be given to the general health of the patient; (4) observation and testing after treatment should be careful and prolonged. There are some failures following even the best methods of treatment and long observation may be necessary before these can be recognised.

### EARLY SYPHILIS

There has been some division of opinion on the question as to whether penicillin alone is sufficient for the treatment of cases of early syphilis or penicillin should be supplemented by a full course of treatment with an arsenical and bismuth or with bismuth alone. Those who have advocated the use of penicillin alone have based their argument on the high proportion of successes obtained and the absence of toxic effects following this treatment. Those who have taken the contrary view have argued that the reported incidence of relapse following penicillin alone, which has been as high as 15 per cent. in some series, is considerable and that in any case experience with penicillin has been insufficient to justify absolute reliance upon it.

In this country clinicians were first inclined to support the more conservative attitude, but with increasing experience it has become evident that the addition of arsenicals and bismuth to penicillin does not increase the proportion of successes in the treatment of early syphilis but does add to the incidence of major and minor toxic effects. With the decline in the incidence of early syphilis in the population of this

country and of the United States the failures of treatment with penicillin alone have become considerably fewer, and it seems reasonably clear that a number of so-called infectious relapses were in fact reinfections; the two conditions often cannot be distinguished with certainty. Thus penicillin alone is the treatment of choice. Experimental work in the United States has indicated that if crystalline benzyl penicillin is used in watery solution in the treatment of early syphilis the optimum dose is about 5 million units and the optimum duration of treatment about 7 to 8 days. Injections should be given day and night at intervals of 2 to 3 hours. An effective method of treatment is to give 100 injections each of 50,000 units intramuscularly, every 2 hours day and night. For such treatment it is necessary to admit patients to hospital.

To avoid admission to hospital and to reduce the number of injections procaine penicillin may be used in oily or watery suspension or, better still, in oily suspension containing 2 per cent. aluminium monostearate. A satisfactory method is to give 10 consecutive daily intramuscular injections each of 600,000 units, totalling 6 million units.

Success from this treatment may be anticipated in 95 per cent. or more of the cases.

Those who advocate the addition of a full course of arsenicals and bismuth to standard dosage of penicillin recommend additional treatment of the following kind:

1st Week	..	..	Neoarsphenamine 0.45 g. intravenously.
			Bismuth metal 0.3 g. intramuscularly.
2nd to 10th Week	..	..	Neoarsphenamine 0.6 g. intravenously.
			Bismuth metal 0.3 g. intramuscularly.

Oxophenarsine may be substituted for neoarsphenamine in dosage of 0.06 g twice weekly.

The practice of using arsenicals is steadily diminishing in favour. The results of our own experience indicate that they now have no place in the routine treatment of syphilis.

*Observation after treatment.*—Following treatment with penicillin the patient should remain under close observation with monthly clinical examinations and tests of the blood for the first 6 months, and thereafter examination and blood tests every 3 months for at least 2 years. During the period of observation the cerebrospinal fluid should be tested. This is often done at the end of 6 months after the completion of treatment and again, finally, 2 years after treatment. It is, however, very uncommon to find changes in the cerebrospinal fluid after treatment with penicillin which proves effective in other respects, and a point against early lumbar puncture is the fact that the procedure can produce a severe reaction which may make the patient quite determined not to repeat the experience. If, therefore, the cerebrospinal fluid is examined and found to be normal at some time during the second year of observation after treatment, it need not be tested again. If, however, the blood tests remain positive beyond the expected period, or if a relapse occurs, it is always advisable to test the fluid earlier.

After 2½ years of observation cure may be presumed, but it is customary and advisable for the patient to be examined and to have blood tests once a year for some years after this period.

*Failures of treatment.*—The critical period for the development of clinical or serological relapse is between the fourth and ninth months after treatment, although relapses, or possibly reinfections, have been observed as early as 4 weeks and as late as 3 years.

The indications for further treatment are three in number:

(1) *Clinical relapse.*—When the relapse is of the muco-cutaneous or infectious type it may be difficult or impossible to be sure that the patient has not been reinfected. Cases of true relapse are often resistant to treatment and on re-treatment it is advisable



to double the original dosage of penicillin and to consider the possibility of giving, in addition, one full course of neosarsphenamine and bismuth. The birth of a syphilitic child to a treated syphilitic mother is a form of clinical relapse.

(2) *Serological relapse*.—This is said to occur when tests originally negative, as with sero-negative primary syphilis, become positive; or tests originally positive become negative and then positive again; or tests originally positive show at first no change or decline in the quantitative titre, but subsequently show progressive rise in titre; or when tests of the cerebrospinal fluid, originally negative, become positive. Serological relapse commonly precedes clinical relapse.

(3) *Serological resistance*.—The decision as to the period of time after which persistence of positive serological tests is regarded as evidence of failure of treatment of early syphilis is an arbitrary one. In much of the experimental work on the subject the period was fixed at 1 year after treatment. For the routine management of cases, failure may be presumed if the quantitative tests show no fall in titre after 4 to 6 months of observation.

### LATE SYPHILIS

After the third or fourth year of infection the details of treatment depend very much on the presence or absence of involvement of viscera and of the nervous system, the treatment of which is discussed elsewhere in this work. In these later cases it is very important not only to examine carefully the cardiovascular and nervous systems, but also to test the cerebrospinal fluid as part of the routine investigation. If tests of the fluid are negative they are unlikely to become positive later, and the central nervous system is unlikely to be affected.

**LATENT SYPHILIS.**—In these cases the only evidence of the disease is the positive serological tests. In the past it was shown that such patients who received full dosage with arsenicals and bismuth remained in good health after prolonged observation in more than 95 per cent. of the cases, whether or not the serological tests became negative. Penicillin is no more effective than arsenic and bismuth in reversing positive serological tests to negative in these cases. Full assessment of the value of penicillin in these cases will take many years. Its use for the treatment of latent syphilis is based on the assumption that, being of value for early syphilis, it must be effective in other cases, which seems a reasonable assumption. Penicillin has the advantage of brevity and safety and it is common practice to use it for latent syphilis in similar dosage to that recommended for the earlier stages of the disease. Many patients with latent syphilis report improvement in general health after this treatment.

**BENIGN LATE SYPHILIS.**—The evidence is that prompt healing of cutaneous, mucosal and osseous gummata, and of other benign late lesions, follows the administration of 2.4 to 4.8 million units of penicillin. Common practice is to use rather more penicillin such as from 6 to 8.4 million units spread over 10 to 14 days. As for early syphilis, it is good practice to give a daily injection of 600,000 units of a reliable preparation of procaine penicillin. The immediate results are as good as those obtained with arsenicals and bismuth, and there is no reason to suppose that the ultimate results will be inferior.

The fact that serological tests remain strongly positive after this treatment in many of the cases is not an indication for further treatment. On the other hand, prolonged observation is important and re-treatment should be undertaken for any evidence of clinical relapse or consistent rise in titre of the quantitative serological tests.

Whether it is justifiable to use penicillin in the treatment of these cases of late syphilis without preliminary treatment with injections of bismuth and perhaps iodide by mouth is an open question. The tendency in the United States is to discount the importance of the Jarisch-Herxheimer reaction in cases of late syphilis except in certain cases of neurosyphilis. There is no doubt that serious effects of this reaction

are rare and they present no problem in the majority of cases. There remains the possibility of some serious effect in an occasional case. It is obviously impossible to exclude by clinical examination the contingency of asymptomatic involvement of vital organs, and nothing is to be gained by speed and intensity of treatment in cases of long standing. On general principles, it is well to give preliminary treatment with weekly intramuscular doses of gr. 0.3 of injectio bismuthi for 4 to 6 weeks, combining the treatment with gr. 5 or 10 of potassium iodide by mouth three times a day.

#### ASYMPTOMATIC NEUROSYPHILIS

In cases of latent syphilis in which positive changes in tests of the cerebrospinal fluid indicate involvement of the central nervous system, it is customary to give a rather longer course of injections of penicillin. Common practice is to give a daily injection of 600,000 units of procaine penicillin for 21 days, totalling 12,600,000 units. In these cases the guide to the efficacy of treatment is the cell count and the protein content of the cerebrospinal fluid. Earliest and most striking is the reduction of the cell count which, in successful cases, returns to normal by 10 to 24 weeks after treatment and remains normal. The protein content also responds, but rather less promptly. Normal values are usually reached by the sixth month and maintained thereafter. The Wassermann reaction and colloidal tests improve more slowly and may show positive changes for an indefinite period. The response of these tests is more prompt and satisfactory with early than late asymptomatic neurosyphilis. The usual practice is to give no additional treatment if the patient remains well and the cell count and protein level in the cerebrospinal fluid remain within normal limits. Tests of the cerebrospinal fluid should be repeated at intervals of 3 months for the first year after treatment and thereafter yearly for some years.

If further treatment is required a second course of penicillin or, if necessary, several courses of penicillin should be given. It is doubtful whether the use of the pentavalent arsenical, tryparsamide, in the treatment of neurosyphilis is now justified. If it is to be used it is essential first to ensure that there is no ophthalmoscopic evidence of optic atrophy and that there is no contraction of the visual fields, for the dangerous complication is toxic amblyopia. For an adult the usual practice is to commence with an intravenous injection of 2 g. of tryparsamide dissolved in 5 to 10 ml. of sterile distilled water. Thereafter weekly injections each of 3 g. of the drug are given for another 9 weeks, which completes the course. Occasionally, during the first course, a patient may complain of subjective visual disturbance such as "shimmering" or mistiness on looking in some particular direction. In such a case the injections must be discontinued and should not be resumed. The visual fields should be charted by perimetry at intervals of 2 weeks during treatment. Several courses of this treatment may be given with intervals of 1 month between the courses. For genuine failures of treatment with penicillin, pyretotherapy is the best form of supplementary treatment. This may be given by inoculation with the parasite of benign tertian malaria, allowing 10 or more paroxysms of fever before suppression with antimalarial therapy. Alternatively, fever may be given by physical means, as with the Kettering hypertherm, or by repeated intravenous injections of vaccine such as typhoid-paratyphoid vaccine (T.A.B.). Pyretotherapy is a highly technical procedure and should not be undertaken without full knowledge of the technique and of possible complications and how they may be avoided or treated.

#### SYPHILIS AND MARRIAGE

For complete safety the syphilitic patient should be advised not to marry, or if already married not to cohabit with the partner in marriage, until cure may be presumed following 2½ years of observation after treatment. This is the kind of advice

which is seldom taken and most clinicians are satisfied with lesser standards. If treatment appears to have been successful the risk is probably very slight after a year of observation and, provided that the partner in marriage is made aware of the slight risk, permission to marry or to resume married life may be given at this time.

## CONGENITAL SYPHILIS

An infected mother can transmit syphilis to her offspring long after she has ceased to be sexually contagious. In general the more recent the infection in the mother the more severe the effects of transmitted infection on the fœtus. The theoretical course of the obstetric history of a syphilitic woman is stated in *Kassowitz's Law*, according to which early pregnancies result in miscarriages progressively later in pregnancy, followed by the delivery of stillborn or macerated fœtuses at term, then by living syphilitic infants and finally by healthy infants. This kind of history, which is presumed to be due to gradual attenuation of infection, is seldom obtained. In practice, miscarriages may alternate with stillborn or living syphilitic children and a healthy infant may be born between two who are infected. It has even occurred that only one of twins was syphilitic. It is now generally agreed that infection always occurs from the mother by way of the placenta and that infection is not transmitted in the first 3 months of life. It may be assumed that miscarriage in the first 3 months of pregnancy is not due to syphilis. In the past it has been stated that the syphilitic placenta can be recognised by macroscopic appearances and, with more certainty, by microscopic changes in the chorionic villi. This view is now discredited and it seems clear that examination of the placenta does not help in this diagnosis unless *T. pallidum* can be found, which is seldom possible.

**Symptoms and Signs.**—The clinical manifestations of congenital syphilis may be divided into three groups, those which appear early, those which appear late and the stigmata. The early lesions are for the most part infectious and resemble those of secondary syphilis in the adult; the late lesions include gummatous lesions indistinguishable from those of tertiary syphilis; and the stigmata are scars or deformities resulting from early or late lesions.

(1) **EARLY.**—*The Skin and Mucous Membranes.*—The syphilitic infant born alive may show an eruption of large, rounded, dusky-red papules surmounted by bullæ containing serum or pus, the so-called, *bullous eruption* or *syphilitic pemphigus*. The fluid contains *T. pallidum* in large numbers. Some 3 to 4 weeks after birth, or perhaps considerably later, various rashes may appear which are identical in appearance with those found in secondary syphilis. The papular eruption is the commonest. All these eruptions tend to be widespread, involving the whole of the trunk and the limbs, but they may be particularly well-marked in the napkin area, on the skin round the nose and mouth and on the palms and soles. Annular lesions are particularly common and there may be extensive crusting. In moist areas, and where the rash is exposed to friction, the affected areas may become reddened and glazed. Condylomata lata may be found especially in the ano-genital area, and, where the rash is profuse and becomes confluent at the angles of the mouth and nose, ulcerative fissures may form. These sometimes leave radiating linear scars, *rhagades*, which remain as stigmata of the disease. Sometimes the skin is yellowish, or yellowish-brown in colour, the so-called *café-au-lait* tint and if, which is common, there is much wasting, the skin may be wrinkled, giving to the infant's face the appearance which has been called the *old man look*. There may be patchy loss of hair, chiefly at the sides and back of the scalp, *syphilitic alopecia*. Rarely, the syphilitic infant may grow an abundant crop of hair, the so-called *syphilitic wig*. Syphilitic papules may involve the nail beds, causing infiltration and oozing of serum round the nail which may be loosened and shed, *syphilitic onychia*. The new nails may be opaque,

irregular and narrowed at the base. Mucous patches may be found in the nose, mouth, throat and larynx. The nasal lesions may cause discharge from the nose which is persistent and may be bloodstained; nasal obstruction may cause difficulty in feeding. The nasal discharge is infectious and syphilitic moist papules may appear at the margins of the nares. Discharge and obstruction give the typical picture of syphilitic *snuffles*. As the result of laryngeal infection the infant's cry may be hoarse and raucous. Gross secondary *anæmia* is common in these severely affected infants.

*Lymphadenitis*.—Rubbery discrete non-tender enlargement of lymphatic glands is common.

*Liver and Spleen*.—As the result of early syphilitic infection the abdomen may be grossly swollen, due to enlargement of liver and spleen. The enlargement of the liver is due to abnormal persistence of fetal blood forming islands and to pericellular fibrosis, resulting from the spirochætal invasion.

*The bones*.—The long bones may be affected in various ways. In the first 6 months of life *osteochondritis* is a very common result of congenital syphilis and may be detected very early by radiographic examination. In severe cases the ends of the bones may be very painful and tender and, because of the pain on movement, the infant may appear to be paralysed, *syphilitic pseudo-paralysis*, or may scream when handled. Swelling of the epiphyseal ends of the bones may be obvious. Pathological fractures, separation of epiphyses and suppurative arthritis are possible sequelæ. Radiologically, epiphyses may be enlarged; the epiphyseal line is broad and irregular; the zone of provisional calcification is sclerotic and shows irregularity like the teeth of a saw; there are irregular patches of osteoporosis in the diaphyses, particularly at the metaphyseal ends; and there is subperiosteal deposition of new bone. In the second 6 months of life the signs of osteochondritis disappear, but the evidence of *periostitis* persists and becomes more marked. Successive layers of new bone are laid down on the surface of the cortex under the periosteum in regular fashion. *Dactylitis* may occur in the second year of life. It may cause fusiform swelling of proximal phalanges of one or more fingers, or, more rarely, toes. *Choroiditis* may occur in the early months of life and may be overlooked. *Iritis* is rare.

(2) *LATE*.—Lesions of the tertiary type may appear as early as the third year of life or at any time subsequently. They occur most commonly between the ages of 7 and 14 but may be delayed until adult life. Gummata involving the skin have no features which distinguish them from similar lesions due to acquired syphilis. Gummata of the mouth and throat are particularly common and may result in perforation of the palate or great deformity of the soft palate and pillars of the fauces. The commonest late lesion is *interstitial keratitis*, which may begin at any age from 4 to 30 years, or even later. Usually it starts in one eye, but in spite of treatment the other is likely to be involved after an interval which may vary from a few weeks to many years. The patient complains of photophobia and pain in the affected eye. At first there is seen to be injection of the sclerotic coat at the margin of the cornea, and from this area blood vessels extend into the deep layers of the cornea, becoming clinically obvious as a pink patch—the so-called *salmon patch*—or detected only with the aid of the slit lamp and corneal microscope. At the same time there is an exudation of inflammatory cells of the lymphocytic type into the deep layers of the cornea, causing haziness or *ground glass* appearance of the normally transparent membrane. The condition is very frequently associated with iridocyclitis which may be masked by the severity of the process in the cornea. The outcome is very variable. The attack may clear in a few weeks without damage to sight, or it may persist for many months and the patient may be prone to subsequent relapses. Even with severe attacks the damage to sight may be slight, but central opacities of the cornea are a common end result and vision may be grossly damaged in consequence. *Nerve deafness* resulting from involvement of the nerve endings of the 8th nerve in the internal ear is common among patients who suffer from interstitial keratitis, but

occurs rather later. It may also occur independently of corneal infection. The result may be bilateral progressive deafness which may become complete. Keratitis, nerve-deafness and characteristic deformities of the upper central incisors are sometimes called *Hutchinson's triad*. Other later effects of congenital syphilis are diffuse *interstitial orchitis* which may occur early in life, low-grade suppurative *otitis media* which may result in deafness without loss of bone conduction of sound, and effusion into both knee joints without pain or interference with movement, so-called *Clutton's joints*, which are found at any time from the ages of 5 to 18. Between the ages of 8 to 14, and sometimes earlier, these children may develop gummatous osteo-periostitis of the long bones, particularly the tibiae. The pathology of this condition is the same as that which occurs in adults, but the process is often widespread and may involve the whole length of the bone. Thickening of the tibiae is commonly most marked on the anterior surface of the middle third of the bone giving a forward convexity and appearance of curvature of the bone, the so-called *sabre-shaped tibia*. There is no true curvature of the bone because the gummatous process strengthens rather than weakens the cortex. In the early years of life there may be areas of localised thickening of the bones of the vault of the skull—so-called *periosteal nodes* or *Parrot's nodes*.

Congenital syphilis may not only cause anaemia and marasmus in infants and young children, but also delay in development and proneness to intercurrent infections in infancy and later years. The visceral and nervous affections of congenital syphilis are described in other sections of this book. Aortitis is rare as the result of congenital syphilitic infection.

(3) STIGMATA.—Scars and deformities result from the lesions which have been described. Facial disfigurement may be due to several causes. Severe and prolonged rhinitis may result in failure of normal development of the bones which surround the nasal cavity. Thus, flattening of the bridge of the nose may give the deformity known as *saddle-nose*; under-development of the superior maxilla may make it appear that the mandible is over-developed—so-called *bulldog jaw*; healed periosteal nodes of the frontal bone may give abnormal prominence of the forehead—*frontal bossing*; and the combination of these deformities is sometimes called the *bulldog facies*. Corneal scarring with empty blood vessels at the periphery of the cornea, rhagades, sabre-shaped tibiae, perforations of the palate and nasal septum, scars and deformities of the throat and tissue-paper scars of the skin are all common stigmata. The fundus oculi may show the changes of old healed choroiditis. The upper central incisors of the permanent dentition may show narrowing at the cutting edge, as compared with the width of the tooth at the gingival margin, together with curving of the margins, antero-posterior thickening and, in some cases, a crescentic notch at the cutting edge—so-called *Hutchinson's teeth*. Less often the 1st lower molars show a dome-shaped deformity of the grinding surface to which are attached the undeveloped cusps in the form of four small projections—so-called *Moon's molars*. These dental dystrophies result from the effect of severe syphilitic infection upon the developing buds of these teeth at or soon after birth.

**Diagnosis.**—If there are bullous lesions or other moist lesions *T. pallidum* can usually be found without difficulty. Scraping of the dry lesions of the skin may also make it possible to find the organism. The results of serological tests must be interpreted with reserve in the first weeks of life. Infants with negative serological tests may be suffering from active syphilis. On the other hand, non-syphilitic infants may give positive serological tests for syphilis if the mothers' tests are positive, due to the fact that they are suffering from long-standing infection or have been treated for early infection late in pregnancy. In cases of doubt antisyphilitic treatment should be withheld and quantitative tests should be repeated at weekly intervals. If the infant is not infected the strength of the test declines progressively to negative, usually within a few weeks and certainly within a few months. If the strength of

the reaction fails to decline or increases over a period of weeks, infection is probable. Confirmatory evidence can usually be obtained from physical examination and from radiographic changes in the long bones which are present very early.

Provided that the possibility of syphilitic infection is remembered the diagnosis should not present great difficulties. The bullous rash may be confused with pemphigus neonatorum, but the former appears earlier and is nearly always found on the palms and soles. Lesions in the napkin area may be mistaken for a napkin rash, but the latter is brighter red in colour and does not extend into the folds of groins and buttocks. The rashes of early congenital syphilis are nearly always associated with other signs.

**Treatment.**—**PREVENTIVE.**—The prevention of transmission to offspring is primarily a matter of prevention of infection of mothers. The precautions to be observed in relation to the marriage of syphilitics and the cohabitation of those who become infected after marriage have been described. Most cases of transmission result, however, from undiagnosed and unsuspected infection, and for this reason all pregnant women should be fully examined and tested serologically during pregnancy. This precaution does not give absolute protection because of the possibility that the mothers may be incubating syphilis when examined or that they may be infected later, but it has certainly prevented many cases of congenital syphilis. Treatment of the syphilitic pregnant woman will almost certainly prevent transmission of infection. In the days of prolonged chemotherapy with arsenicals and bismuth it was the general experience that treatment begun before the end of the fourth month of pregnancy and continued throughout pregnancy nearly always protected the fetus. Treatment begun later or interrupted for any reason was less certain in its effects but still provided a degree of protection corresponding to the amount and duration of the treatment administered. In this respect penicillin has proved a very important advance in efficacy of treatment. Adequate dosage at any stage of pregnancy may be expected to ensure freedom of the offspring from infection in 98 per cent. of the cases. A convenient method is to give the mother a daily intramuscular injection of 600,000 units of procaine penicillin in oily or watery suspension for 10 days, the total dosage being 6 mega units. It is a reasonable precaution to repeat this course of injections of penicillin in succeeding pregnancies even though evidence points to the fact that the mother is already cured.

**CURATIVE.**—There is no justification for treating the newly-born infant of a syphilitic mother for syphilis as a precautionary measure without first confirming the diagnosis. In cases of difficulty the correct diagnosis can always be made with certainty by waiting awhile and the infant is not likely to suffer in consequence. On the other hand, to assume the diagnosis and treat establishes the necessity for prolonged observation, frequent tests of the blood and tests of the cerebrospinal fluid. At the same time a lifelong stigma is attached to the patient, resulting in much unhappiness to everyone concerned. All of this may well be quite unnecessary.

When the fact of infection has been established, the infant should be treated with injections of penicillin, which is well tolerated and very effective. Various schemes of dosage have been recommended; the following is easy to give and efficacious:

Total dosage may be calculated at the rate of 200,000 units of penicillin per pound of body weight. Injections may be given intramuscularly every 3 hours day and night, but missing one dose at night, and administration should be spread over 10 days. Thus for a child of 7 pounds weight the total dosage would be 1,400,000 units, the daily dosage 140,000 units and the individual dose 20,000 units. Alternatively, 150,000 units of procaine penicillin suspension can be given intramuscularly each day for 10 days.

The results of such treatment in cases of early congenital syphilis are so good that further treatment is usually not required. Spirochaetes disappear from surface

lesions within a matter of hours, lesions heal promptly and serological tests for syphilis usually become negative after periods varying from a few weeks to 4 months and thereafter remain negative. It is rare to find pathological changes in cerebrospinal fluid tested 6 months to a year after treatment.

In the event that some indication for further treatment arises, a further course of injections of penicillin can be given with the likelihood of a good result.

In cases of late congenital syphilis the treatment is similar with dosage of penicillin based in the same way on body weight. The results are good but it is to be anticipated that in a number of these cases serological tests will remain positive in spite of treatment, and this is not necessarily an indication to continue treatment. On the other hand, evidence of clinical or serological relapse, as already defined, or of continuing activity of infection of the central nervous system, as shown by a persistent excess of lymphocytes and excess of protein in the cerebrospinal fluid, call for more intensive treatment.

Observation after treatment should be prolonged and certainly should continue until growth ceases, for, although the results of treatment are excellent, there are likely to be occasional failures. Provided that the patient remains clinically well with, in the case of early infection, negative serological tests, the tests of the cerebrospinal fluid need not be repeated if they are negative at the end of 1 year after treatment.

Certain of the late manifestations appear to run their course irrespective of treatment. Interstitial keratitis is a case in point. Antisyphilitic treatment should certainly be given because the patient is suffering from systemic infection, but additional local treatment is required for the eye to prevent damage to sight. The process is ultimately self-limiting and the administration of *cortisone* holds the inflammatory process in check until spontaneous cure results, reducing residual damage to a minimum. The drug may be given systemically, or topically by drops, ointment or subconjunctival injection. The method of choice seems to be the use of drops because it is effective, economical and comfortable for the patient. The drug is supplied as a suspension of 25 mg. of cortisone acetate in 1 ml. of normal saline with 1.5 per cent. of benzyl alcohol added as a preservative. The suspension is used in a 1:5 dilution, to avoid irritation of the eye. Drops are instilled 2-hourly for the first 24 to 48 hours, then 4-hourly and later twice daily as a maintenance dose. Instillation of 1 per cent. atropine solution is continued at the same time, at intervals of 4 hours. The symptoms are remarkably relieved. If administration is stopped too soon, relapse results. Deafness due to involvement of the 8th nerve is another condition which is likely to be progressive in spite of treatment.

**TOXIC EFFECTS OF ARSPHENAMINE PREPARATIONS.—Local.**—An intravenous injection of any arspenamine preparation or, particularly, of oxophenarsine, may cause thrombosis of the vein into which it is injected; this is not a serious complication, but precludes the use of the vein for subsequent injections. Escape of the arsenical solution around the vein causes agonising pain, and swelling and infiltration of the tissues, which may go on to sloughing. This complication should be avoided by careful technique. Such an injection should never be given until the operator is quite certain that the end of the needle is lying freely in the lumen of the vein, as shown by free reflux of blood into the syringe when the plunger is withdrawn.

**General.**—All these compounds tend to damage capillary endothelium. Patients who have died as a result of injections of an arspenamine have been found to have blockage of cerebral capillaries with small surrounding hæmorrhages, hæmorrhagic nephritis, hæmorrhages into lung alveoli, submucous petechiæ and ecchymoses in stomach and bowel, and, in a comparatively few cases, degeneration and necrosis of liver cells.

Toxic effects are manifested by various clinical syndromes which require detailed description. This list is a comparatively long one, but some of the reactions are

preventable, and most are mild and infrequent, so that they do not preclude the routine use of these remedies. They may appear early or late in the course of treatment, as follows :

*During or immediately after the injection.*—(1) Vasomotor disturbances, also known as anaphylactoid symptoms or nitritoid crises; (2) urticaria; (3) syncope and (4) pain in the gums and teeth.

*Following the injection, usually in a few hours, and occurring generally on the same day.*—(5) Rise of temperature and headache; (6) vomiting, diarrhœa, pain in the back and cramp in the legs; (7) herpes labialis.

*At various times from a day or two to a month or longer after the commencement of a course of injections.*—(8) Albuminuria; (9) stomatitis; (10) persistent headache, lassitude, loss of appetite, loss of weight and insomnia; (11) dermatoses; (12) jaundice; (13) arsenical encephalopathy; (14) various blood dyscrasias; (15) polyneuritis.

(1) The *vasomotor symptoms* simulate those of anaphylaxis; they are rare after deep subcutaneous or intramuscular injections. The conjunctivæ become suffused, the face becomes flushed, and the tongue and lips may swell; there may be respiratory distress and the patient may become unconscious. As a rule the symptoms last for about half an hour, but in occasional cases recovery is not complete for a number of hours. Some patients are peculiarly susceptible to this reaction but it may be produced in other cases by too rapid administration or, it is said, by injecting the drug before solution is complete. All these remedies should be injected slowly, except oxophenarsine which does not produce this reaction and should be injected rapidly to prevent venous thrombosis. If precautions fail to prevent the reaction the drug should be changed to oxophenarsine given intravenously or sulpharsphenamine deep subcutaneously. For the immediate treatment of the reaction intramuscular injection of 10 minims of solution of adrenaline hydrochloride (1 in 1000) has been found to be effective. (2) *Urticaria*.—A severe vasomotor attack is sometimes followed by more or less generalised urticaria. (3) *Syncope*.—A feeling of faintness during the injection, or immediately after it, may be merely a precursor of vomiting or due to fear. Occasionally, however, the patient may become unconscious, pale and almost pulseless; fatal cases have been reported. Such an attack usually yields to ordinary restoratives, but may be very alarming for a time. (4) *Pain in the gums and teeth* is probably part of the vasomotor reaction. Some patients complain of a peculiar taste in the mouth, like garlic, or the smell of ether, during the injection. This also is probably a minor manifestation of the vasomotor reaction; it is said to be more common when concentrated solutions are used for injection. (5) *Rigor, rise of temperature and headache* are most common after the first injection. The temperature seldom rises above 101° F. and the reaction is not necessarily of serious significance. If, however, the symptoms recur after successive injections and increase in severity, arsenicals should be discontinued. (6) *Diarrhœa and vomiting* are unlikely to occur unless there have been indiscretions in diet or errors of technique. The patient is usually well by the next day. These symptoms may sometimes be prevented by ensuring that the patient fasts for 2 hours before each injection. (7) *Herpes labialis* may follow the febrile reaction. (8) *Albuminuria* is rare. It is more likely to follow the use of mercury and bismuth. (9) *Stomatitis* is seldom due to arsenical remedies, but there is support for the view that the tendency to this complication, which is shown by patients on treatment with mercury or bismuth, may be enhanced by the concurrent use of arsenicals. (10) *Persistent headache, lassitude, loss of appetite, loss of weight and insomnia* are symptoms of intolerance. They are not very common, but indicate the necessity for stopping the treatment. If they are disregarded major complications of treatment are very likely to follow. (11) *Dermatoses*.—In addition to urticaria and herpes, various affections of the skin



result from administration of organic arsenicals and one of them is a serious and dangerous condition. The mildest presents as slight pruritus which may quickly disappear or may be prodromal to a serious complication. An early eruption is the condition which was called by Milian *erythema of the ninth day*. It appears from the seventh to twelfth day after the start of the treatment and within  $\frac{1}{2}$  to 2 days of an injection. It is preceded by a rapid rise of temperature, to  $101^{\circ}$  F. or higher, headache, back-ache, and sometimes vomiting and diarrhoea. These symptoms are followed by the appearance of a generalised scarlatiniform, morbilliform or polymorphic eruption, which fades in a few days with very slight or no desquamation. In severe cases it may be associated with or followed by jaundice. Prodromal fever and the absence of desquamation are important points of distinction from the more serious exfoliative eruption which indicates permanent sensitisation. It has been stated that treatment with arspenamine can be resumed after erythema of the ninth day has subsided, but if this is done at all extreme caution should be exercised. The most severe dermatosis, usually called *arsenical or exfoliative dermatitis*, is relatively uncommon. It starts as a punctiform erythema which quickly spreads over the body and is accompanied by most intense itching. It often becomes vesicular and desquamation of the surface epithelium follows. So serious are the potential effects of this complication that the complaint of generalised irritation of the skin or the appearance of a rash which shows vesicles or desquamation in the course of treatment with arsenical injections contraindicate further use of these remedies, even though recovery is prompt. Careful questioning as to irritation of the skin and observation for the first signs of erythematous rash will often give timely warning of the complication and, by stopping the administration of more arsenic, may save the patient from a severe attack. Patients suffering from exfoliative dermatitis are very prone to secondary infection of the denuded areas of skin and to intercurrent infections of the respiratory system. They may also suffer from blood dyscrasias. Illness is often prolonged and severe and may be fatal. The patient should be confined to bed and protected from cold. Excellent results have followed the administration of dimercaprol, which should be used in all such cases. Its value in arsenical poisoning is that it competes with tissue cells for the arsenic and perhaps detaches some of the arsenic which has already combined with tissue proteins. It is injected intramuscularly in the form of a 5 per cent. solution of dimercaprol and 10 per cent. benzyl benzoate in arachis oil. Each ampoule contains 100 mg. and injections are given as follows :

1st Day .. ..	4 ampoules at intervals of 4 hours.
2nd, 3rd and 4th Days ..	2 ampoules—1 in the morning and 1 at night.
5th and 6th Days ..	1 ampoule.
Total—1200 mg.	

If further treatment is required the course may be repeated after an interval of 1 week.

In this dosage toxic effects are slight or negligible, but it is important to ensure that the injection is made into the muscle and not into subcutaneous tissue for otherwise local abscesses may occur. Dimercaprol is often remarkably effective in halting the progress of the complication and facilitating recovery of the skin. The diet should be simple and the fluid intake maintained. Calamine lotion or a bran bath may be applied locally. Areas of skin which are moist after exfoliation should be covered with sterile dressings. (12) *Jaundice* following injections of arspenamine preparations was known to be a complication of arsenical therapy for 30 years before its true cause was recognised. In most cases the condition is mild; the patient complains of anorexia and malaise and shows a variable degree of jaundice with enlargement of the liver and perhaps the spleen, with clay-coloured stools and highly coloured urine. Tests show moderate to severe impairment of liver function. Occasionally

the condition is much more serious, with severe epigastric pain, restlessness and delirium, followed by death. The changes found in these rare cases have been extensive degeneration and necrosis of liver cells with round-celled infiltration of the supporting connective tissue, multiple subserous hæmorrhages and, frequently, hæmorrhages into lung alveoli. Jaundice may commence during a course of injections or be delayed for several months after the completion of a course. The incidence of this complication showed a very great increase in the Armed Forces during the War of 1939-1945. In 1943 it was suggested that it might be due to an infective agent, like that in the icterogenic batches of yellow fever vaccine which had been responsible for many cases of jaundice at one period of the war, and that this agent might be strongly resistant to heat and might be contained in minute amounts of blood left in syringes after intravenous injections of arsenical compounds. Later it was shown that the methods of sterilisation employed in many treatment centres were ineffective even against pyogenic organisms. It was then found in military hospitals that post-arsphenamine jaundice could be very greatly reduced if not entirely eliminated by a very strict regimen of syringe sterilisation. Homologous serum jaundice has since been shown to follow not only arsenical injections, but injections of bismuth, penicillin, insulin, gold, acriflavine and other substances. It is fully preventable by strict precautions in the sterilisation of syringes and needles and careful technique of injection. (13) *Arsenical encephalopathy*.—With this complication patients show severe cerebral symptoms with headache followed by mental confusion, epileptiform convulsions and coma, ending in death in a large proportion of cases. The condition has been rare with ordinary schemes of treatment employing standard dosage with injections once or twice a week. The symptoms usually begin from 2 to 5 days after the second injection, but this is not an invariable rule. Necropsy reveals œdema of the brain with dilatation of capillaries, capillary hæmorrhages and sometimes larger ring-shaped hæmorrhages. If the patient survives for some time after the onset of the attack, areas of demyelination may be found in the white matter of the brain. It has been shown that hæmorrhagic encephalopathy is more apt to occur in females than in males, and especially towards the end of pregnancy. It is much more frequent in patients treated by intensive methods of treatment, employing daily injections of oxophenarsine, which were used during the War of 1939-1945, and was, in fact, the chief danger of this form of treatment. Apart from the fatal cases with convulsions and coma, milder forms of encephalopathy occurred in a number of these cases in the form of severe headache and mental confusion. The value of treatment of this complication is doubtful, but various methods have been recommended. If it is to be of value, treatment should be instituted as quickly as possible after the onset of the symptoms. It has been claimed that daily lumbar puncture with removal of 15 to 20 ml. of cerebrospinal fluid, and bleeding to 15 to 20 oz. have been effective. In 1945 Ransome, Paterson and Gupta reported excellent results from nursing patients in the sitting posture, with full sedation to control fits. Lumbar or cisternal puncture was performed at the outset and repeated if coma seemed to deepen. Eagle (1946) claimed good results from the prompt use of dimercaprol. (14) *Blood dyscrasias*.—Three disorders of the blood-forming organs have been described but all of them are rare. They have followed treatment with sulpharsphenamine relatively much more often than treatment by other arsphenamine preparations. They are thrombocytopenia, granulocytopenia and aplastic anaemia. Sometimes they are found in association with arsenical dermatitis. The symptoms, signs and treatment of these conditions are described elsewhere in this volume (see p. 738). (15) *Polyneuritis* is extremely rare with standard methods of treatment. It was a common complication of intensive methods of arsenotherapy.

**TOXIC EFFECTS OF OXOPHENARSINE.**—The toxic effects are very similar to those following administration of the arsphenamine compounds, except that vasomotor symptoms and similar immediate reactions do not occur.

**TOXIC EFFECTS OF TRYPARSAMIDE.**—The main risk is of amblyopia, and for this reason the patient's visual fields were usually tested and charted by an ophthalmologist before treatment was started, and at intervals of a fortnight during treatment. It was essential that treatment should be stopped at the first indication of subjective disturbance of vision.

**TOXIC EFFECTS OF ACETARSOL AND ACETYLARSAN.**—Toxic effects were usually mild. Acetarsol sometimes caused gastro-intestinal disturbance if taken too near a mealtime. Slight erythema occurred sometimes and, very rarely, severe dermatitis of the exfoliative type.

**TOXIC EFFECTS OF MERCURIAL PREPARATIONS.**—Mercury may cause stomatitis, nephritis, colitis, general malaise and dermatitis.

*Stomatitis* can usually be prevented by care. The patient's teeth and gums should receive attention before treatment is begun and he should brush his teeth night and morning. Potassium chlorate is a useful antiseptic in these cases and may be used as a mouthwash or incorporated in a dentifrice. The onset of stomatitis is marked by salivation and pain, tenderness and swelling of the gums. The mucous membranes are rather livid in appearance. Oral fœtor is pronounced and precedes the onset of ulceration. The mercury must be stopped and treatment applied to the mouth in the form of local applications of potassium chlorate or peroxide of hydrogen. An astringent mouthwash should be employed. In severe cases injections of dimercaprol should be given. *Nephritis* rarely results from moderate doses of mercury, but the possibility of damaging effect upon the kidneys should be remembered in cases of patients suffering from renal disease. *Colitis* is extremely uncommon as the result of ordinary dosage of mercury but has occurred in patients with an idiosyncrasy to the metal. It is a serious condition and may be fatal. *General malaise* is apt to result from too heavy dosage; it is always advisable to keep a close watch on the patient's weight and general condition when this kind of treatment is used. *Dermatitis* as a result of mercurial treatment is very rare.

AMBROSE KING.

## YAWS

**Synonyms.**—Frambœsia; Frambœsia tropica; Pian; also many vernacular names such as Parangi (Ceylon), Bubas (Brazil), Coco (Fiji), etc.

**Definition.**—A contagious, inoculable, tropical disease caused by *Treponema pertenue*. The primary lesion is of non-venereal origin and is followed by the secondary stage consisting of an eruption of typically "granulomatous" papules. The tertiary stage, occurring a few or many years later, is characterised by destructive lesions.

**Ætiology.**—Yaws is essentially a disease of indigenous populations of tropical countries. Europeans are rarely affected. It is prevalent in the West and East Indies, Ceylon, the Philippines, Oceania and New Guinea and parts of tropical Africa and South America. Infection usually occurs in childhood, although a few adults escaping infection then may contract it later. The disease is not transmitted congenitally, and infection is generally regarded as occurring only once in a lifetime. Both sexes are attacked. The cause is *T. pertenue*, which is morphologically indistinguishable from the spirochæte of syphilis; on animal inoculation, however, constantly different reactions have been observed. The similarity of yaws and syphilis is greatest in the tertiary stage. Bejel, the non-venereal syphilis of the Bedouin Arabs, has certain epidemiological and clinical similarities to yaws. *T. pertenue* enters the skin through minor abrasions, most commonly on the limbs and especially the legs. The causal organism of the Central and South American disease *pinta* is also morphologically indistinguishable from the spirochæte of syphilis.

**Pathology.**—The primary and secondary lesions are characterised by interpapillary down-growths of epidermis into the corium. There is also œdema and infiltration

with polymorphonuclear leucocytosis and plasma cells both in the proliferated epidermis and in the corium. Spirochaetes are more numerous where the cellular infiltration of the epidermis is most pronounced, but they are also present in the adjacent corium. The tertiary lesions are characterised by necrosis and ulceration with granulation tissue and dense fibrous tissue formation. Giant cells are frequently present, but spirochaetes are not numerous. Though peri-vascular cellular infiltration and vascular endothelial proliferation are usually said not to occur in yaws lesions, there are no generally reliable histological criteria for the differentiation of yaws and syphilitic skin lesions in man.

**Symptoms.**—The incubation period in man is 4 weeks or longer (in monkeys 3 weeks), and may be accompanied by mild general symptoms.

The primary lesion resembles the typical secondary lesions but is often larger. It is most frequent on the lower limb, is usually single and extragenital, and may heal before the secondary eruption appears or outlast it. The adjacent lymphatic glands may be enlarged.

The *secondary stage*, which may appear within 3 weeks of the primary lesion, may be heralded by irregular intermittent fever, headache, bone and joint pains, often worse at night, and a characteristic more or less generalised papular eruption. This commences as small, yellowish papules, which increase in size or coalesce to form larger lesions. The stratum corneum is shed, exposing a granular surface of minute pinkish elevations, separated by a whitish groundwork. Serum containing treponemata exudes and dries, forming a yellowish crust, which later may become discoloured and polished, especially in the case of less active lesions. Pus is not usually present. Healing occurs sooner or later, often leaving but little scarring, although hyperpigmentation, which later disappears, may be seen. The lesions may itch, and, although not very painful, are sensitive to minor irritation, such as flies. The distribution is general, but the trunk is often relatively spared. The body orifices and the soft skin of flexures are particularly involved. Successive crops may appear for from 2 to 3 years. Other types of skin lesion, pathologically related to those just described, are often seen, but usually typical secondary lesions are also present. These include darker macules, desquamation and acuminate papules. General enlargement of the lymphatic glands is often found. The eruption of a yaw on the sole, *clavus* or crab yaws, is particularly painful, and may appear many years after the earlier lesions have healed. Other plantar and palmar changes consist of thickening and desquamation of the epidermis. Yaws papules may also develop on the buccal mucous membrane. Bone lesions are frequent during this stage, and are characterised by swellings. Periosteal deposits and rarefied foci in these deposits and in the cortex are seen radiographically. *Sabre-tibia* may develop, but destructive bone lesions do not occur. Multiple dactylitis is frequent. Ganglia and synovitis with free fluid are seen. Goundou belongs to this stage. All secondary lesions heal spontaneously, although bony thickening may remain. The general health is not usually seriously affected.

The *tertiary stage* may be reached within a year of the healing of secondary lesions, or after a quiescent period of many years. Lesions at this stage are characterised by tissue destruction and ulceration. In the skin superficial ulceration or deep gummatous-like processes may occur, which on healing leave hyperpigmented atrophic scars and occasionally contractures. In the bones, swellings with ulceration associated with bony necrosis ("gummata"), spontaneous fractures, deformities of the digits, periostitis, nodes, synovitis and arthritis are seen. Destructive processes in the mouth and nose may lead to palatal perforation and to gangosa. Epidermal thickening, erosions, fissures and coarse desquamation occur on the palms and soles, some of which may return to normal, but others result in atrophic changes and pigmentation. Juxta-articular nodes, chronic bursitis and patchy depigmentation of the skin are also met with.

**Complications and Sequelæ.**—In severe tertiary cases with many lesions, cachexia may result. Intercurrent diseases may be present. In Fiji and Haiti aneurysm and lesions of the central nervous system have been attributed to yaws, but the evidence is not convincing.

**Diagnosis.**—In localities in which yaws is prevalent there is usually no difficulty in diagnosing the early lesions, but congenital and acquired syphilis, bejel and bromide rashes may occasionally call for consideration. Treponemata can usually be found in serum from early lesions. The differentiation of tertiary lesions from syphilis may be impossible on clinical or pathological evidence, and a history of yaws in the past may be the only guide. Cutaneous leishmaniasis, blastomycosis, leprosy and tuberculosis may lead to confusion. The Wassermann and Kahn reactions are positive in yaws and syphilis after the first few weeks. The absence of visceral, vascular and central nervous system lesions in yaws and its ready response to modern arsenical and bismuth preparations and antibiotics may help to differentiate the two diseases.

**Prognosis.**—All secondary lesions heal spontaneously in a few months or years, and probably some cases become spontaneously cured and develop a negative Wassermann reaction. Yaws is rarely fatal, most deaths being due to intercurrent disease. Modern therapy is effective. In tertiary lesions more intensive treatment is required to produce healing and here, too, spontaneous cure probably occurs although less readily.

**Treatment.**—**PROPHYLACTIC.**—Avoidance of direct contact with cases of yaws is the basis of prophylaxis. Ordinary cleanliness, and the covering of cuts, abrasions and ulcers with suitable dressings to prevent contact with infective material and flies are important.

**CURATIVE.**—As in the treatment of syphilis, trivalent arsenicals, e.g. neoarsphenamine, bismuth compounds and penicillin are of great value. To ensure complete cure, serological follow-up is essential. In practice in yaws areas therapy is intended to reduce infectivity ("blanchiment"). For this, from 4 to 6 intravenous injections of neoarsphenamine (0.05 g. per 10 lb. to maximum dose of 0.75 g.), with from 4 to 6 intramuscular injections of a bismuth salt, e.g. bismuth salicylate (0.02 ml. of 10 per cent. suspension in oil per 10 lb. to maximum dose of 3 ml.) should be given, at weekly intervals, by mobile and static treatment units. Twelve months after injections of either of these preparations the Jamaican Yaws Commission (1935) found about 50 per cent. of primary and secondary cases had negative serological reactions. Other bismuth or arsenical preparations may be used. Following bismuth administration stomatitis may develop in unhealthy gums. Antibiotics are now extensively used in mass campaigns and in the treatment of individual cases. Procaine Penicillin G in oil with 2 per cent. aluminium monostearate is the most widely recommended. Hill gives the following dosage régime: Adults, total dose of 2.4 million units given intramuscularly into the buttock in two equal doses 3 to 5 days apart. Children of 5 to 12 years, total dose of 1.2 million units given in two equal doses as above. Children under 5 years, total dose of 0.3 million units given as a single injection.

Chlortetracycline and chloramphenicol have been used successfully in doses in adults of 1.0 to 2.0 g. per day given daily for a fortnight. Shorter, more concentrated dosage régimes have not been so successful. Oxytetracycline is active in doses of 3.0 g. the first day followed by 2.0 g. daily for the next 2 to 5 days.

Treatment with penicillin is quick, reasonably cheap and at least as effective as with the oral antibiotics. It is regarded as the ideal for mass treatment campaigns.

In tertiary yaws therapeutic response is less rapid. Up to date there has been no tendency for syphilis to flare up where yaws has been reduced.

Local treatment is necessary if there are extensive ulcers and lesions involving the soles of the feet. Deformities associated with periostitis and contractures may need plastic surgery.

## GOUNDOU

**Synonyms.**—Anakhre; Gros Nez; Dog Nose.

**Definition.**—Symmetrical bony tumours of the sides of the nose commencing during the secondary stage of yaws.

**Ætiology.**—This condition is found wherever yaws is prevalent, but has been reported most often from tropical Africa, especially in the west. It is seen in children and adults.

**Pathology.**—There is thickening of the periosteum with production of spongy tissue in which are fibrosis and perivascular plasma cell infiltration. The bony tissue is usually bounded by a thin layer of cortical bone. This hypertrophic osteitis involves the nasal process of the superior maxilla. In marked cases the tumour may encroach upon the nasal passages, orbit or palate.

**Symptoms.**—Pain in the bones and headache may occur in the early stages, but later these subside. The paranasal swelling on one or both sides increases outwards, and may become large enough to obstruct vision. Facial deformity may be the only symptom, but nasal obstruction may also result. The overlying skin is not implicated. Sometimes similar tumours elsewhere on the superior maxilla, or on the inferior maxilla, and other yaws bone lesions may also be present.

**Diagnosis.**—In yaws communities the paranasal swellings are characteristic, but in isolated cases differentiations may be needed from syphilitic osteitis, leontiasis ossea and possibly acromegaly.

**Prognosis.**—Marked deformity is rare. Some reduction in the size of the lesions in early cases may occur spontaneously or after treatment.

**Treatment.**—Energetic anti-yaws therapy is indicated in early cases, and surgical removal of the bony tumour in advanced ones.

## GANGOSA

**Synonym.**—Destructive Ulcerating Rhino-pharyngitis.

**Definition.**—An ulcerative process of tertiary yaws resulting in destruction of the palatal and nasal structures.

**Ætiology.**—This condition is probably to be found wherever yaws is endemic. Its presence in the Pacific Ocean Islands and the East Indies has been stressed. It may commence in older children and adults.

**Pathology.**—The process begins with ulceration of the palate or in the nose, and is followed by destruction of soft tissues and bone. The histopathology is that of tertiary yaws.

**Symptoms.**—Pain, purulent discharge and foul odour accompany the ulceration mentioned above. The amount of destruction produced varies from a small perforation of the soft or hard palate, or some falling in of the nose, to complete destruction of the palate, nose, nasal contents and adjacent tissue of the cheeks and orbit so that the roof of the nasal cavities, pharynx and tongue are exposed. Arrest of the process, either spontaneously or following therapy, may occur at any stage. The larynx is probably not affected.

**Diagnosis.**—In yaws communities this is usually easy, but differentiation from American dermal leishmaniasis, syphilis and leprosy may be necessary.

**Prognosis.**—The progress of the destruction and healing is usually slow, and although the response to adequate treatment is good, tissue losses remain. Death may result from general exhaustion, sepsis, insufflation pneumonia or other intercurrent disease.

**Treatment.**—Energetic anti-yaws therapy is indicated, and intercurrent disease may need treatment.

## JUXTA-ARTICULAR NODES

**Definition.**—Multiple, painless, fibrotic nodules occurring in the vicinity of joints and bony prominences in the later stages of yaws.

**Ætiology.**—This condition is probably found wherever yaws is prevalent, and has been reported from most tropical countries. It is rare in childhood and is characteristically seen in elderly people often together with chronic pre-patellar bursal enlargement. Similar lesions are occasionally met with in late syphilis and in bejel.

**Pathology.**—The nodules consist of hard, greyish-white, avascular fibrous tissue, in which may be opaque yellow spots and occasional areas of necrosis. Foci of chronic inflammatory cells are found microscopically; endarteritis is said not to occur but treponemata have been demonstrated in them. The tumours have no capsules, and merge into the neighbouring connective tissue.

**Symptoms.**—The nodules appear as small round multiple tumours in the sub-cutaneous tissue about joints and bony prominences, especially the knee, elbow and over the femoral trochanter. Only a few are present at any one situation; they are painless, firm and even cartilaginous in consistency, and only rarely break down and ulcerate. They are usually freely movable under the skin, but later some attachment to the skin at the most prominent point may occur. Their development is slow, and the nodules may resolve spontaneously or remain stationary. Their usual size is 1 to 2 cm., but some may become much larger.

**Diagnosis.**—Differentiation from syphilitic, rheumatic and onchocerca nodules may be necessary. Biopsy may be of assistance. In onchocerciasis the tumours are often softer, and embryos may be demonstrated in aspirated fluid; on section they are loculated, and filariæ and embryos are present.

**Prognosis.**—The nodules may cause some discomfort at points of pressure, but do not endanger life.

**Treatment.**—If necessary, troublesome nodules may be excised. Intensive anti-yaws therapy may cause resolution in some and regression in others.

## LEPTOSPIROSIS

Since the causative organism, *Leptospira icterohæmorrhagica*, was first demonstrated in Japan by Inada and Ido in 1915, leptospirosis icterohæmorrhagica has been recognised in many different countries. The earliest observations indicating that strains of *leptospira* other than the classical leptospirosis icterohæmorrhagica strain might produce disease in man was made two years later in Japan when *L. hebdomadis* was shown by Ido, Ito and others to cause Japanese 7-days' fever or Nanukayami disease. Subsequently several strains differing in antigenic structure were discovered in the Dutch East Indies and Malaya. In Europe swamp fever was recognised as a leptospirosis caused by *L. grippa-typhosa*, and in 1934 *L. canicola*, which commonly affects dogs, was shown to produce leptospirosis in man. More recently several new strains have been isolated in Australia, the Argentine and Palestine. Schüffner classified the leptospiroses pathogenic to man on the basis of different antigenic structure as revealed by serological reactions and animal inoculations, the clinical picture, epidemiological considerations and geographical distribution. Many different strains are recognised, and these are separated into two groups, i.e. those capable of producing jaundice and those which fail to do so, but it should be remembered that even in classical leptospirosis icterohæmorrhagica only 50 per cent. of patients develop jaundice. The clinical picture in leptospirosis caused by any of these strains includes conjunctival congestion, fever, prostration, severe headache and generalised muscular pains; meningeal symptoms and rashes may also develop. A neutrophil leucocytosis is characteristic. The outstanding difference is in prognosis, for while many cases

of classical leptospirosis icterohæmorrhagica die, patients infected with other strains almost invariably recover. Early blood culture, inoculation of guinea-pigs with blood or urine, serum agglutination reactions and other serological tests are essential to establish the diagnosis of leptospirosis and determine the strain of leptospira implicated.

### I. LEPTOSPIROSIS ASSOCIATED WITH JAUNDICE

Four strains pathogenic to man are included in this group :

(1) The classical Weil strain, *L. icterohæmorrhagica*, is cosmopolitan in distribution and lethal to guinea-pigs. The natural reservoir is *Rattus decumanus*, and it is known that in many different countries rats of this species pass *L. icterohæmorrhagica* in large numbers in the urine; these organisms infect man through skin abrasions or via the nasal mucous membranes during submersion in contaminated water. Only rarely the disease is acquired from infected dogs and cats.

(2) Akiyami A strain is similar to *L. autumnalis* of Japan and the Rachmat strain of the Dutch East Indies. The natural host is *Apodemus speciosus* in Japan where it has an autumnal prevalence.

(3) The Salinem strain, or *L. pyrogenes*, of the Dutch East Indies is probably identical with the Zanoni strain, which is one of the two leptospires responsible for leptospirosis amongst the cane-cutters of Queensland, Australia, in the rainy season. It has been found in a local species of rat—*R. culmorum*. The strain is lethal to guinea-pigs.

(4) The Batavia strain is found only in Java where *R. decumanus* appears to be the reservoir host. It is less pathogenic for guinea-pigs than the other strains described above.

### II. LEPTOSPIROSIS WITHOUT JAUNDICE

A number of different strains pathogenic to man are included in this group. These include :

(1) *L. hebdomadis* causes 7-days' fever in Japan. It is primarily an infection of the field vole, *Microtus montebelli*, and appears in the urine, which contaminates soil or food. It has recently been found in Sumatra in dogs and man.

(2) *L. grippo-typhosa* gives rise to summer epidemics amongst field workers in Europe, but the reservoir host and mode of infection is unknown. The disease runs a benign course. It has also been isolated from patients with leptospirosis in the Andamans (Andaman B strain).

(3) *L. canicola* produces an epizootic in dogs, from which man acquires the disease by contact. It is most easily isolated and maintained in Syrian hamsters. In canicola fever, though jaundice is absent, the meningitic symptoms often appear more severe than in classical Weil's disease.

(4) The Pomona strain produces fever lasting 3 to 8 days, and has been isolated from agricultural workers in Queensland and in North Italy. It occurs after rain.

(5) The Ballico strain causes leptospirosis in Queensland on the cane plantations after rain. It produces a mild fever lasting a week. It is lethal to guinea-pigs and has been found in local rats.

### LEPTOSPIROSIS ICTEROHÆMORRHAGICA

**Synonyms.**—Spirochætal Jaundice; Weil's Disease; Spirochætosus ictero hæmorrhagica.

**Definition.**—An acute febrile disease with a world-wide distribution, caused by *Leptospira icterohæmorrhagica*, and generally occurring in people with an occupational relationship to rats. In its typical severe form it is characterised by fever, profound



prostration, headache, generalised pains and acute muscular tenderness, conjunctival hyperæmia, leucocytosis, albuminuria, jaundice and a tendency to hæmorrhage. Subclinical infections may occur, and jaundice is absent in about 50 per cent. of cases.

**Ætiology.**—In 1886, Weil first directed attention to this disease, which is now associated with his name. In Japan it was well known amongst miners and labourers in the rice fields, and in 1915 Inada and Ido infected guinea-pigs with blood from human cases and demonstrated *L. icterohæmorrhagicæ* in the tissues. Later, rats (*Rattus decumanus*) were found to be the reservoir host; the leptospiras, which were localised in the kidney, escaped in the urine and often contaminated water, fungal slime and soil. In man infection generally occurs in people who work in rat-infested places, and follow occupations in which minor injuries and abrasions of the skin are common; this accounts for its incidence in sewer labourers, bargemen, canal and dock workers, fish and tripe cleaners, coal miners and farm labourers. In Great Britain the disease is recognised as an occupational one, for which compensation may be claimed under the Workmen's Compensation Act. In trench warfare troops may become infected. The disease may also be acquired via the nasal passages from infected water when bathing or during immersion accidents, which mode of infection is particularly common in Holland.

**Pathology.**—(1) **MORBID ANATOMY.**—In fatal cases there is an acute hepatitis with jaundice, while parenchymatous degeneration of the tubular epithelium of the kidneys, perhaps associated with hæmorrhages into Bowman's capsules, is characteristic. Large and small hæmorrhages are often scattered throughout the tissues and particularly affect the stomach, intestinal mucosa and the lungs.

(2) **ISOLATION OF THE LEPTOSPIRA.**—*L. icterohæmorrhagicæ* may be isolated by blood culture in Fletcher's medium during the first week, or by injecting 5 ml. of infected whole blood intraperitoneally into the guinea-pig up till the tenth day of the disease. In the cultures there is a time lag of 3 to 5 days before leptospiras are found, and of 5 to 8 days before they appear in the viscera or blood of inoculated guinea-pigs. Where meningeal symptoms develop leptospiras may be found in the cerebrospinal fluid, and they are often demonstrable in the urine after the second week.

(3) **SEROLOGICAL REACTIONS.**—The agglutination reaction, using formalised cultures as advised by Schuffner, yields satisfactory results. Agglutinin appears in low titre about the fifth or sixth day, and rapidly increases during the second and third week of the disease; maximal titres up to 1/100,000 have been recorded. Agglutinins persist for many years after an attack, and multiple observations to determine an increase in titre may be necessary in cases in which the titre is low and residual agglutinin may have persisted from a previous infection.

**Symptoms and Course.**—The incubation period varies from 6 to 12 days. In moderately severe cases presenting the classical clinical picture three stages are recognised: (1) a febrile stage, with sudden onset; (2) an icteric stage, associated with renal features, and sometimes hæmorrhage and (3) a convalescent stage, in which febrile relapses are common.

(1) **FEBRILE STAGE.**—This generally lasts 6 to 8 days. As a rule the onset is sudden, with shivery feelings and definite rigor. Headache, nausea, vomiting, profound asthenia, backache, photophobia and generalised muscular pains are characteristic. So severe may the muscular pain and tenderness be that the patient cries out with agony on the slightest movement. Conjunctival injection is common and herpes with hæmorrhage into the vesicles not infrequent. The muscles of the limbs and the abdominal muscles are often exquisitely tender on palpation. There may be some enlargement of liver or spleen but often this is absent even in the icteric stage of the disease. A neutrophil leucocytosis is characteristic; the total count varies between 10,000 to 20,000 leucocytes per c.mm., and the neutrophils equal 80 to 85 per cent.

(2) **ICTERIC STAGE.**—An icteric tinge of the conjunctivæ and lemon-yellow tinting of the skin appear from the fourth to the sixth day, but are only found in about 50 per cent. of cases. The jaundice gradually deepens and may become a deep orange in colour. A direct biphasic van den Bergh reaction develops, with well-marked hyperbilirubinæmia; in a recent series one patient whose plasma contained 56 units recovered, and another with a maximum value of 29 units died of cholæmia. With the onset of jaundice the urine becomes dark brown, and contains bile salts and bile pigments. The stools often contain excess of fat, which is adequately split, and are often pale brown or even white in colour, the result of a decrease of stercobilin.

Evidence of renal involvement is not infrequent and the urine, which is decreased in quantity, contains albumin, renal casts, pus cells and perhaps red blood corpuscles. As renal function fails the nitrogenous constituents of the blood increase and the blood urea attains high values. Anuria may ensue. Hiccough, Cheyne-Stokes respiration, subsultus tendinum, delirium and coma are features common to cholæmia and uræmia, which are frequent causes of death. Skin petechiæ or purpuric patches sometimes appear and bleeding gums, hæmoptysis, hæmatemesis, melæna and hæmaturia may complicate the picture.

(3) **CONVALESCENCE.**—This generally commences in the third or fourth week, by which time the renal and hepatic manifestations have subsided, but it is often 5 or 6 weeks before the patient is fit to leave hospital. Not infrequently in the third week a relapse of fever occurs, which may last from a few days to 3 weeks; it is generally unaccompanied by icterus or other severe symptoms.

**Atypical Clinical Types:** These are frequent, and may or may not be associated with jaundice. They include:

(a) **Anginal type.**—The patient complains of fever, generalised pains and sore throat, and is usually diagnosed as influenza, tonsillitis or rheumatic fever. Unless jaundice develops or the occupation of the patient suggests the possibility of leptospirosis icterohæmorrhagica, laboratory investigations are not made and the true nature of the infection remains unrecognised.

(b) **Abdominal type.**—There is fever, abdominal pain, vomiting and localised or generalised rigidity associated with acute tenderness of the abdominal muscles; the picture may resemble an acute abdominal condition, such as appendicitis, cholecystitis, pancreatitis or peritonitis. A neutrophil leucocytosis is present, and when hæmatemesis occurs, perforated gastric ulcer may be diagnosed.

(c) **Respiratory type.**—There are physical signs of pulmonary consolidation resembling pneumonia, and hæmoptysis may supervene. Jaundice may never develop.

(d) **Meningeal type.**—Not uncommonly leptospiral meningitis, with neck retraction, Kernig's sign, etc., may develop at the onset. Lumbar puncture reveals a clear fluid under increased pressure, containing neutrophil leucocytes, lymphocytes and perhaps monocytes, while leptospiras may be demonstrated by animal inoculation or culture. More rarely, chronic meningitis may supervene months after the acute stage of the disease has subsided, but notwithstanding this the cerebrospinal fluid contains pus cells and leptospiras.

Subclinical infections also occur in which people like sewer workers acquire a symptomless leptospirosis; there is no history of illness yet the blood shows definite agglutination against *L. icterohæmorrhagica*.

**Diagnosis.**—Few diseases are more protean in their clinical manifestations or have remained for such long periods undetected in communities. Leptospirosis icterohæmorrhagica is not generally suspected until the patient develops jaundice and there is known to have been an occupational relationship to rats or a recent water-immersion accident. An appeal to the laboratory under such circumstances will generally enable a delayed diagnosis to be made, either by isolating the leptospira

or by serological tests. Apart from jaundice, a history of possible contact with rat-infected material, the extreme prostration, the conjunctival injection and the severity of the muscular pain and tenderness, and the neutrophil leucocytosis, should arouse suspicion.

**Prognosis.**—Fatal cases are almost invariably jaundiced and die between the ninth and fourteenth day as a rule from cholæmia or uræmia. The mortality rate appears to vary in different outbreaks, but where the diagnosis is reasonably good it is about 9 per cent.

**Treatment.**—**PROPHYLACTIC.**—This includes the protection of bathing pools, abattoirs, fish shops, etc., from rats, and the immediate treatment and protection of any skin abrasions in people whose occupation brings them in contact with rat-infected material. Prophylactic vaccination is under trial. Nurses should be instructed to disinfect the patient's urine.

**CURATIVE.**—Antileptospiral serum given repeatedly in large doses in the febrile period is recommended by some workers.

Penicillin, chlortetracycline and oxytetracycline in big doses may be effective if administered early.

Treatment is unsatisfactory in late cases.

Fluids and glucose should be administered orally, while intravenous glucose (5 per cent.) is a useful adjunct to therapy in severe cases.

## RELAPSING FEVER

**Synonyms.**—Spirochætosis; Febris Recurrens; Spirillum Fever; Famine Fever.

**Definition.**—A group of specific infectious fevers due to spirochaetes (treponemata) and spread by lice or argasine ticks, characterised by a variable number of febrile relapses.

**Ætiology.**—Relapsing fever occurs in many parts of the world and is often seen in epidemic form during wars and famines. It is rare in England, but occurs in parts of Europe including Russia; in Turkey, India, Cochinchina, Algiers, Egypt, Africa and the Americas it is not infrequent. All ages and both sexes are liable. The different varieties of the disease are caused by spirochaetes demonstrable in the peripheral blood during the febrile paroxysms, and they may be divided into the lice-borne and tick-borne fevers. The varieties transmitted by lice include (1) European relapsing fever due to *Treponema recurrentis* (the old spirillum of Obermeier); (2) Northern African relapsing fever produced by *T. berberum*; (3) Indian or Asiatic relapsing fever caused by *T. carteri*; (4) North American relapsing fever attributed to *T. novyi*. The varieties transmitted by the argasine ticks include (1) Central African tick fever due to *T. duttoni* transmitted by *Ornithodoros moubata*, *O. erraticus* and *O. savignyi*; (2) Palestinian and Syrian tick fever caused by *T. sordidum* and transmitted by *O. papillipes*; (3) Persian and North-West Indian relapsing fever caused by *T. persicum* and transmitted by *O. papillipes (tholozani)* or *O. lahorensis*; (4) Spanish relapsing fever attributed to *T. hispanicum* and transmitted by *O. maroccanus*; (5) Central and South American relapsing fever due to *T. venezuelense* is transmitted by *O. venezuelensis* in Columbia and Venezuela, and by *O. talaje* in Panama; (6) Californian tick fever due to *T. turicatae* and transmitted by *O. hermsi*. At present it appears somewhat doubtful whether the creation of the numerous species of spirochaetes detailed above is justified on grounds other than those of convenience. Lice become infective about the sixteenth day, and remain so for about 1 month. Infection is probably conveyed by the faeces, or after the louse has been crushed and the spirochaetes liberated from the coelomic fluid; scratching may play an important part in transmission. Some ticks transmit infection during

the act of biting; in others, like *O. moubata*, the spirochaetes are liberated in the coxal fluid, and the anal excrement is also said to be infected; from this source man generally acquires the disease. The ova become infected and new generations of ticks can pass on the disease in hereditary fashion. Larval ticks are as capable of transmitting relapsing fever as adult ticks.

**Pathology.**—In uncomplicated cases petechial hæmorrhages and occasionally jaundice are found. The spleen is soft and congested and often the site of multiple infarcts, while the liver is enlarged, friable and hyperæmic, and along with the kidneys and heart shows cloudy swelling and fatty degeneration. The long bones contain red marrow. Congestive changes in the cord and brain and iritis have also been described, especially with *T. duttoni*. Microscopically, spirochaetes are demonstrable in endothelial cells throughout the body, especially in the liver and spleen, and also in the brain and cerebrospinal fluid. Monkeys are susceptible and, as in the case of rats and mice, are actively immune after recovery. Krantz has applied the Reichenberg reaction or "adhesion test" to relapsing fever spirochaetes, specific immune serum causing the spirochaetes and blood platelets to adhere together.

**Symptoms.**—A. THE LICE-BORNE RELAPSING FEVERS.

1. *European form.*—The incubation period varies from 2 to 12 days, and in accidental inoculations it is about 5 to 7 days. During this period slight prodromata may occur. The onset is sudden with a rigor, frontal headache and intense pains in the back and limbs. Anorexia, nausea and vomiting are common, and in children convulsions may occur; the temperature and pulse rise rapidly, the former often reaching 104° F. on the evening of the first day. The tongue is coated and moist, the spleen is enlarged and in some epidemics jaundice and a tender enlarged liver may be present. Herpes labialis may develop, and occasionally an erythematous rash appears at onset. Later, rose-coloured spots may involve the skin of the neck, trunk and inner aspect of the thighs. Petechiæ are observed only in severe cases. After the fever has persisted for 5 to 7 days the temperature falls by crisis, accompanied by profuse sweating and possibly diarrhœa and collapse. The patient rapidly improves, but after an apyrexial period a relapse ensues, generally about the fourteenth day, followed by a second crisis about the end of the third week (twenty-first day). This usually terminates the illness, but occasionally a third relapse is noted. Spirochaetes are present in the blood until 24 hours before the crisis, when they rapidly disappear, and are not demonstrable except possibly in thick smears during the apyrexial period when a leucopenia replaces the characteristic febrile neutrophil leucocytosis. The blood remains infective between relapses, and if injected into a mouse or white rat spirochaetes appear in 24 hours.

2. *Asiatic relapsing fever* closely resembles the European form, but rigors are not so common, collapse is more frequent at the crisis, and relapses more numerous. Carter describes two varieties: (a) a short irregular remittent fever; (b) the so-called bilious remittent or icteric fever. This is a severe form of infection associated with spirochætal hepatitis. There is a high fever, intense toxic jaundice, skin petechiæ, splenomegaly, and an enlarged tender liver. The urine contains albumin, bile pigments, bile salts and urobilin. There is hyperbilirubinæmia associated with a direct biphasic van den Bergh reaction in the plasma. Toxic features are marked, and include a dry brown tongue, diarrhœa, abdominal distension, hiccough, stupor, delirium and coma. Death not infrequently results.

3. *North African relapsing fever* is found in Algiers, Tunis and Egypt, and closely resembles the European form. The number of relapses rarely exceeds three, but fatal cases may show jaundice, bilious vomiting, hepatomegaly, splenomegaly with infarctions, and albuminuria, necessitating differentiation from yellow fever.

4. *American relapsing fever* due to *T. novyi* has a low mortality rate and not generally more than one relapse.

## B. THE TICK-BORNE RELAPSING FEVERS.

1. *Central African relapsing fever*.—**Synonyms**.—Tick Fever; Tete Disease; Carapata Fever.

This form is found throughout British and Portuguese East Africa, Nyasaland, Uganda and the Congo Free State.

It differs from the European form in the shorter duration of the initial fever (3 days), the irregular incidence, greater number of relapses and the scantiness of spirochætes in the peripheral blood. The incubation period varies from 5 to 10 days, generally being about 1 week. The tick bites may be accompanied by local inflammatory changes and the prodromata include mental lethargy and sweating. The attack may start gradually with malaise, vomiting and slight temperature which gradually increases, or suddenly with dizziness, headache and generalised pains, the temperature rapidly reaching 104° F. After the pyrexia is established these symptoms may persist and, in addition, chilliness, pain over the spleen, bilious vomiting, bronchial catarrh, diarrhœa, enlargement of the spleen and liver, albuminuria and herpes may occur. Generally after 3 to 4 days the fever terminates by crisis with profuse sweating. The patient feels weak and tired, but slowly regains his appetite and strength until the next febrile paroxysm, which may occur after an interval of 3 to 8 days. Third and fourth relapses are frequent and as many as ten may occur, weakness and emaciation then being marked. In severe and fulminating cases epistaxis, hæmaturia and jaundice may be met with, also occasionally involvement of the central nervous system, with coma and death due to cerebral embolism caused by tangled masses of spirochætes. Cranial nerve pareses are described, and spirochætes may be present in the cerebrospinal fluid, which frequently shows increased pressure and lymphocytosis.

2. *Persian and North-West Indian relapsing fever* presents a primary fever of some 4 days' duration followed by short bouts of pyrexial recurrence; five or more relapses are not uncommon. Some epidemics are very mild, others more severe. Often the spleen is not palpable, and icterus is uncommon except in the more severe epidemics.

3. Spanish relapsing fever caused by *T. hispanicum* resembles the tick fever of Central Africa. The initial fever lasts about 4 days, and is associated with splenomegaly and neutrophil leucocytosis. Iritis and facial neuritis are not infrequent complications during relapses, which do not generally exceed four in number.

**Complications and Sequelæ**.—Bronchial catarrh is not infrequent during the initial fever, and pneumonia and parotitis may also occur. In some epidemics hæmatemesis and hæmaturia have been noted; in others jaundice and hepatomegaly are not infrequent. Rupture of the enlarged spleen has been reported, also ophthalmia, adenitis, neuritis and diarrhœa. In tick-borne relapsing fever (*T. duttoni* and *T. sogdianum*), cranial nerve palsies are not uncommon. The most frequent is unilateral or bilateral facial paralysis, but ptosis of the eyelid, strabismus, deafness and trigeminal neuralgia are recorded. Ocular lesions include optic atrophy, iritis, iridocyclitis, retinal hæmorrhage and opacities in the vitreous. Meningismus associated with pathological changes in the cerebrospinal fluid (lymphocytosis, etc.) is quite common.

**Diagnosis**.—Relapsing fever has to be distinguished from influenza, typhus, malaria and trypanosomiasis, and, if there is jaundice, from yellow fever and Weil's disease. This is done by finding the specific parasite in the blood.

**Prognosis**.—The prognosis varies. With the European types the mortality rate is only 3 to 5 per cent., but with the Asiatic type it is much higher. Jaundice is an unfavourable development. African tick fever is not infrequently fatal, especially in the aged and debilitated, and Central American tick fevers resemble the Central African variety.

**Treatment.**—**PROPHYLACTIC.**—Avoidance of contact with lice and ticks is necessary if infection is to be prevented. Delousing of troops in war-time is important. With *O. moubata* the avoidance of native dung huts, especially at night-time, and of old camping sites, is essential. With *O. papillipes* in Syria and Palestine infection is mainly acquired when visiting caves; these should be avoided.

**CURATIVE.**—Arsphenamine (0.3 to 0.6 g.) and neoarsphenamine (0.6 to 0.9 g.) are specific in all types of louse-borne relapsing fever; generally not more than two injections are needed for cure. These should be given early during the pyrexial period and preferably when spirochaetes are demonstrable in the blood smears. In relapses the dose is repeated. In tick-borne relapsing fever these arsenicals are of doubtful value, and with *T. duttoni* in Central Africa and *T. sogdianum* in Palestine and Syria they do not materially influence the course of the disease, or the relapse rate. Claims have been made that aurothioglucose (Solganol B.) is of value in those cases in which the central nervous system is affected. In the latter, lumbar puncture may be indicated to reduce intracranial pressure. If collapse occurs at the crisis, stimulants should be given.

Penicillin in big doses will terminate the attack but does not prevent relapse. Chlortetracycline 0.5 g. 6-hourly rapidly controls the attack, but may also be followed by relapse.

## RAT-BITE FEVER

**Synonyms.**—Souoku; Sokoshio; Rat-bite Disease.

**Definition.**—A chronic relapsing type of fever following the bite of rats, and due to the *Spirillum minus* (Carter, 1887); it is characterised clinically by a return of the inflammation in the healed wound, lymphangitis, adenitis, rigors, fever and a macular or papular purplish rash.

**Ætiology.**—The disease is common in Japan, China and Bombay, and cases have been reported from France, Italy, Spain, Britain, East Africa, West Indies and Australia. Anyone bitten by an infected rat may acquire the disease. In man the spirochetes were found in the bitten tissues and in the lymph glands by Futaki; they are demonstrable with difficulty in the peripheral blood, appearing as thick, short forms (3 to 6 $\mu$ ), which on cultivation increase in length (20) $\mu$ . About 3 per cent. of house rats in Japan are carriers, and after experimental inoculation spirilla are present in the blood for the first fortnight of infection.

**Pathology.**—In human cases, degenerative changes in the liver and kidneys have been reported, while animals show congestion and swelling of the lymph glands and spleen.

**Symptoms.**—After being bitten the wound heals in an ordinary manner, but in from 2 to 6 weeks pain and swelling appear at the site of the old bite and the scar breaks down. The lymphatics draining the area of the bite become inflamed, with enlargement of the corresponding glands, while an acute myositis is often present; a definite ulcer may now mark the site of the bite, with an angry inflammation spreading away from it, and small vesicles may break out around it. When this has continued for some time, general symptoms make their appearance; the temperature rises to 103° F. or over; there may be rigors, vomiting, nausea, severe headache, joint pains, diarrhoea and general malaise. A specific rash then usually appears as dusky-coloured, purplish-red spots or a coloured, patchy erythema over the limbs, trunk and face, which lasts for some time and slowly disappears. After remaining high for 3 to 8 days, the temperature drops, often by crisis, and the symptoms generally ameliorate. After a varying period of time the first relapse appears with a return of the former symptoms. Pyrexia then disappears, only to be followed by further relapses, which in some of the reported cases have continued for months or even years. Considerable

debility follows the attacks, and finally the patient may pass into a very poor state of health. A transient or permanent nephritis may result, and exophthalmos and paresis have been recorded in some cases. Ultimately the infection tends slowly to disappear.

**Diagnosis.**—The history of rat-bite, the local lesion associated with lymphangitis and adenitis, the specific rash and recurrent fever are typical. In some ways the disease resembles syphilis, but the Wassermann reaction is negative. Spirilla are difficult to demonstrate microscopically in the peripheral blood, and white rats or mice should be inoculated with human blood.

**Prognosis.**—With modern treatment this is quite good, but previously it was not so, many cases continuing with chronic symptoms for years. A mortality of 10 per cent. has been given by some authors.

**Treatment.**—Arsphenamine or some of its derivatives should be given, commencing with doses of 0.3 g. One to three injections at 3-day intervals are usually sufficient to abolish completely all the symptoms and bring about a permanent cure. Penicillin in large doses (up to 2,000,000 units over 1 day) is also effective.

It has recently been shown that rat-bite fever may also result from infection with *Streptobacillus moniliformis*. Arsenic is not active against this organism. Penicillin in large doses (2 or more million units) is effective. Chlortetracycline may be used as an alternative where penicillin resistance is suspected, in doses of 0.5 g. 6-hourly for 10 days.

N. HAMILTON FAIRLEY.

## E. PROTOZOAN INFECTIONS

### MALARIA

**Synonyms.**—Ague; Paludism; Remittent, Intermittent, Marsh or Jungle Fever.

**Definition.**—A protozoal disease of man caused by various species of *Plasmodium* which infect the red corpuscles after undergoing a schizogonous stage in fixed tissue cells (hepatic parenchyma cells) and give rise to periodic fever, splenomegaly and anæmia; transmission is by female anopheline mosquitoes, which bite from sunset to dawn.

**HISTORICAL.**—Malarial fevers were recognised by Hippocrates in the fifth century B.C. In the Middle Ages, people in Europe suffered severely from the ague, being saved from its ravages by cinchona bark, probably brought back from Peru by the Jesuits in the first half of the seventeenth century. This remedy also enabled Sydenham and other physicians to separate malaria from other fevers. Laveran (1880) discovered both the parasite and the phenomenon of ex-flagellation in shed blood, but differentiation into the three species was not made until later. Manson (1894) formulated the hypothesis of mosquito transmission, but he thought that man acquired the disease from infected mosquitoes via water and not by biting. McCallum (1897) recognised the fertilising function of the "flagellating body". Ross (1898) worked out the correct transmission and developmental cycle of bird malaria (*Proteosoma*) in culicine mosquitoes, and having previously observed the partially developed oöcysts of human malaria in dappled winged mosquitoes (anophelines) he predicted a human life cycle similar to that observed in bird malaria. Later in the same year, Grassi, Bignami and Bastianelli (1898) demonstrated the complete development of *P. falciparum* in *Anopheles maculipennis* and transmitted the disease to man by the bite of infected mosquitoes.

**Ætiology.**—Two distinct ecological problems are presented in malaria—the parasite and its environment on the one hand, and the anopheline mosquito and its environment on the other.

Malignant tertian (M.T.) or subtertian malaria greatly predominates in the tropics, and benign tertian (B.T.) in temperate zones, while in the subtropics both these forms and quartan malaria may occur. The last has a patchy distribution. Malaria is not found between latitudes approximately 60° north and 30° south because temperature considerations limit its extension. The critical temperature determining development in the mosquito is about 60° F., and this must be maintained sufficiently long to allow the sexual cycle to be completed. In Europe the disease disappears at about 3000 feet, and in India and Africa at 6000 feet. Seasonal prevalence, which is not marked near the Equator becomes so farther from it. Throughout South-East Europe the malaria season extends approximately from June to October.

All races contract malaria, but European and Chinese are regarded as being more susceptible than Negroes and certain aboriginal races. In endemic areas malaria is commonest in children, but as a result of repeated infections both children and adults gradually acquire a certain degree of immunity (premunure) or tolerance, which only persists as long as parasites persist. In avian and simian malaria this depends on a specific enhanced phagocytic function and hypertrophy of the reticulo-endothelium in the spleen, liver and other organs.

M.T. malaria is chiefly responsible for epidemics, the factors necessary being a sufficient number of (1) good gametocyte carriers, (2) efficient anopheline vectors and (3) non-immune individuals. In hyperendemic areas, good gametocyte carriers amongst the native population are largely confined to infants and young children. Adults and other children developing premunure as a result of repeated infection with the local strains of *P. falciparum* and *P. vivax* rarely become carriers. Newly arrived adults in such an area who have not previously been exposed develop overt attacks of malaria if infected, and become most effective carriers; they are the main source of carriers in epidemic malaria involving armies fighting in the tropics.

In war when large bodies of "unsalted" troops have had to fight in hyperendemic areas of malaria, such as tropical Africa and New Guinea, big epidemics have resulted in which a large proportion of the Forces involved have become rapidly infected. The initial breakdown was caused by *P. falciparum* in about 80 per cent. of cases, but after treatment such individuals, when they relapsed, were found to be infected with *P. vivax*. In civilian life the tropical aggregation of labour may lead to similar consequences. Regional epidemic malaria, of which the Punjab epidemic (1908) and the Ceylon epidemic (1934) are examples, is dependant on the development of a large number of non-immunes consequent on a sequence of healthy years, followed by undue exposure to anophelism. Flood or drought may be the factors leading to an increase in the local anopheline vector. Prolongation of the transmission period is an important factor—especially in North India, where epidemics occur every 8 or 9 years. In the affected areas practically all the infants die, many young children and old people succumb, and the adults are so ill that the life of the whole community is paralysed. In the Ceylon epidemic failure of the crops and the resulting famine further lowered individual resistance, and within 7 months some 80,000 people died of M.T. and B.T. malaria.

**Parasitology.**—The malaria parasites are protozoa belonging to the class *Sporozoa*, genus *Plasmodium*. There are several distinct species affecting man: quartan malaria, caused by *Plasmodium malariae* (Laveran, 1881); benign tertian (B.T.), due to *P. vivax* (Grassi and Feletti, 1890); malignant tertian (M.T.), caused by *P. falciparum* (Welch, 1897); and a tertian malaria, due to *P. ovale* (Stephens, 1922). A fifth form, *P. tenue* (Stephens, 1914), has been described, but its species status remains doubtful. Man is also susceptible to experimental infection with *P. knowlesi*, a plasmodial parasite of monkeys.



*Asexual cycle in man* (endogenous cycle; schizogony). The sporozoites, after inoculation by the mosquito, disappear within 2 hours from the blood which completely loses its infectivity—even when 200 ml. are injected intravenously into a susceptible individual. On the seventh day in *P. falciparum* infection and on the ninth day in *P. vivax* infection the blood regains its infectivity as shown by positive sub-inoculation results, and 2 or 3 days later intracorporeal parasites become demonstrable in blood smears. During the period of non-infectivity the sporozoites leave the blood-stream and enter fixed tissue cells, especially the parenchyma cells of the liver, where they undergo an exo-erythrocytic schizogonous cycle before discharging the first generation of merozoites into the blood-stream. Large nests of these non-pigmented pre-exo-erythrocytic parasites have recently been demonstrated in the liver on the seventh day following experimental hyperinfection of a human volunteer with *P. vivax* by Shortt and his colleagues. Though late tissue forms have not yet been found in benign tertian infection in man, both pre-erythrocytic and late exo-erythrocytic forms have recently been discovered in the liver of monkeys infected with *P. cynomolgi* (Shortt and Garnham).

The pre-erythrocytic parasites in malignant tertian malaria have recently been demonstrated. Subinoculation experiments on human volunteers indicate that this tissue phase lasts only a few days and that once merozoites have been produced, there is every reason to assume exo-erythrocytic forms do not persist in infections with *P. falciparum* as they do in *P. vivax*.

The asexual growing forms (trophozoites) at first have their cytoplasm arranged somewhat crescentically around a central vacuole and contain one or more small masses of chromatin. With increase in the size of the vacuoles definite ring forms result. As the parasite enlarges malaria pigment appears, and medium-sized amœboid-like forms are produced. As the parasite reaches maturity pigment collects centrally and the chromatin divides into two, four or more portions each surrounded by a mass of cytoplasm; this is known as the sporulating, segmenting or rosette form or the schizont. The mature schizont consists of a variable number of young forms (generally 8 to 16), known as merozoites, which soon escape into the plasma and subsequently invade fresh red cells restarting the cycle.

*Sexual cycle in the mosquito* (exogenous cycle; sporogony). In addition to these asexual forms produced during schizogony in man, certain sexual forms (gametocytes) are liable to appear in the blood following a bout of malaria fever. These are large round or oval bodies filling and expanding the erythrocytes in benign tertian infections, and crescent-like bodies in malignant tertian malaria; when these crescents are imbibed by suitable anophelines the corpuscles are ruptured and they revert to a circular form in the mosquito's stomach. Here the male gametocytes produce flagella (microgametes), which separate off (exflagellation) and subsequently penetrate the female gametes (macrogametes) produced by maturation from macrogametocytes. The resulting body, known as the zygote, develops into the elongated travelling vermicle or ookinete which penetrates the stomach wall: here it becomes circular in outline and develops into an oöcyst which finally becomes packed with sickle-shaped sporozoites causing a cyst-like protrusion on its outer surface. These oöcysts subsequently rupture and sporozoites escape into the body cavity (hæmocœle) and ultimately make their way to the salivary gland. When the mosquito bites, the sporozoites pass with the salivary secretion into the new host (see Asexual Cycle in Man). The time taken to complete this cycle varies from 8 to 20 days, temperature conditions being an important factor in rate of development.

*Mosquito vectors of malaria.*—It is not every anopheline mosquito which can transmit malaria successfully. Perhaps the best-known transmitter of malaria is *A. maculipennis*, which is nocturnal in habit, and has been specially studied in Europe and the Eastern Mediterranean. Hackett, Missiroli and others have shown that *A. maculipennis* is not a uniform species, but is divided into "biological races" or

varieties. These races cannot generally be distinguished either as adult or larvæ, but only by their egg characteristics. The breeding grounds, sexual behaviour and feeding habits differ. Thus, the race called *elutus* bites man for choice, and is a dangerous carrier of malaria; other races, like *typicus* and *messee*, bite cattle for choice, and therefore are much less dangerous to man. The larvæ of *elutus* need traces of salt in water, and for this reason they tend to have a coastal distribution. In the Balkans, malaria of the plains is mainly transmitted by *A. maculipennis* var. *elutus*, whereas malaria of the hills is solely transmitted by *A. superpictus*, which especially breeds in running mountain streams with rough rocky beds. It follows that the mosquito vector should be carefully studied in every country and special local methods devised for its extermination. Drainage of swamps, land reclamation, elimination of breeding sites and destruction of larvæ by D.D.T., oiling, etc., are essential factors in malaria control.

There are many different vectors in other parts of the world, some of the more important of which are: *A. albanus*, tropical America; *A. quadrimaculatus*, United States; *A. funestus*, tropical Africa and India; *A. gambiæ* (costalis), tropical Africa, Arabia and Brazil; *A. culicifacies*, India and Ceylon; *A. stephensi*, breeding in wells in cities in India; *A. maculatus*, India, South-East Asia and Netherlands East Indies; *A. minimus*, India, Burma, etc.; *A. sundaicus* (ludlowi), the dangerous brackish-water breeder in the Far East; *A. punctulatus* var. *typicus* and *A. punctulatus* var. *molluccensis*, New Guinea and New Britain.

The danger of the introduction of new anopheline vectors into other countries is illustrated by that most dangerous African vector, *A. gambiæ*. This species reached Brazil, probably by aeroplane or destroyers, in 1930, and was followed by severe outbreaks of malaria, the epidemic in 1938 causing 50,000 cases. More recently *A. gambiæ* appeared in the Nile Valley in Egypt, where the usual vector is *A. pharauti*.

**Parasites in blood smears.**—All forms of *P. vivax*, *P. malariae* and *P. ovale* are met with in the peripheral blood, but in malignant tertian malaria owing to sporulation in the internal organs, generally only the small rings and large crescents of *P. falciparum* appear. Blood smears are stained by Leishman's or Giemsa's stain, while Field's rapid staining method gives excellent results in thick films in routine diagnosis. The following points assist in differentiating the different species. **Ring forms.** The rings of *P. falciparum* occupy about one-sixth of the cell, which may show Maurer's clefts. They are often fine and hair-like, and show irregular or flattened marginal forms. Two chromatin dots and multiple infection of the same corpuscle may occur; occasionally this is seen with *P. vivax*. The rings of *P. vivax* and *P. malariae* occupy about one-third of the cell, are larger and contain more cytoplasm, but the species cannot always be determined if only ring forms are present (Wenyon). **Partly grown forms.** In *P. vivax* the infected corpuscle is enlarged, Schüffner's dots are present, and the parasites are of irregular shape and contain light-brown pigment. With *P. malariae* there is no enlargement of the corpuscle, the pigment is dark brown or black, band forms are common, and Ziemann's stippling may be demonstrated in the red cells by special staining. **Adult forms.** In *P. vivax* and *P. malariae* the schizonts have 16 and 8 merozoites respectively, in contrast with which the gametocytes have a single nucleus and a different distribution of pigment and chromatin. *P. ovale* somewhat resembles *P. malariae* morphologically, but infected corpuscles show Schüffner's dots, and are often oval or distorted in shape with serrated edges.

**Pathology.**—**Clinical.**—In severe and persistent infections there is considerable blood destruction. The intra-corpuscular parasite digests hæmoglobin, depositing the hæm moiety as malaria pigment (hæmatin). Though free hæmoglobin is not generally detected spectroscopically in plasma collected during or after the paroxysm, Schumm's test for methæmalbumin is often positive if the fever be prolonged, indicating that corpuscular lysis with liberation of extracorporeal hæmoglobin is occurring. Hæmatogenous bilirubin also tends to be increased, the indirect van den

Bergh reaction varying from 1.0 to 8.0 units. Hyperbilirubinæmia is responsible for the hæmolytic icterus and pleocholia observed in severe and persisting infections.

In untreated infections, especially M.T., severe anæmia may rapidly develop. Before the disease has become chronic, anæmia in uncomplicated cases is generally normocytic in type. The blood picture may show polychromasia, anisocytosis, poikilocytosis, punctate basophils, and occasionally normoblasts. Hypochromia may develop later. Leucopenia with a left shift and a decrease in both lymphocytes and polymorphonuclear neutrophils occur early in the infection and are a characteristic finding.

The urine may be dark brown in colour due to urobilin. Albuminuria is not uncommon, and casts and other evidences of nephritis may be found in quartan malaria. Bile pigments and bile salts generally indicate malaria hepatitis. Delayed excretion of bromsulphthalein and other tests for liver function may indicate liver damage.

*Morbid anatomy.*—In a fatal case of *acute pernicious malaria* the spleen is enlarged and congested, blackish red in colour, with soft, dark pulp. The liver is also congested and enlarged, while the gall-bladder is distended with brownish-black bile. Small hæmorrhages may be present in both these organs. The serous membranes and mucosa of the gastro-intestinal tract are congested and leaden-coloured and may show small hæmorrhages. Lipoid and fat may disappear from the cortical layer of the suprarenals. The heart muscle is often pale and flabby, showing cloudy swelling or actual fatty degeneration; ecchymoses on the myocardium and pericardium are not infrequent. The marrow of the short bones is dark or chocolate coloured, while that in the long bones presents a variable picture depending on the degree of hyperplasia. In cerebral malaria the meninges are hyperæmic, the cortex is a smoky or leaden-grey colour, while punctiform hæmorrhages are scattered through the white matter.

The *microscopic* study of the organs in fatal cases has done much to explain the varied clinical manifestations of the disease. Thus:

(1) Pigmentation of the serous membranes and internal organs is caused by malaria pigment (hæmatin) contained in parasitised red cells in the capillaries, in macrophages, and R.E. cells, particularly in the red pulp of the spleen or the sinusoids of the liver and bone marrow. A fine, yellow granular pigment, hæmosiderin, giving the Prussian-blue reaction for iron with ferro-cyanide, is also found in the parenchyma cells of the liver, spleen and kidneys. (2) The early enlargement of the liver is mainly due to acute congestion, and in the case of the spleen to congestion and commencing hyperplasia of R.E. cells of the red pulp, some of which may show toxic degeneration. (3) Degenerative changes, due to toxic action or anoxia or both, are manifested in the polygonal hepatic cells, the convoluted tubules of the kidney, the cortical cells of suprarenal glands, and capillary endothelium giving rise to multiple hæmorrhages. (4) Capillary blockage by parasitised corpuscles and possibly vascular spasm lead to local tissue anoxia and possibly vascular spasm with small areas of hæmorrhage and necrosis possibly followed by neuroglial proliferation and the formation of so-called "malaria granulomata". Proliferative changes of the reticulo-endothelium in the capillary areas of the brain leading to granulomata are also described. In *chronic malaria* in which repeated infection has occurred for years the spleen ("ague cake") is very enlarged and hard, the capsule is thickened, and often adhesions bind it firmly to the diaphragm, etc.; sometimes the adhesions are calcified. Microscopic section shows great hypertrophy of the R.E. cells, which often contain malaria pigment, atrophy of the Malpighian bodies and lymphoid tissue generally and extensive fibrosis.

*Symptoms.*—The natural history of malaria in the untreated or ineffectively treated patient includes (i) an incubation period during the later stages of which mild premonitory symptoms may appear, (ii) a stage of primary fever which if the patient

survives is followed by (iii) a period of latency in which demonstrable parasites are generally absent but in which subinoculations of blood may be positive, (iv) a stage of recrudescence, relapse or recurrence.

### (i) INCUBATION PERIOD

In experimentally infected volunteers the average incubation period is 10 days in M.T. and 12 days in B.T. malaria, but variations occur and in natural infections the period may vary from 8 to 23 days. In quartan malaria it is often longer. Occasionally in B.T. infection the primary fever may be suppressed and the incubation period extended to as long as 9 months; this may also happen in individuals taking suppressive antimalaria drugs at the time of infection.

*Premonitory symptoms.*—When thick films are carefully examined the average time for parasites to be found microscopically in experimentally infected volunteers is 9½ days with *P. falciparum* and 12 days with *P. vivax*. For some 3 days previously, however, in heavy infections minor clinical features such as transient headache, backache and generalised aches and pains may be experienced while tenderness of the liver and slight rises of temperature (99° F.) are not uncommon. Though microscopical examination at this early stage generally reveals no parasites, subinoculations of the blood invariably prove positive on the seventh day in M.T. and on the ninth day in B.T. malaria; certain characteristic hæmatological changes also begin to appear, namely, a decrease in lymphocytes and segmented polymorphonuclear leucocytes leading to a leucopenia and later a left polymorphonuclear shift due to an increase in the non-segmented leucocytes. These premonitory minor features may also appear after exposure to heavy infection in volunteers who are taking schizonticidal drugs like mepacrine regularly, as well as in those who are receiving no anti-malarial suppressive drug; in the latter, however, these features are not transient, but increase in intensity until an overt attack of malaria with major symptoms and demonstrable parasites supervenes. In natural infections which are generally lighter than in experimentally infected volunteers these premonitory symptoms are less frequently encountered.

### (ii) PRIMARY FEVER

At the onset of primary fever, parasites are often very scanty and may only be found after prolonged search. The onset of fever is undoubtedly related to segmentation, but it is not dependent exclusively on parasite density; while some pyrogenic substance may be directly responsible, variable host reaction is an important factor. There is often an initial period of continuous, remittent or intermittent fever which lasts a variable period. Intermittent fever generally becomes established at an earlier stage in B.T. than in M.T. primary fever, and though the temperature may be quotidian at first it later becomes tertian in type. Occasionally, the primary B.T. fever may be tertian at onset and quotidian later. Untreated B.T. patients may have intermittent fever every day for many weeks before spontaneous remission occurs, and a tertian periodicity may only be established in recrudescences or relapses. In quartan malaria, which particularly affects children, a quartan periodicity tends to be established early, even in primary fever, and in untreated individuals typical paroxysms of ague may persist for many months before the latent phase becomes established. If there are interpolated attacks due to multiple strains, a double or triple quartan chart may ensue; the last is associated with quotidian fever.

In the ordinary septicæmic type, the onset is either sudden or insidious, with prodromal symptoms, such as tiredness, stiffness of the neck muscles, pains in the muscles and bones and anorexia. Fever, when it appears, is generally associated with headache, backache, aching pains in the bones, malaise and fatigue. Shivering

is often absent, especially in M.T. infections, while nausea, anorexia and vomiting are common.

The spleen though always increased in size is frequently not palpable in the early stages of the disease; later, it is felt as a tender soft mass below the left costal margin, moving on respiration. Splenic pain may be troublesome. The liver is often demonstrably enlarged earlier than the spleen in primary malaria; it is frequently tender and its edge may be palpated below the right costal margin moving with respiration. The gall-bladder may also be distended later, though this is rarely demonstrable. Herpes on the lips and face is common and should suggest the possibility of malaria. Mild bronchitis is another suggestive sign, while abdominal pain, constipation or diarrhoea are not infrequent. If treatment be delayed signs of blood destruction develop; they include (1) anæmia, (2) hæmolytic jaundice, (3) polycholia with bilious vomiting and chocolate-coloured stools and (4) brown urine due to urobilinuria.

Prior to the spleen becoming palpable, influenza, dengue, sand-fly fever, scrub typhus or enterica may be suspected. After the spleen is demonstrably enlarged diseases associated with splenomegaly, such as typhoid, paratyphoid, undulant fever, relapsing fever, kala-azar and trypanosomiasis need differentiation. Amœbic abscess, cholecystitis, pyelitis, subacute bacterial endocarditis or occult sepsis may simulate malaria. In bacterial infections there is often a polymorphonuclear leucocytosis and the febrile attack comes on later in the afternoon or evening than is customary in malaria. When jaundice complicates the picture infectious hepatitis, yellow fever and leptospirosis may need differentiation. So-called typho-malaria may occasionally develop. Here the temperature chart, splenomegaly, hæmorrhage from the bowel or epistaxis and the development of the so-called "typhoid state" with low muttering delirium may suggest typhoid until parasites are found in the blood. Blood cultures should invariably be made to exclude enterica in such cases, as malaria and typhoid may occur together.

Bilious remittent fever is a well-recognised type, characterised by remittent fever, epigastric discomfort, bilious vomiting, chocolate-coloured stools and urobilinuria. The spleen and liver are both enlarged and tender, and the skin and scleræ show icterus. The jaundice may be caused by excessive blood destruction or by toxic degeneration of hepatic cells; in the latter case bile pigment and/or bile salts appear in the urine. Bilious remittent fever may be a manifestation of primary or recrudescing M.T. infection.

*Acute pernicious malaria.*—Apart from the general septicæmic features induced by parasitæmia, and the anæmia and jaundice resulting from blood destruction, there are a number of manifestations classified as acute pernicious malaria, which are mainly dependent on internal sporulation and localised blockage of the capillaries by *P. falciparum* in different organs, such as the brain, heart, intestines and spleen by parasitised corpuscles, which adhere to one another and to the capillary endothelium. This phenomenon is peculiar to *P. falciparum* infections, and is chiefly responsible for the diverse symptomatology of M.T. malaria. Its onset may be suspected if hyperinfection be present. Hyperinfection is diagnosed if more than 5 per cent. of erythrocytes are infected, if more than 5 per cent. of infected corpuscles contain 2 or more parasites, and if pigmented asexual forms of *P. falciparum* are demonstrable in blood films. In extreme cases, 30 per cent. of the corpuscles may show parasites. The chief forms of acute pernicious malaria are as follows:

1. *Cerebral.*—Such patients may develop coma, convulsions, paraplegia, hemiplegia, aphasia, meningismus or hyperpyrexia. Cerebrospinal fever may be suspected, or the condition be diagnosed as primary heat stroke. The coma may come on rapidly, or be preceded by drowsiness and stupor. In some instances there is great excitability and maniacal and suicidal tendencies may develop; alcoholism or lunacy may be diagnosed with disastrous results. Generally the face is suffused, the

pupils contracted and the reflexes modified; increased deep reflexes and extensor plantar responses are common. Malaria coma has to be distinguished from cerebral and pontine hæmorrhage, uræmia, diabetic coma and alcoholic or opium poisoning. The blood always contains parasites. Lumbar puncture shows a clear fluid perhaps under increased pressure; a pleocytosis may be found, especially if meningeal symptoms are present.

2. *Algid*.—The patient presents the picture of severe shock and peripheral circulation failure. There is a Hippocratic facies, the skin is cold and covered with clammy sweat, the respirations shallow, the pulse rapid, thready and weak and the blood pressure very low. Vomiting, diarrhoea and epigastric pain are not uncommon. Though the skin temperature is low the internal temperature is often high. Parasites are plentiful in the peripheral blood smears.

3. *Cardiac*.—There is breathlessness, cyanosis, congestive failure and sometimes sudden death. Degenerative myocardial changes and blocked capillaries are the basis of the syndrome.

4. *Gastro-intestinal*.—In gastric malaria there is epigastric discomfort and tenderness, severe bilious vomiting and occasionally hæmatemesis. Gastric ulcer may be diagnosed. In the small intestinal type, cholera may be simulated but the fluid stools are brown, not colourless. Where the large bowel is involved the stools may contain blood with or without clear mucus; the mucus, however, does not contain cellular exudate, and sigmoidoscopy fails to show ulceration though congestion and small mucosal hæmorrhages may be observed. Occasionally large hæmorrhages occur. Bacillary dysentery or intussusception may be erroneously diagnosed.

5. *Abdominal*.—Abdominal discomfort and pain are not infrequent in primary M.T. malaria. If associated with vomiting and tenderness over the liver, gall-bladder, epigastrium or cæcum, an erroneous diagnosis of cholecystitis, gastric ulcer, pancreatitis or appendicitis may be made. In malarious areas a careful blood examination should invariably precede any abdominal operation; only by so doing can serious mistakes be avoided.

6. *Purpuric*.—Petechial or purpuric skin eruptions, epistaxis, hæmatemesia, hæmoptysis, melæna, hæmaturia or vaginal hæmorrhages are occasionally encountered.

7. *Renal*.—Albuminuria is common, and in severe infections may be associated with renal casts and red blood cells in the urine.

It is to be noted that acute pernicious malaria may also occur in M.T. recrudescences as well as in primary fever. If the patient survives the primary attack and has not been cured, a period of latency supervenes.

### (iii) PERIOD OF LATENCY

Fever and clinical symptoms are absent, though enlargement of the spleen may be found. Though parasites cannot be demonstrated even in thick films, malaria fever results in M.T. infection when blood is subinoculated into a susceptible individual, but subinoculations are frequently negative in B.T. infections. All available evidence indicates that this is due to the persistence of secondary exo-erythrocytic forms in B.T. which are absent in M.T. malaria. Persons with latent M.T. malaria are always unsuitable donors for blood transfusion, while those with latent B.T. infection occasionally transmit malaria to the recipients. If the latently infected individual be injected with blood containing his own strain of parasites, malaria fever and parasites fail to develop (premunition; premunity); but if he be injected with another strain of the same species or with another species of *Plasmodium*, a typical attack of malaria results. This specificity is probably dependant on specific opsonins, which prepare parasitised cells for phagocytosis by hypertrophied R.E. cells and macrophages. This phase of latency—especially in B.T. and quartan malaria—may

last from many weeks to many months before fever reappears. Certain factors such as chill, wetting, exposure, exhaustion, blood loss, anæsthetics, surgical trauma and high-altitude flying (anoxia), may upset the biological balance between host and the parasites and induce recrudescence or relapse.

#### (iv) RECRUDESCENCES AND RELAPSES

This stage is characterised by periodic intermittent fever and typical ague attacks with cold, hot and sweating stages. In M.T. and B.T. malaria pyrexia occurs on alternate days, in quartan fever every fourth day. Onset of fever is generally in the morning or early afternoon.

In *M.T. malaria*, pyrexia generally recurs in from 1 to 6 weeks, and under these circumstances is classified as a recrudescence rather than a relapse. The fever, which at onset may be quotidian in type, soon establishes tertian periodicity. The temperature rises less abruptly and is generally lower than in B.T. ague, and chilliness rather than a rigor is characteristic. The hot stage tends to be more prolonged and the sweating stages less intense, while paroxysms last longer, *i.e.* 12 to 24 hours. Fatigue, backache, headache, pains in the limbs, anorexia, nausea and vomiting, which may be bilious in type, are common. If the fever is uncontrolled by treatment the spleen becomes rapidly enlarged and tender, and hepatomegaly, hæmolytic anæmia and perhaps jaundice develop. Unless the individual has been taking an antimalarial drug for suppressive purposes, parasites are readily demonstrated in recrudescences even at the beginning of fever; as in primary fever hyperinfection and acute pernicious manifestations may develop with fatal results. Unless cured, liability to relapse persists for about 6 months.

In *B.T. malaria*, a longer period generally intervenes between primary fever and secondary attacks, *i.e.* relapses rather than recrudescences are the rule. With some strains of *P. vivax*, however, secondary attacks supervene some 4 to 6 weeks after the primary fever. They are characterised by typical attacks of tertian ague similar to those in the primary attack.

**Cold stage.**—The patient feels listless and develops headache, backache, pains in the limbs and chilliness. Then the rigor begins. He lies curled up in bed with chattering teeth, shivering violently. The face is pinched and the skin cold and blue. Blankets and rugs are applied in an effort to keep warm. Nausea and vomiting are not uncommon. After  $\frac{1}{2}$  to 2 hours the axillary temperature rises rapidly, attaining a height of 103° to 106° F.

**Hot stage.**—The skin becomes burning hot and bedclothes are discarded. Fever is now high, the face is flushed, the pulse is rapid, the carotids throb and the head aches. In severe cases delirium may develop. This stage persists for 8 to 10 hours.

**Sweating stage.**—The skin now moistens, profuse sweating ensues, pains and headaches disappear, the pulse slows, the tongue becomes moist, the temperature falls, slowly at first and then more rapidly, until a normal or subnormal level is reached. At the end of the attack the patient feels reasonably well.

Splenomegaly, anæmia and herpes are characteristic of recurrences, especially if fever is not early controlled by treatment. Usually relapses tend to get milder, with progressively longer intervals between. Liability to relapse may persist for 2 to 3 years.

In *Quartan malaria* relapses, the paroxysm is often shorter than in B.T. ague (6 to 8 hours), and the temperature tends to be higher; temperatures of 105° to 106° F. are common. Spontaneous recoveries are few, and long periods of latency occur between relapses. Infections may persist for 7 years or longer, while solid premunity is rarely established.

**Malaria cachexia.**—In old-standing cases, especially if there are repeated infections with different strains and species of parasite and inadequate treatment, the spleen

becomes stony hard and very enlarged, and perisplenitis may give rise to severe splenic pain and discomfort. Cachexia, anaemia, a dirty earthy-coloured skin, digestive disturbances, enlargement of the liver, physical inertia, oedema of the feet and ankles, deterioration of memory and lack of concentration may develop. There may be long intervals of apyrexia or subnormal temperature, but transient bouts of fever may occur in which parasites are demonstrable in the blood for a short time only.

The clinical picture at this stage is often complicated by the effects of dietary deficiency. Thus, (1) hæmolytic macrocytic anaemia may follow lack of good biological protein and possibly vitamin B complex as in Macedonia, (2) microcytic hypochromic anaemia occurs if there is lack of iron in the diet, as in parts of India; ankylostomiasis here may also be a complicatory factor, and (3) neuritic manifestations may follow deficiency in B<sub>1</sub>.

**Complications and Sequelæ.**—Complications include herpes of the lips, nose, eyelids and cornea, supraorbital neuralgia, anaemia, malaria hepatitis, pigment gallstones, nephritis, with or without oedema and ascites (especially encountered in quartan infections in childhood), abortion and premature birth. Ocular complications include conjunctival hæmorrhage, corneal ulceration, keratitis, iritis, choroiditis, retinal hæmorrhages, optic neuritis and malaria amblyopia. Dendritic corneal ulcers are the most common ocular complication, the lesions being generally superficial, seldom penetrating into the deeper corneal layers. The mild lesions clear up in 2 to 4 weeks, the more severe taking months to heal. They frequently develop from herpetic lesions but may also arise without previous corneal involvement. Malarial amblyopia may follow cerebral malaria; the disks are a cherry-pink colour with blurred edges, in contrast to the pale or white disks observed in quinine amblyopia. Retinal hæmorrhages may also follow cerebral malaria, but they are most commonly associated with severe anaemia. Agranulocytosis and purpuric manifestations with petechial hæmorrhages into the skin occasionally develop.

Splenic complications include (1) perisplenitis, (2) subcapsular hæmatoma, (3) rupture and (4) torsion of the pedicle. Rupture of the spleen is an important complication which may occur in either acute or chronic malaria. It may occur spontaneously or follow trauma or such acts as sneezing or straining at stool. The onset may be sudden or gradual; in the latter case a small tear may lead to a subcapsular hæmatoma which may rupture later. Tears generally occur on the visceral side close to the hilum. A subcapsular hæmorrhage may be associated with severe splenic pain, and if a subcapsular hæmatoma impinges on the diaphragm it may produce (1) left shoulder pain, (2) splinting or elevation of the left diaphragmatic leaf and (3) evidence of collapse or consolidation involving the lower lobe of the left lung. When rupture occurs through the capsule into the peritoneal cavity there is local evidence of splenic and peritoneal involvement combined with symptoms of internal hæmorrhage. In cases with chronic malarial splenomegaly ("ague cake spleen"), dislocation of the spleen or torsion of its pedicle may occur. Both rupture of the spleen and twisting of the pedicle necessitate immediate operation, but subcapsular hæmorrhage may be treated conservatively by medical means.

The most important sequela of malaria amongst Europeans in the tropics is black-water fever, which is described separately.

Certain mental conditions, including psychoses, aphasia, sexual impotence and loss of memory, have been described as sequelæ of long-continued malaria. Many of these are undoubtedly functional in origin, and associated with the mental stresses or strains of life in the tropics.

**Diagnosis.**—Malaria is an arch simulator, and in acute pernicious malaria or primary fever before periodicity has become established, and splenomegaly and anaemia have developed, a certain diagnosis can only be made by demonstrating parasites. Owing to the absence or scarcity of demonstrable parasites in the early stages, thick as well as thin blood films should be examined, and several examinations should



be made before malaria can be excluded. Antimalarial drugs should never be administered before collecting the specimen. If patients have been taking mepacrine or quinine for suppressive purposes, the difficulty in finding parasites is further increased. When acute pernicious malaria is suspected it is better to take blood films and commence treatment without waiting for the laboratory report.

Outstanding considerations in making a diagnosis are: (1) Blood examination for parasites. Polychromasia, a leucopenia with a left shift and a decrease in lymphocytes and neutrophils are suggestive of malaria infection. (2) Febrile attacks of typical ague having a tertian or quartan periodicity. (3) Demonstrable enlargement and tenderness of the spleen and/or liver. (4) Evidence of blood destruction, including anæmia, hæmolytic jaundice and urobilinuria. (5) Herpes on the lips and face. (6) The therapeutic test. It is very rare to find uncomplicated primary malaria fever persist for more than 4 or 5 days after adequate specific drug therapy has been instituted.

In the tropics the differential diagnosis largely depends on geographical considerations and what fevers are prevalent at the time. As the subject has already received detailed consideration in the section on Symptoms, it need not be further commented on here.

**Prognosis.**—Malaria is the chief cause of death in the tropics, being specially serious (1) in pregnancy causing abortion, premature birth and possibly death of the mother, (2) in infants and young children and non-immune Europeans before premunity has developed and (3) in the aged. In M.T. infections the prognosis is dependent on early diagnosis, and the speed with which appropriate treatment is instituted. Hyperinfection, with or without coma or cardiac failure, accounts for most deaths. Blackwater fever or rupture of the spleen may also prove fatal. Death in B.T. and quartan malaria is generally associated with rupture of the spleen or intercurrent diseases, e.g. pneumonia, dysentery, ankylostomiasis and anæmia, or malnutrition or pregnancy. In the absence of specific drug treatment, M.T. infections are frequently fatal, while those showing acute pernicious manifestations invariably die. The death-rate with appropriate treatment should be low. In troops infected while fighting in hyperendemic areas in New Guinea, not more than 1 in 2500 died of uncomplicated malaria; this was especially remarkable, as they practically all suffered from M.T. malaria and many had B.T. infections as well.

**Treatment.**—**PROPHYLACTIC.**—Tropical residents should live in mosquito-screened houses whenever possible, or use mosquito nets at night. Immediate destruction of adult vectors by the use of a spray containing pyrethrum and D.D.T. is important. Residual spraying of bungalows and huts with a 5 per cent. solution of D.D.T. in kerosene is of the greatest value. After sunset appropriate clothing should be worn, including mosquito boots or some form of ankle protection, while a mosquito repellent such as dimethylphthalate should be applied as a lotion or cream to exposed parts.

**Suppressive drug treatment.**—Quinine in a dosage of gr. 5 to 10 daily may suppress B.T. or M.T. infections, but in hyperendemic areas it often fails to suppress heavy infections with certain strains of *P. falciparum*. The failure of quinine in suppressive dosage to eradicate infections with *P. falciparum*, and its tendency to induce a state of chronic latent or relapsing M.T. malaria which is essential for the development of blackwater fever, afford adequate reasons for not using it as a suppressive drug. Mepacrine in a dosage of 0.1 g. daily is definitely superior to quinine in these respects, since it suppresses B.T. infections completely, and suppresses and generally radically cures M.T. infections, provided the daily dosage can be continued for 4 weeks after leaving the malarious area. Chloroquine diphosphate (Aralen) has a similar action to mepacrine but is given in a single dose of 2 tablets, i.e. 0.5 g. once a week; unlike mepacrine it does not discolour the skin. Subinoculation experiments in experimentally infected volunteers while taking mepacrine and chloroquine show

that M.T. and B.T. parasites appear in the blood at the usual time, but that if the drug is present in adequate concentrations, the asexual parasites are destroyed; neither drug has any action on pre-erythrocytic parasites (Fairley). Other chloroquine salts are obtainable, such as the sulphate (Nivaquine). The adult dosage is the same, i.e., 2 tablets once weekly.

Proguanil (Paludrine) is probably the best suppressive drug; in non-toxic dosage it is a true causal prophylactic in M.T. malaria. It inhibits the production of asexual parasites from pre-erythrocytic forms in B.T. infections while the drug is being taken (partial causal prophylactic) and in addition it has a schizonticidal action on asexual parasites. Its administration need not be commenced until 24 hours before arrival in a malarious area. The dosage advised each day is 100 mg. for adults, 50 mg. for children of 6 to 12 years of age and 25 mg. for those under 5 years and infants. Daily administration is recommended for non-immunes, not because it is essential, but because it is more readily remembered. Experimental evidence indicates that 1 tablet (100 mg.) if invariably taken once every 3 days would suffice to prevent falciparum infections and effectively suppress vivax infections. Alternatively, a single dose of 0.3 g. may be given on the same day once a week, but owing to the long interval between successive doses not all pre-erythrocytic forms will be destroyed by this regimen and asexual parasites will sometimes gain access to the blood. Under these circumstances subsequent suppression and cure will depend on the schizonticidal action of proguanil. This weekly regimen is particularly useful in native labour groups with some degree of premunity and where its regular administration can be supervised.

It has been shown recently that drug resistance may appear in certain areas. Where this is suspected proguanil should be stopped and mepacrine or chloroquine substituted.

Pyrimethamine (Daraprim) has been shown to have an action similar to that of proguanil. It may be given in doses of 25 mg. (1 tablet) once weekly in adults and half this dose in children of 6 to 12 years. Unfortunately, cross-resistance has been shown between this drug and proguanil, so that where proguanil resistance is suspected, pyrimethamine should be withdrawn and mepacrine or chloroquine substituted.

**CURATIVE.**—The best-known antimalarial drugs are quinine, mepacrine, pamaquin, chloroquine and proguanil. Arsenic compounds have distinct therapeutic action on the schizonts and gametocytes of *P. vivax*. Not all strains of malaria parasites of a given species, necessarily respond therapeutically to the same dosage of a given antimalaria drug, and for this reason the optimum dosage and the particular course of treatment may need to be varied within limits in different geographical areas. Antimalaria drugs in tablet form are best administered with a copious draught of water after food.

**Quinine.**—This is a crystallisable alkaloid obtained from cinchona bark; chemically it is a quinoline compound of complex molecular structure which has recently been synthesised. Various salts are available, the insoluble sulphate and the soluble bishydrochloride being mainly used. Quinine exerts schizonticidal action on all human species of plasmodia, and is gametocidal for all except *P. falciparum*. Regarding dosage, opinions differ, but in primary malaria if quinine is used alone it is sound therapy to give gr. 30 of the bisulphate for 10 days and gr. 20 for the next 10 days. The drug is best given in a mixture in  $\frac{1}{2}$ -oz. doses as follows: Quinine sulph. gr. 10; Acid sulph. dil. m. 10; Syr. simplex dr. 1; Aq. chlorof. ad. oz.  $\frac{1}{2}$ . If vomited, the dosage should be repeated. Children bear quinine well, the dosage being appropriate to age. Toxic effects such as tinnitus, deafness, gastric and visual disturbances including amblyopia may develop. Idiosyncrasy may result in severe erythematous and urticarial rashes. The administration of quinine even in therapeutic dosage does not precipitate blackwater fever in recent malaria infections; there is general agreement, however, that there is some relationship between its administration and the

onset of blackwater fever in patients suffering from chronic recurrent or latent malignant tertian infections, especially where they have been irregular quinine takers. For this reason and also because they are more potent schizonticides, mepacrine or chloroquine possess certain advantages for therapeutic use.

**Mepacrine (Atebrin; quinacrine).**—Mepacrine hydrochloride is a synthetic acridine derivative which compares very favourably with quinine; it is a good schizonticidal drug and destroys the gametocytes of *P. vivax* and *P. malariae*, but not of *P. falciparum*. The following course is suitable for the treatment of non-immune adults. During the first 24 hours an initial dose of 0.2 g. of mepacrine should be given, followed by 0.2 g. at 6-hourly intervals (total = 0.8 g.). On the second day 0.2 g. is given thrice daily, and for the next 4 days the dosage is 0.1 g. thrice daily (total course = 2.6 g.). A maintenance dose of 1 tablet (0.1 g.) daily should be taken for 1 month to ensure radical cure. Mild gastro-intestinal symptoms including nausea, abdominal discomfort and vomiting may occasionally occur, but real idiosyncrasy is very rare. Harmless and transient yellow staining of the skin may follow. With this dosage, toxic nervous features are not observed in healthy adults but if it be increased to a total of 2.0 g. in the first 48 hours occasionally toxic psychoses or transient convulsions may result. In individuals who are taking mepacrine (0.1 g. daily) for suppressive purposes over long periods, a lichen planus-like eruption occasionally develops; once this happens the drug should not be given again.

**Pamaquin (plasmoquin).**—This is an 8-amino quinoline derivative synthesised by Schuleman, and which can destroy M.T. gametocytes but has practically no effect on the schizonts of *P. falciparum*; in B.T. and quartan infections it exerts lethal effects on both schizonts and gametocytes and in many cases on the EE forms. As a gametocide, 1 tablet of pamaquin naphthoate, that is, 23 mg. of the salt (*i.e.*, 10 mg. of base) or 18 mg. of the salt (*i.e.*, 8 mg. of base), is very effective when given thrice daily for 3 days. Pamaquin is also very valuable when used in conjunction with quinine, proguanil or chloroquine in producing radical cure of B.T. malaria.

Dosage régimes are: Quinine gr. 10, pamaquin 8 to 10 mg. base, given three times a day concurrently. Proguanil 100 mg. may be substituted for quinine. The treatment is continued for 10 days, during which the patient should be kept in bed and encouraged to drink plenty of fluid.

Headache, colicky abdominal pain and cyanosis due to methæmoglobincythæmia may follow pamaquin administration. Pamaquin hæmoglobinuria is a rare complication which has to be differentiated from blackwater fever in which no methæmoglobin is found within the corpuscles.

Other 8-amino quinolines recently introduced are pentaquine, iso-pentaquine and primaquine. The action and dosage of these drugs are similar to those of pamaquin. Primaquine is regarded as the most active and least toxic, and is given in doses of 15 mg. daily together with a schizonticide as above.

Mepacrine should not be used in conjunction with the 8-amino quinolines.

**Chloroquine diphosphate (Aralen).**—This is a 4-amino quinoline compound which is colourless and does not discolour the skin. It is rapidly and almost completely absorbed, produces a high blood concentration, is stored in the internal organs such as the liver, spleen and kidneys and is excreted slowly—at about the rate of 60 per cent. per week after drug administration ceases. It has a similar antimalaria action to mepacrine, being an excellent schizonticide and a good suppressant; it exerts no causal prophylactic effect in M.T. or B.T. malaria, nor has it any direct action on M.T. gametocytes.

It produces rapid clinical cure and often radical cure in M.T. malaria and effectively controls the acute febrile attack in B.T. infections but does not prevent vivax relapses. For treatment of overt attacks a total course of 2.5 g. is advised, 6 tablets on the first day and 2 tablets on the second and third days. Each tablet of Aralen contains 0.25 g. of chloroquine diphosphate (= 0.15 g. of base). Toxic symptoms

include mild and transient headache, visual disturbances such as blurred vision and difficulty in focusing, pruritus and gastro-intestinal complaints. As with mepacrine, lichen planus-like lesions occasionally supervene after prolonged administration for suppressive purposes. Other 4-amino quinolines such as camoquin are also successful. The sulphate of chloroquine (Nivaquine) is now commonly used. Tablets contain 0.15 g. of the base and are given in the same dosage as the diphosphate.

*Proguanil (Paludrine hydrochloride).*—This is a biguanide, discovered by Curd, Davey and Rose in 1944, which has a wide range of action on different phases of the malaria parasite. It is rapidly and almost completely absorbed reaching a peak concentration in about 3 hours. Excretion of the drug is more rapid than with mepacrine or chloroquine, and even with a dosage of 1.0 g. daily the blood concentration falls below assayable level 7 days after its administration ceases, while it cannot be detected in the urine after 9 days. It acts as a true causal prophylactic in infections with Pacific, Asian, American and also African strains of *P. falciparum*, exerting a highly selective action on the pre-erythrocytic forms and is an effective suppressant for B.T. malaria when given in appropriate dosage. For the treatment of overt attacks of M.T., B.T. or quartan malaria in semi-immune subjects in malarious areas such as labour forces and rural populations, a single dose of 300 mg. of proguanil will usually suffice to produce clinical cure. Such treatment should cause a minimal degree of interference with premunity, is readily carried out and is satisfactory economically.

Overt attacks of B.T. malaria in non-immunes are clinically cured by a course of proguanil but relapses generally follow later. With the object of attaining radical cure in adults, 100 mg. of proguanil, and 10 mg. of pamaquin base or 20 mg. of pentaquine base, is given thrice daily for 12 days. Bed rest is essential during this treatment. If this is not feasible and relapses are troublesome, an alternative course is 100 mg. of proguanil thrice daily for 10 days, followed by a single dose of 300 mg. of proguanil on the same day each week for 1 year.

Variable results have been obtained in the proguanil treatment of overt M.T. attacks in non-immunes in different countries, and the schizonticidal action of the drug appears to vary considerably with different strains of *P. falciparum* in regard to radical cure rate. For this reason, and because the clinical response is slower in M.T., B.T. and quartan malaria than with other schizonticides like quinine, mepacrine or chloroquine, it appears advisable to reinforce proguanil with mepacrine or chloroquine for the first day or two of treatment. A 10-day course of treatment with proguanil, 0.2 g. thrice daily, reinforced with 0.3 g. of mepacrine thrice daily on the first day of treatment only, has been advocated by Covell, Nichol and Shute on the grounds that there is a rapid clinical response, absence of relapses over a 3-monthly period and sterilisation of gametocytes. In strains, such as the Lagos strain, which are less susceptible to the schizonticidal action of proguanil it is essential that radical cure of the overt attack should be attained; this is especially necessary in malarious areas where proguanil prophylaxis is in force for otherwise further overt attacks may be wrongly attributed to fresh infections when they are really recrudescences of the original infection in which parasitaemia had persisted in a submicroscopic density after the original clinical symptoms had temporarily disappeared.

Proguanil does not destroy M.T. or B.T. gametocytes in the human carrier, but it prevents the development of the sexual cycle in the stomach of the mosquito vector provided it is present in the imbibed blood—even in minute quantity. This effect is evident within 3 hours of administering 0.15 g. to a human carrier, and may persist after the blood concentration is too low to be estimated. Toxic manifestations are very rare with the ordinary therapeutic dosage; with larger doses such as 0.5 g. twice daily epigastric discomfort, vomiting and diarrhoea are occasionally noted and transient haematuria has been very rarely recorded. Large doses should be given with a copious draught of water after food.

*General treatment.*—Rest in bed is essential during the febrile period, and is advisable for 3 days after the temperature reaches normal, or longer in cases with primary M.T. fever. A suitable aperient, such as magnesium or sodium sulphate, is administered at the onset of fever and should be repeated if necessary. During an attack of ague, hot drinks and plenty of blankets are necessary in the cold stage. Cold drinks, an ice cap and an aspirin-phenacetin mixture decrease discomfort in the hot stage. When the temperature exceeds 104° F. tepid sponging is indicated. Drinks should be sweetened with sugar (4 oz. daily). In the sweating stage, hot drinks are indicated, and bedclothes and pyjamas require changing. During convalescence, a well-balanced diet is essential. A tonic pill containing iron (Ferri. sulph. gr. 3) is advisable thrice daily should there be anæmia, and, if it be severe, blood transfusion will accelerate convalescence. When malaria is the cause of anæmia, administration of antimalarial drugs is followed by a specific reticulocytosis reaching a maximum some 7 to 10 days later and, provided that the diet is well balanced and adequate in vitamins and blood-forming constituents, blood regeneration is generally rapid.

*Treatment of ordinary overt attacks.*—As described above there is a choice of several different courses of treatment with quinine, mepacrine, chloroquine or proguanil; any one of these generally produces clinical cure of overt attacks of M.T., B.T. or quartan malaria. Intensive quinine treatment (gr. 30 daily) if continued for 3 weeks generally results in the radical cure of primary malignant tertian malaria. The use of quinine therapeutically in chronic recurrent or latent malignant tertian malaria is questionable owing to the possible precipitation of blackwater fever. The highest proportion of radical cures in M.T. malaria is probably obtained by intensive treatment with chloroquine or mepacrine; with mepacrine at least the duration as well as the intensity of drug administration is important. Though proguanil is effective in the radical cure of some strains of M.T. malaria (New Guinea strain) it fails with others (Lagos strain); for reasons already stated when treating overt M.T. malaria with proguanil it is better to combine it with mepacrine in the initial stages.

For the radical cure of B.T. malaria it is advisable to give one of the 8-amino quinoline compounds like pamaquin or primaquine with quinine or proguanil. The usual course advocated consists of quinine sulphate (gr. 10) with 0.008 to 0.010 g. pamaquin base thrice daily after food for 10 days (Sinton). Each standard tablet contains either 0.018 or 0.023 g. pamaquin naphthoate (0.008 or 0.010 g. base respectively); 3 are administered daily. Primaquine is said to be somewhat less toxic than pamaquin and a combination of quinine hydrochloride (gr. 10), t.d.s., and primaquine base (total daily dose of 0.015 g.) daily for 10 days gives excellent results. Patients should be kept in bed under strict medical supervision during such treatment. The dosage with children should be reduced in accordance with age and body-weight.

*Treatment of acute pernicious malaria.*—In all cases of hyperinfection or with clinical manifestations suggesting acute pernicious malaria or where a patient is vomiting excessively or cannot swallow, intravenous injections of quinine bihydrochloride (0.3 g.) should be given without delay. These injections can be repeated in 4 to 6 hours' time if necessary. As soon as possible the oral administration of quinine, mepacrine, chloroquine or proguanil in appropriate dosage should be commenced.

Intravenous quinine therapy is often a life-saving procedure. The injection consists of gr. 10 of quinine bihydrochloride in 10 ml. or more of isotonic saline solution. Precautions to be observed are (1) sterility of the solution, (2) adequate dilution and (3) slow injection. At least 3 minutes should be taken, the reason being that too rapid injection may lead to lowering of blood pressure and occasionally to collapse. Adrenaline, however, should never be employed with the idea of preventing a fall in blood pressure.

Aseptic venous thromboses not infrequently follow such injections of quinine dihydrochloride but they are harmless and call for no treatment. No fatal results were recorded in many thousands of intravenous injections of quinine given to troops in New Guinea. Intramuscular injections of quinine should be reserved for those cases in which it is impossible to use the intravenous route. Though effective therapeutically, such injections are often painful, cause muscle necrosis and may result in a chemical or bacterial abscess. In young children or adults in whom intravenous injection is difficult, quinine can be given intramuscularly.

Mepacrine hydrochloride and Atebrin musonate can be used for intramuscular injection in a dosage of 0.3 g. and 0.375 g. respectively, and such injections may be repeated in 6 hours where necessary. Indications for their use are similar to those for intravenous quinine therapy; they should be replaced by oral medication with mepacrine or one of the other schizonticidal drugs as soon as possible. A total dosage of 1.0 g. of mepacrine should not be exceeded in the first 24 hours of treatment. Chloroquine has been successfully used parenterally in solutions of the sulphate containing 40 mg. of the base per 1.0 ml. The adult dose is 5 ml., *i.e.*, 200 mg. intravenously, repeated after 8 hours if necessary.

Apart from the immediate parenteral injection of quinine dihydrochloride or mepacrine hydrochloride it is most necessary in all hyperinfections including cerebral and algid malaria to combat dehydration and to maintain an adequate blood volume by the intravenous injection of large quantities of such fluids as isotonic saline (0.85 per cent.) or glucose (5 per cent.), given by continuous drip or intermittently. When there are algid manifestations or the blood pressure is unduly low, quinine dihydrochloride should be given intravenously in a pint of one of the above solutions in the first instance or mepacrine hydrochloride (0.3 g.) intramuscularly be substituted. In cerebral malaria if the cerebrospinal fluid is under increased pressure, the withdrawal of 10 to 20 ml may prove useful. In malarial hyperpyrexia intravenous quinine should be combined with hydrotherapy as in the case of primary heat stroke. The naked patient is placed under a fan on a wire or rush mattress and covered with a sheet which is kept continually moist by spraying with ice-cold water. The rectal temperature is carefully noted and hydrotherapy stopped when it reaches 102° F.

## BLACKWATER FEVER

**Synonyms.**—Hæmoglobinuric or Melanuric Fever; Malarial Hæmoglobinuria.

**Definition.**—An acute complication of overt or latent malignant tertian malaria, characterised by one or more intravascular hæmolyses of considerable severity, hæmoglobinuria, fever, vomiting, jaundice and anaemia. Anuria followed by uræmia is a common mode of death.

**Ætiology.**—Blackwater fever occurs where malaria is hyperendemic; it has a somewhat patchy distribution in tropical Africa, India, South-East Europe (especially Macedonia), South America, South-East Asia and New Guinea. Native populations may enjoy apparent immunity, while colonists, imported natives and occasionally even visitors develop it. Children and adults are susceptible. Multiple attacks are common which suggests some individual susceptibility to the condition. The malady is most frequent in residents of 1 to 5 years' standing, but exceptionally it may supervene within 3 months. The latter cases are rare; they are generally associated with hyperinfection in which 10 to 40 per cent. of corpuscles may be parasitised and probably originate as a direct parasitic effect on the corpuscle, such as occurs in monkeys infected with *P. knowlesi*. By far the majority of patients with blackwater fever, however, fall into a different category; parasites are either scanty or present in usual numbers at the onset of the attack and there is a history of chronic malaria, often associated with irregular quinine intake.

The chief precipitating factor is the administration of quinine to a patient suffering from an ordinary attack of malaria fever. Mepacrine and proguanil appear to have less tendency to precipitate blackwater fever than quinine, possibly because they more frequently produce radical cure of M.T. infections. Where hæmoglobinuria follows pamaquin administration, there is generally an associated methæmoglobin-cythæmia; under such circumstances the condition is really one of pamaquin hæmoglobinuria due to idiosyncrasy or hypersensitivity to the drug.

At the onset of the attack blood examination may reveal parasites of *P. falciparum*, while in others *P. vivax*, *P. malariae* or *P. ovale* may be found; even so, the available evidence entirely supports the view that to develop true blackwater fever a patient must be suffering from a latent or an overt infection with *P. falciparum*.

Various theories, none of them very convincing, have been put forward to explain the hæmolysis. Some have ascribed it to a biological hæmolysin, and others think it may have an anaphylactic origin. Recently it has been suggested that red cells, modified by the malaria parasite and the administration of an antimalaria drug, form an autoantigen; this stimulates the formation of an autohæmolysin which causes intravascular hæmolysis (Gear). Prehæmolytic swelling of the corpuscle has been demonstrated in attacks of hæmoglobinuria induced experimentally by giving quinine to a patient of blackwater fever diathesis suffering from M.T. malaria; after cure by mepacrine quinine administration no longer produced hæmoglobinuria.

**Pathology.—Morbidity anatomy.**—The skin is jaundiced, the blood watery and the serum sometimes tinged with hæmoglobin. The liver is enlarged and soft, the bile thick and tarry, the spleen big and its pulp almost diffuent, and the kidneys are dark, swollen and congested. Microscopically, hæmosiderin is found in the liver and spleen, in which malarial pigment (hæmatin) may also be evident. Eosinophilic granular debris blocks a variable proportion of the renal tubules, and there is toxic degeneration and desquamation of the cells of the convoluted tubules. There is cloudy swelling and necrosis of liver cells, especially in the centre of the lobule, while malarial pigment may be found in Kupffer's cells.

**Clinical pathology.**—Malarial parasites, which are present in blood smears at the beginning of the attack, generally disappear after 24 hours, and are not demonstrable at necropsy. The urine shows albumin, oxyhæmoglobin and urobilin in excess; methæmoglobin is generally also demonstrable, especially in acid urine. Bile is present only in the more severe cases, and ketones may also appear. The characteristic sediment consists of brown granular debris and granular casts. Red blood corpuscles are scanty or absent.

The plasma contains hæmoglobin and later methæmalbumin. Hyperbilirubinæmia is characteristic. The blood urea is markedly raised.

Renal failure depends on several factors, chief of which is decreased glomerular filtration. According to Maegraith and others, tissue anoxia suffices to explain the tubular lesions, while reduction or absence of glomerular filtration leads to decreased urinary flow and anuria. Severe intravascular hæmolysis results in shock and reflex spasm of the intrarenal vessels; cortical ischæmia follows, the glomeruli which are normally responsible for water secretion are by-passed and oliguria and anuria result. In other cases polyuria is marked; here interference with glomeruli responsible for water secretion must be slight and the high blood urea which is present results in increased diuresis if the fluid intake be adequate. Where anuria results, renal acidosis develops; this is associated with lowering of the  $\text{CO}_2$  combining power of the plasma, a decrease in serum calcium and an increase in the blood phosphorus. Anæmia is frequently profound, and in severe cases 50 per cent. of the corpuscles may be destroyed overnight. A study of the excretion curves of urinary hæmoglobin shows that several distinct intravascular hæmolyses may occur.

**Results of hæmoglobin disintegration.**—Hæmoglobinuria ensues whenever the concentration of the extra-corpuscular hæmoglobin exceeds the renal threshold. It

is unknown whether actual blockage of the tubules with pigmented debris follows or precedes the failure of renal secretion, but when many nephrons are blocked restoration of renal function will be correspondingly more difficult. Provided urinary secretion continues, red urine containing unchanged oxyhæmoglobin is generally found when the reaction is alkaline, whereas porter-coloured or black urine is generally passed if the reaction be acid due to the conversion of much of the oxyhæmoglobin into methæmoglobin. Part of the circulating hæmoglobin is absorbed directly by the reticulo-endothelial cells, with the production of hæmosiderin and bilirubin. The resulting hyperbilirubinæmia accounts for the hæmolytic jaundice and also for the pleocholia which is responsible for the bilious vomiting and dark-brown stools, while the absorption of surplus stercobilinogen causes urobilinuria, especially in the presence of liver damage. Finally, any residual circulating hæmoglobin is split into globin and hæm or reduced hæmatin, which is oxidised to hæmatin and unites with serum albumin to form methæmalbumin (Fairley).

**Symptoms.**—No recognisable pre-blackwater fever stage exists. The patient rightly thinks an attack of malaria is impending, for which quinine, as a rule, is taken. The onset, which generally occurs within 24 hours, but may be delayed for 1 to 2 weeks, is usually sudden, with chill and loin pain, but in mild cases red or black urine may be the first indication. A rise of temperature is almost invariable, rigor is common, and nausea, bilious vomiting and epigastric discomfort are characteristic. The urine, which may be reddish at first, generally becomes port-wine or porter coloured, presenting the characteristics described. As the condition progresses, polyuria, oliguria or anuria may develop. Within a few hours yellowish discoloration of the skin and conjunctivæ is apparent. This increases in intensity if hæmoglobinuria continues, but only in the severest cases is bile found in the urine. The pulse is rapid and of low tension at first, and the blood pressure in severe cases is markedly depressed (S/D equals 80/50) at onset, though later it rises. There may be severe headache, photophobia, great restlessness, anxiety, pallor, cold extremities and thready pulse occasioned by the rapidly developing anæmia. Hiccough and Cheyne-Stokes breathing may also develop in severe cases. As many as 2,000,000 red cells per c.mm. may be destroyed in 24 hours. The spleen and liver are generally demonstrably enlarged and tender, and may cause discomfort; the former decreases in size during the attack. Localised tenderness over the distended gall-bladder may also occur and loin pain, due to renal involvement, is common. The fever at onset resembles a malarial paroxysm, is highest at first, becomes intermittent or remittent later, and generally declines in 3 to 4 days, as the vomiting subsides and the urine clears. Post-hæmoglobinuric fever may appear after hæmoglobinuria has ceased and persist well into convalescence. Hyperpyrexia may develop, especially in the late phases of the disease, while some cases show a marked tendency to hæmorrhages in the skin and the gastro-intestinal tract.

Several different clinical types are encountered: (1) Mild hæmoglobinuria, especially common in children, in which blood pigment in the urine may only be found for a few hours and perhaps only in one or two specimens. The hæmoglobinuria associated with hyperinfection in M.T. malaria may fall into this category. (2) Severe hæmoglobinuria, associated with the clinical features already described. These are separated into two groups: (a) the polyuric type in which renal excretion is well maintained despite evidences of nitrogenous retention; and (b) the oliguric and anuric types. Catheterisation at first shows small quantities of highly albuminous, perhaps bile-stained urine, followed later by complete suppression. Anuria may set in early, and is associated with a normal or subnormal temperature. Hepatogenous jaundice may also develop. Life may be prolonged for many days, and death may occur with renal acidosis and uræmia. Toxæmic features are common in both these types. (3) Intermittent hæmoglobinuria, in which blood pigment is present in the urine from time to time, while in the intervals it disappears entirely. In these cases



the temperature may continue for some time, post-hæmoglobinuric fever is common, and icterus and anæmia are well marked.

**Complications.**—Complications include anuria, post-hæmoglobinuric fever, anæmia, retinal hæmorrhages, biliary colic, pigment calculi and cholecystitis.

**Course and Prognosis.**—About 10 per cent. of cases relapse during the course of an attack (Ross). Convalescence may be prolonged, owing to anæmia and transient renal dysfunction, but there is no evidence that chronic nephritis results. The outlook depends to a considerable extent on the rapidity of the hæmolysis and the quantity of corpuscles destroyed. The mortality rate varies from 15 to 40 per cent., and though some cases are probably doomed from the onset, in others modern therapy and good nursing favourably influence the course of the illness. Thus, in a recent series receiving large blood transfusions and alkaline medication the mortality was only 15.0 per cent. Unfavourable features include rapidly increasing jaundice, grave anæmia, severe hiccough, anuria and hyperpyrexia.

**Treatment.**—**PROPHYLACTIC.**—The prophylaxis of blackwater fever is the cure of M.T. malaria. As a result of measures designed to cure M.T. infections in troops in New Guinea, the incidence of blackwater was reduced to less than 1 per 3,000 cases of malaria. In malaria patients in whom there is a previous history of blackwater fever, abundant fluid with citrates should be given and quinine avoided; proguanil, chloroquine or mepacrine should be substituted in treating overt attacks.

**CURATIVE.**—In most cases of blackwater fever parasites are not plentiful and rapidly disappear from the blood, and therefore specific drug treatment can generally be postponed until convalescence. If, however, hæmoglobinuria follows intravenous quinine injections for hyperinfection, antimalarial drug therapy must be continued, and abundant fluid and alkalis administered. In the absence of knowledge concerning the rational control of hæmolysis in blackwater fever, the therapeutic indications are to combat anæmia and heart failure on the one hand, and renal acidosis and uræmia on the other, for these are the chief causes of death. Measures directed to these ends include absolute rest in bed, fluids by different routes, administration of alkalis and blood transfusion.

Blackwater fever patients should not be moved unless it is impossible for them to be treated where they are. Careful nursing is most important, and the patient should be kept recumbent throughout the illness. In collapsed cases with low blood pressure, early blood transfusion, warmth and elevation of the foot of the bed are advisable. The diet should consist of bland fluids, fruit juices and sweetened drinks; later, milk, fruit jellies, junket and Benger's are allowed. Copious fluids are given by mouth; they should contain sufficient sodium bicarbonate or potassium citrate to combat acidosis and alkaline the urine. Once established, the alkaline reaction should be maintained until hæmoglobinuria has ceased, provided symptoms indicative of alkalosis, such as muscular cramps, tetany and Trousseau's sign do not supervene. Rarely alkalosis may develop while the urine is still acid in reaction; estimations of the plasma bicarbonate afford valuable data in this regard and should be carried out when practicable. Maegraith and Havard consider that if an acid urine persists after 20 g. of alkali have been given in the 24 hours no further alkali should be administered.

If vomiting proves troublesome, gastric lavage may be practised and fluids containing alkalis and glucose are given intravenously. In cases in which the urine is acid in reaction, 1 pint of bicarbonate of soda (150 grains to 1 pint) may be immediately injected intravenously. This solution should be sterilised by filtration or by adding the weighed bicarbonate to cooling boiled water, since boiling is liable partially to convert it into the toxic carbonate. Alternatively 10 ml. of a saturated solution of sodium bicarbonate and 10 ml. of sodium lactate (four molar) may be injected; the latter exerts a more delayed and sustained effect than does the more rapidly acting bicarbonate. Such injections may be repeated as required.

It is always important to prevent dehydration, assist the heart and maintain a good urinary output. For this purpose a sterile solution of 5 per cent. glucose should be given intravenously when required, either intermittently or by continuous drip; as much as 2000 ml. may be administered in 24 hours when fluid is not being taken satisfactorily per os.

Blood transfusion is the best means of combating anæmia, anoxæmia and circulatory failure, and it also probably assists in combating renal failure by increasing glomerular filtration pressure. Up to 2 pints may be given intermittently as required, or better still, a reasonable blood count can be maintained by continuous intravenous drip administration. When the hæmolysis is severe and prolonged, or when the hæmoglobinuria is of intermittent type, many pints of blood may be necessary. In the polyuric type, blood transfusion is a life-saving procedure but its effect in the anuric type is more uncertain, the renal damage often proving irreversible despite all treatment. One reason for this is that blood transfusion is not undertaken early enough, i.e. at the onset of the shock and circulatory failure which accompanies any severe intravascular hæmolysis.

Treatment of anuria is largely conservative. Diuretics are ineffective. A fluid intake-output record must be kept, included in which should be all fluids administered parenterally. The latter should be limited to produce a slightly positive fluid balance, otherwise the patient may become waterlogged and develop pulmonary œdema.

Institution of the Borst and Bull<sup>1</sup> régime consisting of the intra-gastric administration of a litre of 40 per cent. glucose in arachis oil and gum acacia given daily, plus a volume of water equivalent to fluid lost may be worth a trial. The prognosis in the anuric patient is bad, but most unexpected recovery may occur, followed by a short period of polyuria, and the passage of unconcentrated urine.

*Convalescence.*—Once hæmolysis has ceased, marked reticulocytosis, followed by rapid blood restoration, proceeds automatically in the well-fed European; iron in adequate dosage is indicated in convalescence, and liver extract or Marmite may prove necessary in peasant populations living on diets deficient in good animal protein. In all cases blood transfusions are advisable if the rate of blood regeneration is unsatisfactory.

As mepacrine, chloroquine and proguanil appear to have less tendency to induce blackwater attacks than quinine or pamaquin, a full course should be given with one or other of these drugs during convalescence with the object of attaining radical cure.

## LEISHMANIASIS

Leishmaniasis is the term applied to a group of diseases caused by parasites of the genus *Leishmania*. Some of these are general infections, others are local. Of the first, there is kala-azar due to *Leishmania donovani* (Laveran and Mesnil, 1903), and infantile or Mediterranean kala-azar, caused by *L. infantum* (Nicolle, 1903). Both morphologically and serologically they appear to be the same parasite, and there seems to be little reason for separating them. Both Mediterranean and Sudanese kala-azar, however, are much more difficult to cure than the Indian type. Oriental sore, due to *L. tropica* (Wright, 1903), and American dermal leishmaniasis, due to *L. braziliensis* (Vianna, 1911), are generally regarded as distinct species, belonging to the second group.

### KALA-AZAR

**Definition.**—Kala-azar, or black fever, is a specific disease associated with enlargement of the spleen and liver, anæmia, great emaciation and irregular fever of long

<sup>1</sup> *Lancet*, 1953, ii, 791.

duration, caused by the protozoon *L. donovani*, present in the blood and reticulo-endothelial cell system.

**Ætiology.**—The disease has definite geographical limitations, being commonest in India, Assam and the Mediterranean littoral, 90 per cent. of these cases occurring in children; it is also found in China, Indo-China, the Sudan, Abyssinia, Russian Turkestan and Mesopotamia. Natives appear more susceptible than Europeans, probably owing to different habits of life. In Assam villages the introduction of an infected case generally precedes other cases, and often it appears to be a house infection (Rogers). Children and young adults are specially liable, and males appear more susceptible than females. In the Mediterranean area very young children and dogs suffer from kala-azar, whereas in India and North China the disease occurs in older people and rarely in dogs.

The non-flagellate stage of the parasite is a small oval body, 2 to  $5\mu$  long by 1 to  $2\mu$  broad, containing (1) a large round laterally placed nucleus (macronucleus or trophonucleus), staining bright red with Romanowsky's stain; and (2) a kinetoplast (micronucleus, centrosome) which is usually rod-shaped, stains a deep reddish-purple and has one end pointing toward the nucleus. It can be cultivated on rabbit-blood agar (N.N.N. medium) if grown for 2 to 3 weeks at room temperature ( $72^{\circ}$  to  $77^{\circ}$  F.), provided the culture material has not been contaminated. During growth, *Leishmania* bodies develop into leptomonads measuring up to  $24\mu$  in length, with a flagellum and centrosome at one end and a central macronucleus.

This flagellate represents the stage attained in the insect vector—i.e. some sand-fly of the genus *Phlebotomus*. If after an infective feed on blood containing *L. donovani*, the sand-flies (*Phlebotomus argentipes*) are nourished on raisins and not on blood, the flagellates rapidly multiply and fill the anterior portion of the stomach, block the pharynx and extend forward to the buccal cavity and mouth parts. Blocked sand-flies cannot ingest blood, and in an effort to do so discharge flagellates into the skin. Highly successful experimental transmission to mice, hamsters and man has recently been reported by Swaminath, Shortt and Anderson using blocked sand-flies, and the problem of kala-azar transmission has at last been finally solved. The chief vectors are *P. argentipes* in India, *P. perniciosus* in the Mediterranean area, and *P. chinensis* in North China. Though viable *L. donovani* may be discharged from ulcers in the intestine, naso-pharynx or bladder of a kala-azar patient, it is most unlikely that man ever becomes infected except by sand-flies.

**Pathology.**—Leishman-Donovan bodies multiply by fission, and are found crowded together in endothelial cells of the blood vessels and lymphatics, especially those of the spleen, liver, bone marrow and skin. They are also found in the mononuclear and polymorphonuclear leucocytes in the blood. At necropsy emaciation is marked, the spleen and liver are generally enlarged, while dropsical effusions and intestinal ulceration may occur. The spleen is at first soft, pulpy and friable, and later it becomes hard and fibrous; the capsule is thickened, and perisplenitis and infarcts may also be found. The liver is firm and friable, the capsule is thickened, and fatty degeneration and a nutmeg appearance are common; cirrhosis may eventually result. The bone-marrow is generally red and soft, showing a decrease of fat. The mesenteric glands are often enlarged, presenting a central necrosis. The heart is dilated and flabby, while the entero-colon may show superficial or deep ulcerations; the latter at least are of dysenteric origin.

**Symptoms.**—The incubation period is probably from 1 to 4 months, but cases may occur  $1\frac{1}{2}$  years after exposure. The onset may be sudden, with fever simulating malaria or typhoid, or insidious. Often in febrile cases the diagnosis is not made until relapses occur and the more classical features of the disease develop. These may be classified as follows: (1) Irregular, remittent or intermittent pyrexia, which, though not necessarily high, is characteristic. Periods of apyrexia spontaneously develop, and may lead to confusion with Malta fever. A double daily rise may occur

in the afternoons and evenings, but this may also be noted in other diseases and is not pathognomonic. (2) Loss of hair and deepening colour or pigmentation of the skin—hence the name black fever. (3) Anæmia, with the characteristic blood changes. (4) Rapid loss of weight and cachexia. (5) Splenomegaly, which may be the first sign or only be noted after 1 to 2 months of fever. In the early stages the spleen feels soft and doughy, but not tender; later, it hardens and may reach very large dimensions. (6) The liver is generally palpable (88 per cent.), presenting a sharp lower edge. (7) Diarrhœa. There is a good appetite associated with poor digestion, which itself may lead to intermittent diarrhœa (Napier). If blood and mucus be present, intercurrent dysentery should be suspected. (8) Other features include night sweats, persistent irritating cough, palpitation, dyspnœa, low blood pressure, *i.e.* below 100 mm. of mercury, œdema of the extremities and occasionally puffiness of the face. Amenorrhœa often develops, but conception may occur with congenital transmission from the mother (Low and Cooke). The blood changes, which include anæmia, leucopenia and reduction in platelet count, are due to replacement of both the leucoblastic and erythroblastic marrow by clasmatocytic tissue. The hæmoglobin is often proportionally reduced, so that the colour index may equal 1.0; in other cases it is 0.7 or 0.8. The blood picture may show anisocytosis, poikilocytosis, polychromasia and normoblasts. The leucopenia is extreme, often sinking to 2000 per c.mm.; in 80 per cent. of cases it is less than 4000 per c.mm. The differential count reveals a relative increase in lymphocytes and monocytes, with a decrease in neutrophils and eosinophiles. In some instances true agranulocytosis may develop. The coagulability of the blood may be prolonged, the calcium, blood sugar and serum albumin are reduced, and the total globulin content of the blood is raised, euglobulin increasing at the expense of the pseudo-globulin fraction.

**Complications and Sequelæ.**—Owing to debility and bone-marrow involvement with leucopenia, the resistance to bacterial infections is markedly decreased, and broncho-pneumonia, lobar pneumonia and tuberculosis are common causes of death; otitis media and cancrum oris may occur, especially in children. Watery diarrhœa and intercurrent dysentery are frequent. Purpura, epistaxis, bleeding from the gums and melæna may be encountered. The sequelæ include chronic splenomegaly plus severe anæmia and cirrhosis of the liver, sometimes associated with ascites. Jaundice frequently appears within 3 months of treatment and may persist for several months.

Post-kala-azar dermal leishmaniasis is being increasingly recognised. Areas of depigmentation appear about a year after antimony injections and papillomatous nodules, in which leishmania can be found, occur the following year. A xanthoma-like condition is also described, but ulceration never occurs. Parasites are demonstrable in smears and culture and apparently they are mainly confined to the skin, as splenic puncture generally yields negative results. The condition may also appear in persons who give no history of previous kala-azar or of treatment. When the face is affected the condition has to be differentiated from leprosy. In the Sudan, non-ulcerative papillomatosis and nodules of the skin are common in kala-azar patients, and muco-cutaneous lesions similar to espundia have been reported (Kirk).

Diagnosis is generally dependent on the demonstration of *L. donovani* in smears from lymphatic glands, sternal marrow, the liver or spleen or cultures on N.N.N. medium obtained from the peripheral blood. Parasites are less common in the peripheral blood in Mediterranean than in Indian kala-azar. Aspirated material for microscopical examination must be collected in an absolutely dry syringe. Sternal marrow is satisfactory for microscopical examination or culture; sternal puncture is free from the danger of hæmorrhage and causes little pain. Enlarged lymphatic glands along the saphenous vein or elsewhere may be punctured with a dry hypodermic needle without a syringe, and the juice which enters the needle blown on to a slide and stained.

The formal-gel or aldehyde test of Napier is of considerable value in the diagnosis of kala-azar, especially when the result is positive and associated with a leucopenia. The test is performed by adding 1 drop of commercial formalin (30 per cent. formaldehyde) to 1 ml. of clear serum, which is immediately shaken and left at room temperature. When the reaction is positive the serum immediately becomes viscid, and within 1 or 2 minutes assumes a whitish opalescent appearance and sets so that the tube can be inverted without spilling. In from 3 to 20 minutes it forms a solid opaque coagulum like the white of a hard-boiled egg. For the first 3 months the reaction is of doubtful value, but after this it is generally positive.

Kala-azar has to be differentiated from the febrile splenomegalies of the tropics, especially chronic malaria, undulant fever and enteric fever; schistosomiasis, Banti's disease and leukaemia must also be considered, and owing to the danger of hæmorrhage in the latter disease splenic puncture should never be undertaken until blood examination has excluded it. In childhood Mediterranean kala-azar has to be differentiated from Cooley's anaemia, commonly found in Greece, von Jaksch's anaemia and acholuric jaundice.

**Course and Prognosis.**—Bentley showed in the Assam epidemics, prior to the introduction of antimony, that the disease lasted 1 to 2 years in chronic cases. The mortality rate, if untreated, is about 90 per cent. Intercurrent disease, severe intestinal symptoms and cirrhosis with ascites are of grave significance. Modern therapy generally results in recovery, provided the condition is not too advanced and intercurrent disease absent.

**Treatment.**—**PROPHYLACTIC.**—Segregation and treatment of the sick, and abandonment of infected houses and rebuilding at distances not less than 300 yards have been effective in India. Destruction of the sand-fly vector by spraying its breeding-places with D.D.T. is indicated. For other measures, see *phlebotomus* fever (p. 189).

**CURATIVE.**—The patient is put to bed on a milk or light diet adequate in vitamins. Intercurrent disease and complications should receive appropriate treatment. Three groups of specific drugs are known, namely, the trivalent antimony compounds, the pentavalent antimony compounds and certain aromatic diamidines introduced by Yorke and Ewins. The effects of specific drug treatment are to reduce the temperature to normal, decrease the splenomegaly and hepatomegaly, increase body weight and restore the leucocytes to normal numbers. Cure is indicated by an absence of clinical symptoms for 6 months, a negative aldehyde test, an increase in serum albumin associated with a decrease in total globulin involving the *euglobulin fraction* and a permanent disappearance of parasites.

(1) *Trivalent antimony compounds.*—Antimony potassium tartrate or antimony sodium tartrate are administered intravenously, as described in the section on schistosomiasis (p. 321), the only difference being that a longer course totalling some gr. 40 to 60 is required.

(2) *Pentavalent antimony compounds.*—These have replaced the trivalent antimony derivatives owing to their more rapid action, reduced toxicity and superior parasitocidal action. They include Neostam, Ureastibamine, Neostibosan and Pentostam. The adult dosage of the first two is 0.1 g. initially, 0.2 g. as a second dose and 0.25 g. for each subsequent injection. In the case of Neostibosan an initial dose of 0.2 g., with subsequent doses of 0.3 g. is advised. Debilitated patients require small doses, while children, although tolerating proportionally larger doses than adults, should receive smaller initial doses. The length of the course varies from 10 to 15 daily injections. Toxic features include nausea, vomiting, giddiness and more rarely diarrhoea, hepatitis and jaundice, and an anaphylaxis-like syndrome characterised by urticaria, puffiness of the face and cardio-vascular collapse. The response of Indian and Chinese kala-azar to Neostibosan is in most instances highly satisfactory, but Mediterranean kala-azar requires at least three times as much of the drug to effect

a cure. Sudanese kala-azar is even more refractory, and complications, such as intractable diarrhoea, hæmorrhages, cancrum oris and lobar pneumonia, are particularly prone to develop.

Pentostam (sodium stibogluconate) contains 100 mg. of pentavalent antimony per ml., and the normal adult course of treatment consists of 6 to 10 injections of 6 ml. each. It can be given either intramuscularly or intravenously without undesirable local or systemic effects. The response to the drug is generally rapid, the temperature falling within 4 days. In India and China the recovery rate has been high, and in Mediterranean infantile kala-azar and Sudanese kala-azar it is reported to be effective.

(3) *Aromatic diamidines*.—Stilbamidine has been used effectively in different types of kala-azar but its use has now been abandoned owing to the incidence of severe toxic complications, such as delayed acute yellow atrophy of the liver and central nuclear degeneration, especially involving the 5th cranial nerve. It has been replaced by pentamidine isethionate (given in doses of 2 to 4 mg. per kg. body weight), which appears to be effective therapeutically in kala-azar without producing undesirable toxic features; it should be specially useful for cases which are antimony resistant. The course of treatment is similar to that advised for trypanosomiasis (see p. 273).

#### AMERICAN DERMAL LEISHMANIASIS

**Synonyms.**—Espundia; Uta; Pian Bois; Pian Cayenne; Forest Yaws; Bosch Yaws; Bubas Braziliana.

**Definition.**—An infective granuloma due to *Leishmania braziliensis*, producing cutaneous nodules and ulcers on exposed surfaces; the buccal and nasal mucous membranes may be extensively involved, and also the lymph glands and lymphatics.

**Etiology.**—The disease is found in South and Central America with the exception of Chile. It is especially frequent amongst wood-cutters and people living in forests. Sand-flies are almost certainly the transmitting agent. Morphologically, *L. braziliensis* is similar to *L. tropica*, but differs in the fact that it involves mucous membranes in 10 to 20 per cent. of cases in addition to the skin.

**Symptoms.**—The incubation period is about 2 months. The lesion originates as an itching papule, which may develop into a blind nodule or may ulcerate, producing fungoid granulations. In 10 to 20 per cent. of cases, ulcers appear at the margins of the mouth and nose, often subsequently involving their mucous surfaces, the larynx and nasal septum. Fever, joint pains and bronchitic symptoms now appear, but many years may elapse before the patient succumbs to intercurrent disease or cachexia.

**Diagnosis.**—Demonstration of the parasites, either in scrapings from the spreading margin of the ulcer or by culture, completes the diagnosis. Syphilis, rodent ulcer, leprosy and tuberculosis closely resemble the destructive form of *L. braziliensis*, which, however, never involves bone.

**Prognosis.**—This is only dangerous to life if the mucous membranes be involved (10 to 20 per cent.). If untreated, such patients die of intercurrent disease like pneumonia.

**Treatment.**—In South America the trivalent antimony compounds, such as tartar-emetic and stibophen (Neo-antimonan: Fuadin), appear to be preferred to the pentavalent antimony compounds. Otherwise the treatment is similar to that outlined for kala-azar and oriental sore.

#### ORIENTAL SORE

**Synonyms.**—Aleppo Sore; Baghdad Button; Delhi Boil; Biskra Button; Ashkabad Sore; Pendeh Sore; Bouton d'Orient.

**Definition.**—An infective granuloma of the skin and subcutaneous tissues caused

by *L. tropica* producing either a "dry" type of chronic papular lesion with late ulceration, or a "moist" type of papular lesion with early ulceration.

**Ætiology.**—Cutaneous leishmaniasis is common in Mesopotamia, Arabia, Persia, Central Asia (Russian Turkestan), North-West Frontier of India, Asia Minor, Northern Africa, Egypt, the Sudan, Nigeria, Spain, Italy and Greece.

The "dry" type is urban in distribution, occurring in cities like Baghdad, Delhi and Lahore. Practically nothing is known regarding its reservoir hosts, though, wherever it occurs, sand-flies (*P. papatasi* and *P. sargenti*) are common. The remarkable development into virulent flagellates occurring in the mid-gut and extending forward into the proboscis after feeding them on oriental sores indicates that these insects are transmitters. The disease has also been transmitted by rubbing into the excoriated skin a saline extract of crushed *P. papatasi* sent from an endemic area. The disease is auto-inoculable, but not through the unbroken skin. It is possible that occasionally it may be transmitted by personal contact with an infected case. Dogs, cats, guinea-pigs and mice are susceptible.

The "moist" type is rural, occurring in open or desert country. In Middle Asia the endemic foci are rural settlements adjoining the desert; here desert sand-flies (*P. caucasicus* and *P. papatasi*) breed exclusively in the burrows of wild rodents (gerbils), which often have sores on their ears due to *L. tropica*. It has been conclusively proved that these infected gerbils serve as reservoir hosts for cutaneous leishmaniasis of "moist" type which is transmitted to man by sand-flies breeding in the burrows of these rodents.

**Pathology.**—Infective granulomata are produced, sections showing atrophy of the epidermis, infiltration of the corium and its papillæ with lymphocytes, plasma cells and macrophage endothelial cells containing *L. tropica*. If the nodule ulcerates secondary bacterial infection ensues, destructive and degenerative changes predominate, and leishmania become scanty. From the histo-pathological viewpoint acute and chronic oriental sores differ in the intensity and degree of the inflammatory process. In secondary lesions appearing later, the infiltration has a tuberculoid structure, with few or no parasites, while the keloid type may show epithelial cell nests. Unlike the American form the mucous membranes are rarely involved.

**Symptoms.**—The incubation period for the "dry" type with late ulceration is 2 to 6 months. The lesion commences as a small red papule which gradually enlarges, softens and becomes purplish, glazed and scaly, being surrounded by a narrow dull-red zone of inflammation. This may remain as a sort of blind boil for a year or more before disappearing, or, especially if injured, it may become covered with a yellow crust and ulcerate in 3 or 4 months, the ulcer having well-defined rounded edges and a granulation tissue base exuding thin pus. Under these circumstances there may be some enlargement of the neighbouring lymph glands (10 per cent.). The sores may be single or multiple, as many as 35 having been recorded, and are common over exposed parts, especially the hands, wrist, forearms, ears, nose, face, feet and legs. Parasites are numerous in these lesions, and the virulence to mice is low.

The "moist" form has a short incubation period of 1 to 6 weeks, and rapidly ulcerates in 1 to 2 weeks. Lymphangitis is common (70 per cent.), secondary bacterial infection frequently occurring. Parasites are scanty and the virulence for mice is high. The duration of the lesions is less than 6 months.

Since infection or recovery from one form does not confer immunity to the other, it is probable that the two types of lesions are dependent on infection with different strains of *L. tropica*.

Various other forms of dermal leishmaniasis due to *L. tropica* have been described. They include: (1) small firm discrete nodules occurring in the course of the lymphatics; (2) warty or papillomatous outgrowths, which may resolve or ulcerate; (3) lupus-like nodules, which may implicate the cheek and (4) a keloid form characterised

by raised, shiny soft masses of infiltrated tissue covered by pinkish skin which gradually resolve without ulceration.

**Diagnosis.**—This is dependent on demonstrating the parasite. If ulceration has occurred, the skin at the edge of the ulcer should be sterilised with iodine, allowed to dry, punctured with a glass pipette, and the material so obtained inoculated on to N.N.N. medium. Bacterial contamination prevents growth. Direct microscopical examination of this material often shows *L. tropica* in the endothelial cells.

**Prognosis.**—The condition is practically never fatal even when untreated, but under these circumstances it may last 18 months, after which the patient generally possesses an immunity.

**Treatment.**—**PROPHYLACTIC.**—Sand-flies and their breeding grounds should be eradicated. (See phlebotomus fever, p. 189.)

**CURATIVE.**—In cases which have been secondarily infected, hot boracic fomentations or antiseptic dressings should be applied until sepsis is controlled and the crusts separate. Sulphonamides or penicillin may be helpful in cases in which the secondary infection is difficult to clear up. Such forms of treatment as carbon dioxide snow, radiotherapy, radium, zinc ionisation and diathermy are useful as well as local applications of ointments containing methylene-blue, iodoform, salicylic acid, protargol or Rivanol. Good results have been claimed for Orisol ointment containing berberine sulphate, and dithranol (Derobin, Cignolin) paint, applied with a camel-hair brush and strictly confined to the ulcer surface. Russian investigators advise infiltration with 5 per cent. mepacrine injected at several points; later a 10 per cent. mepacrine ointment may be used.

Vaccines have their advocates. Neostibosan or Pentostam is also worthy of trial when multiple lesions are present.

## TRYPANOSOMIASIS

A group of diseases caused by flagellate parasites of the genus *Trypanosoma*. In Africa, man may be infected with *T. gambiense* or *T. rhodesiense*, and in South America with *T. cruzi*. Trypanosomes also produce disease in animals, the most important being nagana affecting horses, dogs, cattle and wild game in Africa caused by *T. brucei*, which is probably identical with *T. rhodesiense*. *T. evansi* produces surra and *T. equiperdum* dourine, the latter disease being transmitted during coitus.

### AFRICAN TRYPANOSOMIASIS

**Synonym.**—Sleeping sickness.

**Definition.**—This disease, transmitted by the bite of tsetse flies, is caused by *T. gambiense* (Dutton, 1902) or *T. rhodesiense* (Stephens and Fantham, 1910). After initial invasion by trypanosomes, blood infection ensues with adenitis, irregular remittent fever, rapid pulse, œdema and circinate erythematous rashes; later a meningo-encephalitis results with lethargy, mental and physical degeneration, tremors, shuffling gait, convulsions, coma and death. Mild cases, with headache and slight fever, are common.

**Ætiology.**—The disease is limited geographically to areas where the tsetse fly abounds and occurs in Western and Central Equatorial Africa, including the Congo, Uganda, East Africa, Rhodesia, Nyasaland, etc. Natives and whites are both affected, and children and adults of both sexes prove equally susceptible. The two species of trypanosome are indistinguishable in human blood; they possess a nucleus, a posteriorly situated blepharoplast and a flagellum. *T. rhodesiense* is identified by inoculating blood into white rats, when posterior nuclear forms develop; this so rarely occurs with *T. gambiense* that the test is one of real value in distinguishing these two trypano-



somes. Furthermore, *T. gambiense* manifests an uncertain pathogenicity to laboratory animals, and is relatively insusceptible to the action of normal human serum. Glossinæ take up trypanosomes from the blood during biting; these multiply in the gut and pass forward via the proventriculus and salivary ducts to the salivary glands, where further development ensues. Glossinæ become infective in 3 to 7 weeks and remain so for life; they bite mainly in the daytime. *T. gambiense*, the central African type, is transmitted by *G. palpalis* and *G. tachinoides*; possibly the natural reservoir of infection is game, such as the reed and bush buck, etc., encountered near lakes and rivers by which these flies live, depositing their larvæ in shady, sandy soil. Man contacts these two riverine species repeatedly at fords, washing places, water points and in shaded villages, and as he seeks water and shade at the time of the day when these tsetse flies are most active, repeated and close proximity with the fly is assured. *T. rhodesiense*, on the other hand, is spread by *G. morsitans* and *G. swynnertoni* which are widely distributed independently of water. The reservoir of infection is the infected game of the area: Bruce identifies this disease with nagana and regards *T. rhodesiense* as identical with *T. brucei*. As the pathology and symptomatology produced by the two African trypanosomes are similar they may be considered together.

**Pathology.**—The lymph glands, which are at first swollen, congested and hæmorrhagic, later undergo degenerative changes and extensive fibrosis. Enlargement of the spleen due to lymphoid hyperplasia and proliferation of endothelial cells also occurs, while thickening of the capsule is common. In the late stages trypanosomes are demonstrable in the intercellular spaces of the brain and cord, the microscopical appearances of which resemble those of meningo-encephalitis and meningo-myelitis. Mott has stressed the resemblance to general paralysis, perivascular lymphocytic infiltrations being invariable. Neuroglial cell overgrowth is also characteristic, and diffuse glial proliferation affects both the white and grey matter in the cord; the ganglion cells show chromatolysis of their nuclei, most marked in the cerebral cortex and endothelial proliferation in the arteries may occur.

**Symptoms.**—Two phases are recognised: (I.) a stage of trypanosome fever when the trypanosomes are demonstrable in the blood and gland juice; (II.) the sleeping sickness stage when the cerebrospinal fluid contains lymphocytes, globulin and perhaps trypanosomes. The incubation period probably varies from 1 to 3 weeks, and occasionally an intense local reaction follows at the original inoculation site. In many respects trypanosomiasis resembles syphilis. (I.) *Trypanosome fever*.—This is invariably seen in Europeans, but not always in natives. Its main features are: (1) an irregular remittent or intermittent temperature low in the mornings, higher at night; apyrexial periods may occur, lasting for weeks. (2) A low tension, rapid pulse of 100 to 120 per minute, which tends to persist despite a fall in the temperature. (3) An increase in the respiratory rate to 20 or 30 per minute. (4) Patches of circinate erythema, involving mainly the trunk. (5) Localised puffiness and œdema involving the feet, legs and face: the skin may be dry and irritable. (6) Polyadenitis: enlargement of the posterior cervical glands (Winterbottom's sign) is very characteristic; the epitrochlear, axillary, supraclavicular and axillary glands may also be involved; they are soft, elastic, not tender and do not coalesce or suppurate. (7) An enlarged spleen which is generally palpable. (8) Deep hyperæsthesia, especially over bones like the tibia and manifesting a definite latent period (Kerandel's sign). Long latent periods of several months (rarely several years) may elapse before the central nervous system becomes involved, and probably some cases undergo spontaneous cure where the virulence of the trypanosome is low. Once the stage of sleeping sickness has become definitely established, the untreated patient rarely survives for longer than a year. (II.) *Sleeping sickness*.—In the earliest phase the patient may complain of headache, lack of concentration, disinclination for work and insomnia, associated with loss of weight, enlargement of lymphatic glands and slight

tremor of the tongue. In the *intermediate phase* the countenance becomes sad, apathetic and morose, laziness and emotional instability increase, and the patient is always dropping off to sleep, even in tropical sunlight or when eating. The speech becomes mumbled and slow, the gait shuffling and fibrillary tremors of the tongue, lips and hands develop. The reflexes are exaggerated and Romberg's sign is present. In the *final phase* all these symptoms become more pronounced; muscular weakness is extreme, saliva dribbles from the mouth, bed-sores and flexure-contractions may develop, the patient becomes entirely bedridden and coma and convulsions generally terminate the picture.

The classical picture of sleeping sickness described above represents that encountered in areas where the virulence of the trypanosome is high. Recent investigation has shown that in both East and West Africa many mild cases occur in which slight toxic features, such as headache and a little fever, are the only manifestations of the disease. Prolonged observation, however, reveals that symptoms are usually periodic and patients are frequently incapacitated temporarily. A stupid or sad appearance is often obvious, while early and slight facial asymmetry, hypotonia, insomnia, rheumatic-like pains, loss of strength and impotence are common (McLetchie). The mildness of the clinical symptom, however, may be very misleading for when a group of such cases was followed up by Kinghorn on the Gold Coast nearly half of them were dead within 13 months. It is the trypanosome of low virulence which causes epidemics. Lester classified strains of *T. gambiense* into three categories, (1) low virulence with high transmissibility producing mild symptoms, scanty blood infection and rarely proving tryparsamide resistant, (2) medium virulence producing nervous symptoms in 6 to 12 months, (3) high virulence resembling *T. rhodesiense*, and feebly transmissible, liable to relapse after treatment and very resistant to tryparsamide. Fortunately resistance to suramin appears to be rare.

**Complications.**—Intercurrent infections like dysentery and pneumonia often cause death, and abortion and still-births are not infrequent. Keratitis, iridocyclitis and choroiditis occur, and during treatment with tryparsamide a careful watch has to be made for the onset of optic atrophy.

**Diagnosis.**—Irregular fevers, especially if associated with cervical adenitis, should arouse suspicion in patients who have been exposed to infection, and under such circumstances laboratory assistance is invaluable. Autoagglutination of the blood is frequently observed. Trypanosomes may be found in thin or in thick blood films, or in smears from centrifuged citrated blood. Even more satisfactory is the method of early gland puncture, provided the gland juice be aspirated in a dry syringe, when 87 per cent. of cases with adenitis show trypanosomes (Broden). Inoculation of white rats or guinea-pigs with blood or emulsified excised gland is also a very valuable procedure. Lumbar puncture is essential in later cases; typically the cerebrospinal fluid, which is often under increased pressure, shows an increase in globulin and lymphocytes, and later in medium-sized and vacuolated mononuclear cells as well. The advanced cases have counts of from 15 to 100 cells per c.mm.; trypanosomes are often difficult or impossible to demonstrate, even after centrifuging the fluid and animal inoculation. In relapses after suramin it is rare to find trypanosomes in gland juice or blood and here diagnosis must be made on clinical grounds or by lumbar puncture.

**Prognosis.**—The prognosis is very hopeful in *T. gambiense*, provided modern treatment be commenced before the central nervous system is involved: after this it is more doubtful, though many cases recover. *T. rhodesiense* is a far more virulent type of disease, and most patients succumb despite treatment once the nervous system is involved, owing to tryparsamide resistant strains. Seriously ill toxemic patients and advanced nervous cases often react badly to high dosage and require skilled treatment. A careful follow up of all patients, whether mild or severe, to ascertain the need for a second course is essential.

**Treatment.**—**PROPHYLACTIC.**—The only permanent method of control is to eliminate man-fly contact wherever possible (Lester). Immediate control is achieved by chemotherapy-mass treatments of epidemics. Next comes anti-tsetse measures such as protective clearance of forest and bush around lakes, rivers, fords and water-points for the riverine species, and fly destruction by D.D.T. sprayed from the air. Finally come administrative measures like concentration of the population, re-settlement, improved dietary and general welfare.

Personal prophylaxis is important. White clothes are advised in tsetse country, shorts should not be worn and veils and gloves are used if feasible. Where possible travelling should be done at night.

Drug prophylaxis is also proving very valuable—especially in mining camps. Single injections of suramin (2 g.) give protection for 6 weeks but not 3 months, as was previously thought. Pentamidine isethionate, 250 mg., given intramuscularly every 4 or 5 months appears to afford regular protection (McLetchie).

**CURATIVE.**—Mass treatment of epidemics aims at the radical cure of individual sick patients, sterilising the carrier and rendering him physically fit. Several specific drugs are of proved value and the use of two drugs simultaneously is now generally advocated owing to synergic action.

(1) Suramin (Antrypol, Bayer 205, Germanin) is a complex organic urea compound, which is injected intravenously (1.0 g.) at intervals of 2 or 3 days until a total of 10.0 g. have been given. It is especially useful in sterilising the blood in early cases infected with *T. gambiense* or *T. nigeriense* and has a prolonged prophylactic action. Sometimes toxic effects on the kidneys are found, and when possible the urine should be watched for albuminuria and casts.

(2) Tryparsamide (sodium N-phenylglycineamide-*p*-arsonate) is given intravenously at 5 to 7 days' interval in doses of 20 to 40 mg. per kg. (1.5 to 3.0 g. for an adult) until a total dosage of 30.0 g. have been administered. Children receive relatively larger doses. Tryparsamide is the only safe and effective drug in the advanced stages of sleeping sickness where the central nervous system has been involved, but owing to the frequency of resistant strains and its very moderate trypanocidal activity it should be given in conjunction with suramin or pentamidine isethionate for field use. Untoward symptoms are jaundice, exfoliative dermatitis and optic atrophy, the onset of which may be indicated by failing sight, contraction of the fields of vision, flashes of light, ocular pain, lacrimation and photophobia. The greater the changes in the cerebrospinal fluid, the greater the tendency to optic nerve degeneration; more often than not this complication is due to the disease rather than the drug. Where the nervous system has been involved it is not justifiable to conclude that cure has resulted until the cerebrospinal fluid has remained normal for 6 months, and when it is found to be abnormal after treatment another course should be given.

(3) Pentamidine isethionate is an aromatic diamidine compound which has marked trypanocidal properties and is valuable in the treatment of early cases of *T. gambiense*. It appears to be free from dangerous toxic effects and is non-toxic in combination with tryparsamide; from this viewpoint it is most useful when patients are intolerant to suramin. It is very valuable as a prophylactic drug and appears to have some slight action in cases with involvement of the central nervous system. The drug is administered parenterally in a 10 per cent. solution preferably as an intramuscular injection up to 2 to 4 mg. per kg. body weight; local discomfort may follow. If given intravenously the patient should receive 3 mg. per kg. body weight for 10 consecutive days; owing to possible depressor effects the patient should be recumbent and the injection given slowly, 3 minutes being taken.

**Combined treatment.**—Owing to synergic action it is advisable for field use to give suramin or pentamidine in combination with tryparsamide. A mixture of 0.5 g. of suramin and 1.5 g. of tryparsamide is injected at intervals of 5 days. Eight

injections are given in early cases and 20 injections in advanced cases. An alternative treatment, and one specially valuable where patients are intolerant to suramin, consists of pentamidine isethionate 150 mg. daily for 5 to 7 days, followed by a course of intravenous trypanamide injections at 5 to 7 day intervals. The first dose of trypanamide should be 1.0 g., succeeding doses 1.5 or 2.0 g. A course of 5 doses of trypanamide is given in moderately severe cases, and up to 10 doses in advanced cases. The pentamidine may be given concurrently with the trypanamide, provided that doses of the latter are given at the usual 5 to 7 day intervals (McLetchie). Whatever treatment is adopted the patient's general health must be built up in every way and intercurrent disease eliminated.

#### SOUTH AMERICAN TRYPANOSOMIASIS

**Synonyms.**—Chagas' Disease; Schizotrypanosomiasis.

**Definition.**—A disease occurring in parts of South America caused by the pleomorphic trypanosome, *Trypanosoma cruzi* (Chagas, 1909), which occurs both in the blood and in a Leishmanial stage in the myocardium, somatic muscle, brain and liver.

**Ætiology.**—The disease, which has been recorded in several states in Central and South America, affects children and occasionally adults of both sexes. *T. cruzi* is a short, broad trypanosome (20 $\mu$  long) with a central nucleus and large, ovoid, posteriorly situated kinetoplast. The disease is conveyed to man by certain reduviid bugs, of the genera *Triatoma*, *Rhodnius* and *Eratyrus*, which have imbibed trypanosomes during their meal of blood. After a developmental cycle of 6 to 15 days, metacyclic trypanosomes are discharged in the excreta and infect man via lesions in the skin or mucous membranes. In Brazil the chief vector is *Triatoma megista*. The trypanosomes are found in the peripheral blood only for a short time after infection, after which they assume a Leishmanial form within the cells of different organs where they undergo division, and from time to time pass back into the peripheral circulation. *T. cruzi* is a natural parasite of opossums and armadillos, and man is only occasionally and accidentally infected (Strong).

**Pathology.**—The Leishmanial forms are found especially in the heart, voluntary muscles, brain and liver, where they multiply, causing cell destruction, cellular infiltration, hyperplasia of connective tissue and fibrosis. The central nervous system shows lesions resembling meningo-encephalomyelitis.

**Symptoms.**—The incubation period averages about 9 days, varying from 7 to 14 days. The acute stage occurs in infants under 1 year and is characterised by high fever of continuous type, unilateral conjunctivitis, facial œdema which may extend to the trunk and enlargement of the liver, spleen and lymphatic glands. Trypanosomes are demonstrable in the blood only during the fever. Death may occur from cardiac failure or with encephalo-meningitic symptoms due to parasitic involvement.

The chronic stage may supervene following the acute attack in children, or affect older children or adults. There may be irregular fever, anæmia, hepatomegaly, splenomegaly and adenitis, but trypanosomes are only found in the blood if the temperature be raised and then only with difficulty. Many of the symptoms previously attributed to this stage of the disease are now known to be due to endemic goitre with superadded infection with *T. cruzi*. Serious disturbances of heart rhythm and neurological manifestations with paralysis may result from local involvement of the myocardium or central nervous system.

**Diagnosis.**—In the early acute stages this is made by finding trypanosomes in fresh blood, in stained thick or thin films or in stained films prepared after centrifuging 5 to 10 ml. of citrated blood. Occasionally puncture of the voluntary muscles may reveal the Leishmanial forms. Inoculation of guinea-pigs is sometimes successful, and a reliable complement fixation reaction has been worked out by Machado and others, using extracts of heavily infected heart muscle or cultured trypanosomes.

**Prognosis.**—The prognosis in acute cases, especially where the central nervous system or heart is involved, is grave.

**Treatment.**—**PROPHYLACTIC.**—Destruction of the reduviid bug vectors by chemical means, fumigation, etc., is necessary. Better houses and the use of mosquito nets are important factors in preventing infection.

**CURATIVE.**—No specific treatment is available, the various drugs successful in African trypanosomiasis being ineffective.

## AMÆBIASIS

1. Intestinal amœbiasis and amœbic dysentery.
2. Amœbic hepatitis and liver abscess.

Five forms of amœbæ may occur in human fæces, namely *Entamœba histolytica*, *Entamœba coli*, *Endolimax nana*, *Dientamœba fragilis* and *Iodamœba bütschlii*. Of these only the first, *Entamœba histolytica*, is known with certainty to be pathogenic to man. One fatal case of amœbiasis in a Japanese prisoner-of-war was found by Derrick at necropsy to show amœbic ulceration of the colon and stomach and extensive amœbic involvement of the lungs and brain. Tissue sections all showed dense infection with a small amœba which Wenyon and Hoare could not differentiate in tissue section from *I. bütschlii*. Unfortunately this amœba was never studied in the fæces so its identity remains doubtful. As it was not *E. histolytica*, the only alternatives are that it was a new amœba pathogenic to man or that under conditions which are not understood, *I. bütschlii* can occasionally become virulently pathogenic and invade human tissues with fatal consequences. During the War of 1939–1945 amœbic infection was responsible for from 10 to 20 per cent. of all cases of dysentery in the tropics, subtropics and Middle East, and was specially severe and prevalent in India and Burma. The problem created by the return of large numbers of infected troops to the United Kingdom was considerable, especially as a number of patients appeared to be infected with a strain or strains of *E. histolytica* which were relatively emetine resistant, and amœbic granulomas simulating malignant growths appeared to be no longer rare. Liver involvement has always been a frequent complication of amœbic infection of the colon, but owing to their clinical importance, intestinal amœbiasis and amœbic dysentery on the one hand and amœbic hepatitis and liver abscess on the other will be separately considered.

### 1. INTESTINAL AMÆBIASIS AND AMÆBIC DYSENTERY

**Definition.**—Amœbic dysentery results from infection of the colon with *E. histolytica* (Schaudinn, 1903), and is generally characterised by an afebrile diarrhoea, several voluminous stools containing brownish mucus and dark-red blood usually being passed daily. Latency is a marked feature, relapses are frequent, while amœbic hepatitis and liver abscess not infrequently supervene (p. 279).

**Ætiology.**—This disease is widely distributed throughout the tropics and subtropics, but occasionally occurs in temperate regions. Both sexes and all ages are liable, though it is less common in young children. *E. histolytica* gains access to the body in its cystic form via the mouth in drinking water or food, especially vegetables, contaminated by convalescent or contact carriers, while flies either directly or indirectly may convey the infection. The cysts pass through the stomach intact, after which their walls are dissolved by the pancreatic juice, and the encysted amœbulae escape and ultimately invade the colonic mucosa. During this stage it is the large, actively motile, tissue-invading amœbæ (20 to 30  $\mu$  in diameter), containing ingested red blood cells, which are present in fæcal mucus, but later, as the lesions become quiescent and begin to heal, precystic amœbæ appear in the excreta, etc.

superficially by binary fission from the more deeply situated tissue-invading forms. Precystic amœbæ are much smaller (7 to  $18\mu$  in diameter), less actively motile, contain no erythrocytes, and must be distinguished from *E. coli*. Different races of amœbæ give rise to cysts of different size containing one, two or four nuclei and the characteristic chromidial bodies; they are met with in the faeces of chronic cases and carriers.

**Pathology.**—After passing into the glands of the large intestine, the tissue-invading amœbæ multiply, cause toxic degeneration of the lining cells, with blockage of the tubules and the production of slightly raised yellowish nodules (Wenyon). Simultaneously, the inter-glandular connective tissues are invaded, and a toxic, gelatinous necrosis is produced, characterised by an absence of polymorphonuclear leucocytes and occasionally by thrombosis of adjacent mesenteric venules. Small abscesses form which rupture, producing superficial ulcers with undermined edges. The process now extends through the *muscularis mucosæ* to the submucosa, larger bottle-neck ulcers sometimes resulting which are often an inch or more in diameter, and are filled with mucoid material, cell debris and amœba. The brown mucus and degenerated blood so characteristic of the amœboid stool originate in such lesions. Following rupture of the primary ulcer others are similarly produced, the maximum involvement being in the cæcum, ascending and sigmoid colon, which may be considerably thickened, and the rectum. Ulceration rarely extends above the ileo-cæcal valve, and even in extensive colonic involvement the intervening mucosa does not generally appear inflamed. Frequently ulcers heal with pigmented scarring of the mucosa and thickening on the peritoneal surface, while in other instances ulceration extends to the muscular layers; adhesions may form, and more rarely sloughing and perforation may lead to a fatal peritonitis. Secondary bacterial invaders probably play a prominent rôle in the development of extensive ulcerative and gangrenous lesions of this type. Tumour-like amœbic granulomas known as amœbomas may involve the colon, being situated especially at the sigmoid, splenic and hepatic flexures, the rectum, mid-transverse colon and cæcum.

Rectal amœbomas may present as a wart-like mass extending around the anal margin or internally appear as a firm grey mass with an ulcer crater which exudes dark or reddish-brown thin pus containing vegetative *E. histolytica*. If amœbæ are not demonstrable in the exudate, a snipping removed during proctoscopy or sigmoidoscopy will enable a diagnosis to be made. An amœboma involving the cæcum or the ascending, transverse or descending colon may produce a palpable tumour, show radiologically as a constrictive filling defect of the bowel, and clinically produce features of colonic obstruction. If undiagnosed and operated on without anti-amœbic treatment, death may result.

Invasion of the mesenteric venules may produce so-called hepatitis (miliary amœbic abscesses), or solitary or multiple amœbic abscesses of the liver, lung, brain and spleen, the chief pathological feature of which is the presence of tissue-invading amœbæ in their non-fibrous necrotic walls.

**Symptoms.**—The incubation period varies from 3 weeks to 3 months. The onset is generally insidious, commencing with an afebrile diarrhœa; later, three or four bulky, fetid stools containing brown mucus and degenerate blood may be passed daily. Occasionally the onset is acute, as in bacillary dysentery, with fever, pain, griping and purging associated with the frequent evacuation of bloody, brown, mucoid stools containing *E. histolytica*; tenesmus occurs if the rectum be involved. As the condition progresses considerable weight is lost, the skin may become dry and earthy brown, and anorexia, dyspepsia, anæmia of secondary type and a mild neutrophil leucocytosis may develop. Examination often reveals thickening and tenderness of the colon, especially of the cæcum and sigmoid. Tenderness and enlargement of the liver and abnormal physical signs at the base of the right lung should also be sought for. Sigmoidoscopy generally shows the typical amœbic lesions; in the early stages

small superficial yellowish nodules and petechial hæmorrhages may be noted, while later painless yellow ulcers surrounded by zones of hyperæmia appear; scrapings reveal large tissue-invading *E. histolytica*. As a rule the intervening mucosa appears normal, but occasionally a generalised proctitis may be observed which completely clears up under emetine treatment.

Patients from the tropics may give no history of dysentery yet cysts of *E. histolytica* are found in the stools. In this group recurrent abdominal pain is sometimes complained of, and physical examination may reveal localised tenderness over the cæcum, the transverse colon or the sigmoid. Nausea, flatulence and constipation are common, and a few complain of dyspepsia and diarrhœa. Sigmoidoscopy reveals no abnormality. Appendicitis, cholecystitis, gastric or duodenal ulcer, gastritis or diverticulitis may be suspected; yet treatment with emetine-bismuth-iodide which generally results in the disappearance of cysts from the fæces is not infrequently followed by the amelioration of gastro-intestinal symptoms and under such circumstances they can with reasonable justification be regarded as of amœbic origin. Many other cyst carriers from the tropics, however, complain of no symptoms whatever, and in the absence of a history of dysentery or recurrent diarrhœa it remains uncertain whether *E. histolytica* is living on bacteria in the lumen of the gut as a harmless commensal, or has invaded the bowel wall without producing macroscopic lesions and clinical symptoms. Such individuals constitute a potential source of danger to the community, may develop liver abscess later and are better treated once a definite laboratory diagnosis has been made.

**Complications.**—Post-dysenteric adhesions, retro-colic abscess, intestinal hæmorrhage and perforation with peritonitis may result by an extension of the ulcerative process. Perforations are not infrequently multiple, and are often associated with extensive gangrene of the bowel wall. The appendix has been found involved in 7 per cent. of cases. Amœbic hepatitis and amœbic abscess are frequent complications and owing to their clinical importance are separately considered (pp. 279, 280). More rarely, amœbiasis of the lungs, brain, spleen, seminal vesicles and testicles has been recorded. Amœbic ulceration of the skin and subcutaneous tissues may develop around the sinus associated with a liver abscess, a colostomy wound or amœbic lesions involving the anus. Amœbiasis of the urinary tract is generally secondary, a colonic or rectal amœbic ulcer involving the bladder or a liver abscess rupturing into the pelvis of the kidney.

**Course.**—The majority of cases run a chronic course, and even without specific treatment the tendency for amœbic dysentery is to improve temporarily, but relapses are frequent and very characteristic of the disease. Latency is marked, and contact carriers are frequently encountered who never suffered from dysentery.

**Diagnosis.**—The diagnosis is made by finding the large tissue-invading forms of *E. histolytica* in the fresh mucus in acute cases, and the pre-cystic forms or cysts in the fæces of chronic cases and carriers. Scrapings obtained during sigmoidoscopy may reveal amœbæ despite previous negative reports on the fæces, and in any case of doubt instrumental examination should be carried out. Cytologically fewer pus cells are present in amœbic exudate than in bacillary dysentery, and Charcot-Leyden crystals also not infrequently occur. Radiographic examination after a barium enema eliminates many other lesions entering into the differential diagnosis, while in distinguishing malignant disease, chronic bacillary dysentery, ulcerative colitis, bilharzial and balantidial ulcerations of the colon from chronic amœbiasis and amœboma, sigmoidoscopy, reinforced by laboratory methods of examination, becomes indispensable. A complement fixation reaction has been perfected by Craig using an alcoholic extract of cultures of *E. histolytica* as antigen, but the test is not yet suited for routine diagnosis.

**Prognosis.**—With modern methods of treatment uncomplicated cases of amœbic dysentery almost invariably recover, and a large proportion are permanently curable. The prognosis is naturally more serious where complications like amœboma or liver

abscess exist. Colonic perforation with peritonitis is frequently, and brain abscess almost invariably, fatal.

**Treatment.**—**PROPHYLACTIC.**—As the disease is acquired by faecal contamination of food and water, it becomes important to ascertain that personal servants and cooks are not carriers. Food should be protected from flies, and measures should be taken to avoid contamination of water and uncooked vegetables.

**CURATIVE.**—Long before amœbic and bacillary dysentery were differentiated, ipecacuanha was recognised as effective in certain cases. Later, one of its alkaloids, emetine, was proved of great value by Rogers in India, and more recently other preparations, including bismuth-emetine-iodide, emetine periodide and auremetine, have been introduced. The toxic properties of emetine and its compounds should never be forgotten, and during intensive treatment it is essential that the patient be kept in bed on a simple, non-irritating, low-residue diet, milk being citrated to avoid clot formation.

*Emetine* is indicated where the tissue-invading amœbæ have produced visceral complications like hepatitis and amœbic abscess, and also early during the acute primary attack. Emetine hydrochloride is injected intramuscularly or subcutaneously in 1-grain doses daily for a period not exceeding 10 days in a normal-sized adult, but the dose should be decreased in debilitated persons and those of low body weight. Children receive a dose proportional to age, for those under 3 years never exceeding  $\frac{1}{4}$  grain, and for those under 6 years  $\frac{1}{2}$  grain per day. Emetine is a muscle poison and, owing to the cumulative action of the drug, treatment should not be repeated within 2 to 3 weeks. Diarrhoea is commonly induced, and toxic symptoms include asthenia, cardio-vascular depression, low blood pressure, tachycardia, extrasystoles, extreme muscular weakness causing paresis or even paralysis of the limbs; death may occur from cardiac failure, with paroxysmal tachycardia or auricular fibrillation.

*Emetine-Bismuth-Iodide (E.B.I.).*—This drug is preferable to emetine hydrochloride in chronic cases and carriers showing cysts, but it has the disadvantage of causing considerable nausea and vomiting, and is best given on an empty stomach late at night in specially coated tabloids (B. W. & Co.) or in gelatine capsules, 4 hours after the last feed. Phenobarbitone (gr. 1) is given half an hour previously when necessary. Nightly doses, of gr. 3, are given for 10 to 12 doses, the total course varying from gr. 30 to 36. During the course patients often lose weight, and usually there is a fall in blood pressure and slowing of the pulse.

*Carbarsone*, which is a pentavalent arsenical, is a moderately effective amœbicide in intestinal infections acting on both the cyst and vegetative forms, but the proportion of radical cures achieved is not high. It is of no value in hepatitis, liver abscess or other visceral complications. The drug is administered in tablets containing 0.25 g., one being given twice daily after food for 10 days.

*Chiniofon.*—Chiniofon (Yatren) is sodium iodo-oxyquinoline-sulphonate, and can be given by the mouth or as a retention enema. The adult dose is  $\frac{1}{2}$  to 1 g. of the powder in gelatine capsules thrice daily for 10 days, repeated if necessary after a week's interval. If given *per rectum* the bowel should be first washed out with 1 pint of 2 per cent. sodium bicarbonate solution to remove mucus, and an hour later 200 ml. of a 2.5 per cent. solution of chiniofon is run into the rectum and retained for as long as 8 hours if possible. Two somewhat similar preparations, Vioform (40 per cent. iodine) and Diodoquin (60 per cent. iodine) are widely used for oral treatment, but are too irritant for rectal use. Diodoquin is available in tablet form (0.2 g.), the standard course consisting of 2 tablets thrice daily after food for 3 weeks. In intractable emetine-resistant cases this dosage may be doubled.

**Combined treatment.**—An effective combination in chronic relapsing amœbiasis and cyst cases consists of a 10-day course of retention enemas of chiniofon in the morning and E.B.I. at night, followed by a 10-day course of carbarsone. During the latter period a liberal diet reinforced with vitamins is advisable. Prior to the war



this treatment almost invariably resulted in clinical cure and gave a radical cure rate approximating to 90 per cent. In Burma and India during the war amœbic dysentery was especially severe and prevalent, and a number of patients returning to England were found to relapse repeatedly despite combined treatment of this type. Hargreaves stressed the importance of secondary bacterial infection in severe refractory cases and advocated the additional use of penicillin combined with sulphaguanidine or succinylsulphathiazole as a life-saving measure in such patients. Though almost all patients with chronic relapsing amœbiasis are curable, exceptional ones are encountered who fail to respond even to massive doses of penicillin, sulphonamides, emetine, emetine-bismuth-iodide and other amœbicidal drugs; they occasionally die with vegetative amœbæ which appear resistant to all known forms of treatment. Amœboma, liver abscess or other complications are, however, almost invariably present in such patients. It has not yet been determined how far this failure to respond to treatment is dependent on (1) the strain of *E. histolytica* being resistant to emetine, (2) inability of the drug to reach inaccessibly situated amœbæ in effective concentration or (3) the presence of secondary bacterial infection. Penicillin and the sulphonamides are of value only in the presence of those relatively rare superadded infections with bacteria sensitive to these drugs; there is no evidence that they enhance the specific amœbicidal properties of emetine in uncomplicated refractory cases.

**Antibiotics.**—Adams recommends chlortetracycline or oxytetracycline orally 0.5 g. 6-hourly for 10 days. Parasites disappear from stools after 3 or 4 days of treatment. Some cases may relapse but a high proportion of both symptomatic and asymptomatic cases are sterilised. Antibiotics given in conjunction with amœbicidal drugs may be even more effective.

**Surgical treatment.**—Amœbomas generally respond to anti-amœbic drug treatment but occasionally surgical excision is necessary to establish radical cure. Perforation of the colon demands immediate laparotomy; large areas of the bowel may be gangrenous, more than one ulcer often sloughs through and this complication is generally fatal. Patients with amœbic brain abscesses almost invariably die despite surgical intervention. The treatment of liver abscess and its complications are dealt with in detail in the section that follows.

For BACILLARY DYSENTERY, see p. 112.

## 2. AMŒBIC HEPATITIS AND LIVER ABSCESS

**Ætiology.**—Amœbic hepatitis and liver abscess are invariably secondary to a primary infection of the colon with the tissue-invading amœba, *E. histolytica*. Amœbic dysentery may precede the onset of hepatic symptoms by weeks, months or years. In others there may be a history of attacks of diarrhœa without blood or mucus, while some patients cannot recollect any intestinal disturbance whatever. The stools frequently do not contain the cystic or vegetative forms of *E. histolytica* in demonstrable numbers at the time when hepatic symptoms appear. Liver abscess may develop within 3 months of the primary intestinal infection or be delayed for as long as 40 years after leaving an endemic area.

**Pathology.**—In amœbic hepatitis, amœbæ reach the liver via the portal vein in small emboli containing *E. histolytica* derived from the thrombosed veins draining submucous ulcers in the colon. Small intrahepatic portal thromboses and infarctions result and cytolytic enzymes from the amœbæ lead to peptonisation of the necrosed areas. The great mass of hepatic cells between amœbic foci are unaffected, and in so-called amœbic hepatitis liver function tests reveal little, if any, abnormality.

Liver abscesses are formed by fusion of a number of these small adjacent foci. The walls of the abscess are lined by a shaggy necrotic zone of hepatic tissue, and, deeper in, vegetative *E. histolytica* are found. A fibrous tissue capsule probably only

forms in the presence of secondary bacterial infection and this is especially marked where the abscess cavity has been drained. The commonest site for liver abscess is the superior surface of the liver on the right side. Some 80 per cent. of liver abscesses are located in the right half of the liver, 10 per cent. in the left half and 10 per cent. in both. The predominant right-sided distribution is due to streamline effects in the portal vein, the blood from the superior mesenteric vein being thereby diverted to the right branch and that of the inferior mesenteric to the left branch of the portal vein. In fatal cases of liver abscess in Indians, Rogers found 66·6 per cent. of the intestinal lesions were limited to the cæcum and ascending colon; blood from here drains into the superior mesenteric vein—hence the frequency of right-sided amœbic abscesses of the liver. A large destructive abscess involving one half of the liver leads to compensatory hypertrophy of the other half. When an amœbic abscess reaches the surface adhesions are formed with adjacent structures and pointing and rupture may follow. In uncomplicated cases the pus is chocolate coloured or resembles anchovy sauce and microscopical examination reveals necrosed liver cells, degenerating leucocytes, red blood corpuscles and fat droplets. Large motile *E. histolytica* containing ingested red blood corpuscles appear later, though they are not evident at first in the aspirated material. In the 15 per cent. of cases in which secondary bacterial infection has ensued, creamy-yellow or greenish-yellow pus is found containing abundant polymorphonuclear leucocytes: culture reveals the identity of the secondary invaders. These include streptococci, pneumococci, *Bact. coli*, *Ps. pyocyanea* *Staphylococcus aureus*, *Cl. welchii* and other anaerobes.

Of the liver abscesses that rupture, over 50 per cent. do so into the lungs, pleural cavity or pericardium, 25 per cent. rupture into the peritoneal cavity and the remainder into adjacent structures such as the transverse colon, stomach, intestines, vena cava and kidneys. Rupture rarely occurs into a bile duct.

**Symptoms.**—The clinical picture in hepatic amœbiasis depends on whether the hepatitis has gone on to frank abscess formation or not. Generally only one abscess is present but two, three or even four may be found.

#### AMŒBIC HEPATITIS

This condition generally commences insidiously with irregular or remittent fever and sweating and these may be the only obvious clinical features for weeks. Generally, however, the liver is demonstrably enlarged and tender, while anorexia, hepatic pain, tenderness and epigastric discomfort sooner or later develop. Jaundice is rare. There is often a mild degree of leucocytosis with slight increase in the neutrophil polymorphonuclear leucocytes. The temperature generally responds within 3 days to emetine treatment and in cases of doubt therapeutic trial is justified even though the stools contain no *E. histolytica*.

#### AMŒBIC ABSCESS

The preliminary symptoms are similar to those described above. As the condition progresses intermittent fever may result associated with progressive deterioration of health, loss of weight and energy, lassitude, a dirty coated tongue, flatulent dyspepsia and bowel irregularity. Nervous irritability and sleeplessness follow. The complexion may be sallow and a moderate anaemia sometimes develops. Localising features depend on the site and size of the abscess.

(1) *Right half of the liver.*—If the abscess is situated in the upper right half of the liver it tends to produce pressure on the diaphragm causing referred pain to the right shoulder and a dry cough (tussis hepatica). Physical signs such as diminished breath sounds, dullness and crepitations are often present at the base of the right lung. This condition is generally not due to direct amœbic involvement of the lung but

results from immobility of the diaphragm occasioned by an adjacent liver abscess which leads to defective ventilation; air absorption, pulmonary collapse and possibly secondary bacterial infection with pneumonia may follow. If the abscess points through the diaphragm it may rupture into the pleural cavity or into the lung when a pulmonary abscess with or without hæmoptysis may be produced. If the abscess opens into a bronchus, large quantities of pus resembling anchovy sauce may be coughed up and this may result in cure provided emetine be given. Amœbic abscess involving the lower right half of the liver and its inferior surface is less common and is associated with marked downward enlargement, localised or generalised tenderness along the edge of the liver and rigidity of the right rectus and adjacent muscles. Occasionally a localised area of tenderness may be demonstrable on the anterior surface of the liver. Sometimes pain may be referred to the right iliac fossa, and there may be associated tenderness over the cæcum due to amœbic ulceration. In some instances the abscess may bulge into the right loin space, simulating a renal condition. At times pain may first manifest itself at night during sudden movements or a feeling of weight may be felt when walking; the patient may hold his right arm and forearm to the side to splint the liver and for the same reason he not uncommonly sleeps on the right side. In large abscesses there may be bulging on the right side, widening of the intercostal spaces and restricted movement. In doubtful cases the chest should be measured to determine unilateral enlargement. Localised tenderness and œdema of the chest wall may indicate the site for exploratory puncture.

(2) *Left half of the liver.*—An amœbic abscess in the left half of the liver may simulate gastric conditions owing to pressure on the stomach. Not infrequently the abscess presents in the epigastrium, and tenderness and rigidity of the left rectus are evident; later, redness, œdema, bulging and even fluctuation may be demonstrable in advanced cases. Rupture may occur into the stomach, pericardium, the base of the left lung or the left pleural cavity.

*Special investigations.*—As a rule the stool presents no naked-eye abnormalities, but mucus and blood may be present. Microscopical investigation may reveal vegetative forms of *E. histolytica* or more frequently amœbic cysts. Three specimens of stool should be examined, at least one being collected after a saline aperient. Repeated negative stool examinations do not, however, exclude hepatic amœbiasis.

Sigmoidoscopy may reveal scattered amœbic ulcers, and rarely an amœboma or an amœbic proctitis. The lesion should then be gently curetted and the scrapings examined microscopically for *E. histolytica* without delay. Usually, however, the mucosa presents a normal appearance.

In uncomplicated cases of amœbic hepatitis or abscess there is generally a leucocytosis of 10,000 to 20,000 leucocytes per c.mm. with a differential count of 65 to 80 per cent. neutrophil polymorphonuclear leucocytes. When secondary bacterial infection ensues the total count generally rises above 20,000 leucocytes per c.mm. while the neutrophils constitute 80 to 90 per cent. in the differential count.

Radiological investigation is of special value owing to the frequent pressure of the liver abscess exerted on the diaphragm. Elevation and diminished movement or "splinting" of the right cupola of the diaphragm is frequently present. Later "humping" of the diaphragm indicates the abscess is pointing towards the lung. Abnormal shadows at the base of the right or left lung may be due to pulmonary collapse, pneumonia, pulmonary amœbic abscess or pleural effusion. Sometimes an area of increased density in the liver indicates the site of the abscess. Left lobe abscesses are difficult to demonstrate, though they may produce characteristic pressure deformities on the barium-filled stomach (Miles).

*Complications.*—The most fatal complications include rupture above or below the diaphragm and secondary bacterial infection. Jaundice is not common but does occur. Hæmatemesis is rare.

*Diagnosis.*—Liver abscess is not infrequently diagnosed as basal pneumonia or

pleurisy with effusion; it may simulate suppurating hydatid cyst of the liver, subphrenic abscess or perinephric abscess, all of which tend to implicate the pleural cavity or base of the lung via the diaphragm. It is sometimes confused with bilharzia cirrhosis especially when associated with bilharzia dysentery (*S. mansoni* and *S. japonicum*), suppurating pylephlebitis, cholecystitis, septic cholangitis especially complicating *Clonorchis sinensis* infestation, malaria hepatitis and carcinoma of the liver with primary involvement of the colon. In diagnosis the history of exposure to infection in an endemic area or of definite amœbic dysentery, an intermittent or remittent temperature associated with an enlarged tender liver, leucocytosis and physical signs at the base of the right lung are important features. Immobility, elevation and "humping" of the diaphragm are characteristic radiological features. The finding of "anchovy sauce" pus during aspiration of the abscess is pathognomonic though it may take 48 hours before motile *E. histolytica* appear. The dramatic fall in temperature within 72 hours of commencing emetine injections favours an amœbic origin, though occasionally it takes 5 days before the temperature reaches normal. The presence of cysts or vegetative forms of *E. histolytica* in the stools is presumptive evidence that the hepatomegaly has an amœbic origin, but in many instances sigmoidoscopy and repeated examination of the stools show no evidence of intestinal amœbiasis. At least 25 per cent. of patients give no history of previous dysentery or diarrhœa.

**Prognosis.**—Where the diagnosis is made early and appropriate treatment is adopted the prognosis is almost invariably good. The presence of multiple abscesses of the liver or of such complications as rupture or secondary bacterial infection increase the gravity of the condition. Open operation and drainage carries with it the risk of superadded bacterial contamination, and should only be undertaken if secondary bacterial infection has already occurred.

**Treatment.**—*Emetine.*—Amœbic hepatitis and even small amœbic abscesses generally respond rapidly to injections of emetine—grains 1 daily for 12 days. Provided secondary bacterial infection be absent pain and discomfort rapidly lessen, the temperature falls to normal in about 3 to 5 days, and the leucocytosis decreases; when there is anæmia due to amœbic infection a reticulocytosis follows about the seventh day. If relapse is to be avoided, the course of emetine injections should be followed by a course of emetine-bismuth-iodide (3 grains nightly for 12 days) combined with chiniofon or other amœbicidal drugs to eradicate latent colonic infection. Owing to the cumulative action of emetine it is advisable to allow 2 or 3 weeks between the two courses of treatment. Where a large amœbic abscess has formed aspiration in addition to emetine therapy is advisable, but it should be postponed until the hepatic congestion has been relieved by several injections of emetine (Rogers).

*Chloroquine diphosphate* (Aralen) is a 4-amino-quinoline derivative which is amœbicidal and selectively stored in the liver in great concentration. Each tablet contains 0.25 g. of the salt (=0.15 g. base) and the course consists of 4 tablets daily for the first 2 days and 2 tablets daily for the next 14 to 19 days (Loeb: Conan). Adams recommends a shorter course of 1.0 g. of the salt daily for 6 days followed by treatment of the gut infection. This drug exerts a remarkable amœbicidal effect in hepatic amœbiasis, but its action on vegetative and cyst forms of *E. histolytica* in the colon is much weaker. Chloroquine is of special use in those rare cases of hepatic amœbiasis failing to respond satisfactorily to emetine and emetine-bismuth-iodide therapy, but here a full course of treatment as recommended on page 278 may prove necessary in addition, in order to eradicate the associated amœbic infection in the colon.

**Aspiration.**—Owing to the viscosity of amœbic pus an exploratory needle of fair-sized calibre must be used and it should not be inserted more than 3½ in. owing to the risk of perforating the inferior vena cava. During exploratory puncture continuous aspiration should be maintained by means of a large syringe or a Potain's aspirator. If there is local tenderness, redness, œdema or bulging, the liver should

be explored over this site. In the absence of localising features the liver should be systematically examined commencing by inserting the needle inwards, backwards and slightly upwards in the eighth or ninth intercostal space in the right anterior axillary line. Several exploratory punctures may be necessary before pus is obtained. An average liver abscess contains about 2 pints of pus, but as much as 6 pints may be aspirated. The operation may be performed under general or local anaesthesia. Generally one aspiration suffices provided it is preceded and followed by adequate emetine treatment, but sometimes fever and leucocytosis persist or recur, the abscess cavity refills and repeated aspirations may prove necessary.

*Open operation with or without drainage.*—Where an uncomplicated abscess involves the inferior surface of the right or left lobe of the liver, laparotomy may be necessary but the pus from such an abscess should be aspirated, and the wound closed without drainage unless bacterial infection be present. Practically the only indication for incision and drainage of an amœbic abscess is secondary bacterial infection and here penicillin, sulphonamides or streptomycin may prove of great value depending on the sensitivity of the secondary invaders to these different drugs. If an hepatic abscess ruptures into the lung, an hepatico-bronchial fistula may form and the pus be completely coughed up; treatment with emetine and postural drainage is generally effective. Should the abscess burst into the pleural cavity, empyema is likely to follow; aspiration and emetine injections should suffice unless there be secondary bacterial infection when drainage is necessary. Rupture into the peritoneal cavity is very serious, localised or generalised peritonitis resulting; immediate laparotomy is essential.

When it is necessary to drain a liver abscess the transpleural and the transperitoneal route should be avoided if possible. Where feasible the twelfth rib should be resected posteriorly and an extra-serous route be adopted (Ochsner and Debaeky). When a transpleural approach is essential, a two-stage operation should be carried out. Occasionally, where an amœbic abscess has been drained the sinus continues to discharge pus containing vegetative *E. histolytica* despite intensive courses of treatment with emetine, emetine-bismuth-iodide and Diodoquin reinforced with sulphonamides, penicillin and streptomycin to combat secondary bacterial infection. Under such circumstances, an intensive course of chloroquine may produce healing of the sinus and radical cure where all other drugs have failed.

## CILIATE DYSENTERY

**Definition.**—An ulcerative condition of the colon caused by *Balantidium coli* (Malmstren, 1857).

**Ætiology.**—Human infections generally occur amongst those having occupational contact with pigs, which also harbour this ciliate; cases have been reported from Europe, America, Asia and Africa. The ciliate is egg-shaped, 50 to 80 $\mu$  long by 30 to 55 $\mu$  broad; large and smaller forms are described. At its anterior end is the peristome; its interior contains a sausage-shaped macronucleus, a micronucleus and vacuoles, while externally the whole body is covered with longitudinal rows of cilia. Encysted forms, 50 to 60 $\mu$  long, also occur in the fæces. As healthy carriers are frequently encountered, it is possible that there is some secondary bacterial or other factor which determines the pathogenicity of *B. coli*.

**Pathology.**—The colon, and more rarely the ileum, shows ulcers distinguishable from amœbic lesions only by the demonstration of *B. coli*, which is found both in the cavity of the ulcer and the surrounding submucosa; it may also invade adjacent lymph glands, but not the liver.

**Symptoms.**—In many cases the disease remains latent and symptoms are absent. In others the onset is insidious, with loose motions, later followed by sanguineous,

mucoid stools typical of chronic dysentery; anæmia may develop. Intestinal perforation has been reported, but never liver abscess.

**Diagnosis.**—Sigmoidoscopy may show colonic ulcers, but diagnosis is dependent on demonstrating *B. coli* or its cysts in the excreta, or in scrapings from the ulcers themselves.

**Prognosis.**—The mortality rate including latent cases is about 7 per cent. (Walker), but in those showing active dysentery it may reach 29 per cent. (Strong).

**Treatment.**—Most of the remedies tried have not been satisfactory. Aguilar advises restricting carbohydrates and increasing protein and fresh vegetables. Stovarsol in doses of 0.25 g. (4 grains) twice daily after meals for 1 week or carbarsone in a similar dosage for 10 days holds out some prospect of cure. High colonic irrigation with solutions of iodine, quinine and silver nitrate have been recommended, but owing to the spontaneous disappearance of the ciliates from time to time the value of different remedies is difficult to assess.

## FLAGELLATE DIARRHŒA

There are three common intestinal flagellates of man, *Giardia intestinalis* (Lambl, 1859) which inhabits the upper intestine, *Trichomonas hominis* (Lavaine, 1860) and *Chilomastix mesnili* (Wenyon, 1910) found in the cæcum and colon. Considerable controversy has arisen regarding their pathogenicity and, though admittedly they are more common in cases of diarrhœa than in healthy individuals, nowhere do they actually invade the intestinal mucosa. Encysted flagellates are frequently found in normal stools, and Dobell has pointed out that the free flagellate forms which are naturally adapted to a fluid medium only appear when the stools become liquid or loose. From a clinical viewpoint, however, *G. intestinalis* has some claim to pathogenicity.

### GIARDIA INTESTINALIS (Lambl, 1859)

**Synonyms.**—*Lamblia intestinalis*; *Giardia lamblia*.

**Ætiology.**—This parasite inhabits the jejunum and duodenum and occasionally reaches the bile ducts. It is a pear-shaped flagellate (10 to 18 $\mu$  long  $\times$  5 to 10 $\mu$  broad), possessing a concave sucker on its ventral surface, and in the encysted form may persist for many years in the fæces. As with certain other flagellates decreased or absent secretion of hydrochloric acid in the stomach appears to predispose to infection, and after gastro-jejunostomy they may be found in aspirated gastric juice.

**Pathology.**—In animals the glands of the small intestine may be found packed with giardia, and though they never cause ulceration or hæmorrhage, hyperinfection may lead to surface irritation (Wenyon). It is possible that in this fashion catarrhal enteritis results.

**Symptoms.**—Though encysted forms are often found in the fæces in healthy individuals, periodic attacks of diarrhœa may occur associated with the passage of large quantities of clear mucus or ochre-yellow stools in which enormous numbers of free flagellates occur. The demonstration of these flagellates in the bile by means of a duodenal tube does not constitute evidence of pathological invasion of the biliary passages and gall-bladder, and the present tendency to attribute all manner of symptoms to giardia infection is to be deprecated.

**Prognosis.**—This is good; fatal cases in man are unknown.

**Treatment.**—Mepacrine hydrochloride (Atebrin) in a dosage of 0.1 g. t.d.s., p.c. for a period of 7 days eradicates giardia infection permanently in some instances; in others relapses occur.

N. HAMILTON FAIRLEY.

## F. RICKETTSIA DISEASES

## INTRODUCTION

Rickettsiae are small, non-motile, Gram-negative bodies usually less than  $0.5\mu$  in diameter which stain well by Giemsa's method. They are more or less pleomorphic, and are found in both host tissues and arthropod vectors. They are cultivated in the yolk sac of the developing chick or in agar tissue culture, and suspensions can also be obtained from the lungs of infected rats and mice. In tissue they are mainly located within mesothelial cells, either in the cytoplasm or the nucleus. Ricketts (1909) first noted these bodies in guinea-pigs and monkeys with Rocky Mountain spotted fever, and since then several varieties affecting man have been described. Thus, classical louse typhus is caused by *Rickettsia prowazeki*; murine or flea typhus by *R. mooseri*; Rocky Mountain exanthematic spotted fever by *Rickettsia* or *Dermacentroxenus rickettsi*; tsutsugamushi disease by *R. orientalis*; trench fever by *R. quintana*; and "Q" fever by *R. burneti*.

An ever-increasing number of typhus-like fevers is being described in different parts of the world caused by rickettsiae, and carried by arthropods like lice, fleas, ticks and mites in which rodents play an important rôle as reservoirs of infection. They have been classified on a geographical basis, according to their insect vectors, or in terms of their agglutination reaction with OX2, OX19 and OXK strains of *Proteus vulgaris*.

Rickettsiae possess heat-labile and heat-stable antigens, and sera from typhus patients contain or may contain the two corresponding types of antibody. Complement fixation reactions are of specific value in the diagnosis of epidemic typhus, murine typhus, Rocky Mountain spotted fever and "Q" fever.

*The Weil-Felix Reaction.*—This reaction is due to the production by certain rickettsiae of non-specific agglutinins against the "O" non-motile variant of certain strains of *Proteus* X. Suspensions of OX19, OX2 and OXK strains are employed.

Originally the reaction was carried out with living suspensions, but now the alcoholic method, which destroys the flagella and preserves solutions of "O" antigen is used. In general it may be said that OX19 is the main antigen for louse and flea-borne typhus, OXK for mite typhus, while the sera from patients with tick typhus, as a rule, react in low titre to all three strains. Felix thinks the strain forming the main antigen for the tick-borne group has yet to be discovered. The serum from patients with "Q" fever or trench fever does not react with any of these strains.

For clinical purposes, a rising titre exceeding 1 in 125 may be taken as diagnostic. The test should be made as early as possible in order to estimate subsequent rises in titre. A significant rise is generally well established by the tenth day. The usual maximum titre of 1/1000 to 1/5000 may not be attained until convalescence, after which the reaction weakens and gradually becomes negative. Exceptionally, a maximum titre of 1/100,000 is attained.

Though the Weil-Felix reaction is of little diagnostic utility during the first week except in louse typhus, and may occasionally fail to reveal agglutinin in significant titre in severe cases until convalescence is reached, it is a reliable test of very real clinical value. Non-specific stimulation of the proteus "O" agglutinin in other bacterial infections of man has been observed in tularaemia, chronic brucellosis, typhoid fever and infections with *Proteus vulgaris*; progressive rises in titre during the course of these diseases, however, do not occur.

The modified table on page 286, published by the Army Pathology Laboratory Service (1941), summarises data regarding the Rickettsial diseases affecting man.

DISEASE.	RICKETTSIA.	GEOGRAPHICAL DISTRIBUTION.	INSECT VECTORS.	POSSIBLE VERTEBRATE RESERVOIRS
Exanthematic typhus.	<i>Rickettsia prowazeki</i> .	Europe, Abyssinia, North Africa, Belgian Congo, Asia Minor, Persia, North China, Mexico.	Louse <i>Pediculus humanus</i> .	Man.
Endemic or murine typhus.	<i>R. mooseri</i> (= <i>R. muricola</i> ).	Worldwide.	Rat flea <i>Xenopsylla cheopis</i> .	Rat (squirrel shrew).
Tsutsugamushi disease.	<i>R. orientalis</i> (= <i>R. tsutsugamushi</i> ).	Japan, Formosa, Malaya, Java, Sumatra, New Guinea, North Queensland.	Larva of <i>Trombicula akamushi</i> (Japan) <i>T. deliensis</i> (India). <i>T. fletcheri</i> (New Guinea).	Vole. Rat. Bandicoot.
Trench fever.	<i>R. quintana</i> (= <i>R. volynica</i> and probably <i>R. weigli</i> ).	North Africa.	Louse <i>P. humanus</i> .	Man.
Rocky Mountain spotted fever (Eastern and Western forms).	<i>Dermacentor xenus rickettsi</i> .	U.S.A.	<i>Dermacentor andersoni</i> , <i>D. variabilis</i> .	Goats, hares and other rodents. Dog.
São Paulo rural typhus.	<i>D. rickettsi</i> var. <i>brasiliensis</i> .	Southern Brazil.	Tick <i>Amblyomma cajennense</i> .	Opossum. Dog.
Fièvre bouton-neuse.	<i>D. rickettsi</i> var. <i>conori</i> .	Mediterranean zone.	Dog tick. <i>Rhipicephalus sanguineus</i> .	Dog.
South African tick typhus.	<i>D. rickettsi</i> var. <i>pijperi</i> .	South Africa. <sup>1</sup>	Tick <i>Hamaphysalis leachi</i> .	Dog.
"Q" fever.	<i>Rickettsia burneti</i> (= <i>R. diaporica</i> ).	Australia, U.S.A.	Ticks <i>Hamaphysalis humerosa</i> , <i>Dermacentor andersoni</i> , <i>D. occidentalis</i> , <i>Amblyomma americanum</i> , <i>Rhipicephalus sanguineus</i> ?	Bandicoot.

## FLEA TYPHUS

Synonyms.—Murine Typhus; Hone's Disease; Ship Typhus; Typhus Murin; Endemic Typhus; Urban Tropical Typhus; Shop Typhus.

<sup>1</sup> Tick-borne typhus also occurs in Abyssinia and in Kenya where the dog tick *Rhipicephalus sanguineus* acts as vector.



**Definition.**—A mild typhus-like fever, with a worldwide distribution, occurring in non-epidemic form, and caused by *Rickettsia mooseri*. It is conveyed to man by the rat flea, *Xenopsylla cheopis*, from infected rats or other rodents which are natural reservoirs of the disease.

**Ætiology.**—That some connection might exist between the handling of grain and rats was first suggested by Hone (1922) in South Australia. Dyer and others (1931) found that fleas collected from rats and injected into guinea-pigs produced the disease. Nicolle (1933) described the same disease under the title "Typhus murin" in sailors in French warships.

*R. mooseri* has a similar morphology to *R. prowazeki*, which causes epidemic typhus, and the Weil-Felix reaction with OX19 strains is similarly positive in the two diseases. The two diseases can be differentiated serologically only by complement fixation and agglutination tests with rickettsial antigens. They also differ inasmuch as *R. mooseri* gives a positive scrotal reaction when inoculated into guinea-pigs. It may be most important to differentiate early between outbreaks of epidemic (louse-borne) and murine (flea-borne) typhus.

**Pathology.**—Patients rarely die with flea-borne typhus, but there is no evidence that the lesions differ from those of mild epidemic typhus. In infected animals pathological changes are very similar to those caused by *R. prowazeki* except in the guinea-pig, where the scrotum becomes dusky red, swollen and inflamed, the tunica is thickened and may show hæmorrhage and exudate, and the testicle is swollen. Rickettsiæ are found in large numbers in the cytoplasm of the serosal cells of the tunica vaginalis. This is known as the Neill-Mooser reaction, and is feeble and inconstant with *R. prowazeki*.

**Symptoms.**—The incubation period is generally 8 to 14 days. As a rule the onset is rapid, with chilliness or a mild rigor and moderate temperature, or it may start more gradually with irregular initial symptoms and slowly increasing fever. The face becomes flushed, the conjunctivæ are somewhat injected, and headache, pains in the back and cough, perhaps associated with pulmonary basal congestion, are commonly found. The rash usually appears about the fourth or fifth day, on the chest, abdomen and inner surfaces of the arms, extending later to other parts. It consists of rose-red or dusky-red macules, fading on pressure and, unlike classical louse typhus, petechiæ are uncommon. In dark-skinned people the rash may be so inconspicuous as to be missed altogether. The fever lasts 7 to 14 days, the temperature falling by lysis.

Complications are few, but broncho-pneumonia and pleurisy with effusion may occasionally supervene.

**Diagnosis.**—A history of association with rats, the mild nature of the illness and the strongly positive Weil-Felix reaction to OX19 strain of *Proteus* with negative agglutination to OXK and OX2 antigens will generally enable a diagnosis to be made, especially if the disease occurs in countries where louse typhus is not endemic.

**Course and Prognosis.**—The disease runs a mild course, has a low case mortality rate (1 per cent. or under), and convalescence is rapidly established.

**Treatment.**—PROPHYLAXIS consists essentially in rat proofing, rat destruction, and the avoidance of contact with rats. Experimentally induced immunity is good against the murine strains of rickettsia, but owing to the sporadic nature and mildness of the disease large-scale vaccination is unnecessary.

The general measures adopted in mite and louse typhus are also applicable. Chlortetracycline, oxytetracycline and chloramphenicol are all remarkably effective. Response is very rapid, fever usually subsiding in 24 to 48 hours. Mortality is very low in treated cases. The antibiotics are usually administered orally. An initial loading dose of 2 to 3 g. (for a patient weighing 70 kg.) is given in the course of 2 hours and is followed by 0.5 g. 6-hourly until the temperature has been normal for 2 days.

## MITE TYPHUS

A number of varieties of mite typhus has been described due to the one virus, *R. orientalis* or *R. tsutsugamushi*. For many years the scrub or rural form of tropical typhus described by Fletcher in the Federated Malay States, and transmitted by *Trombicula deliensis* from infected rats, was regarded as differing from tsutsugamushi disease in as much as there was supposed to be an absence of a primary lesion, lymphangitis and bubo. Lewthwaite and Savor (1940) have now identified the two viruses, and shown that in rural typhus there may be either a persisting eschar or a fleeting papular lesion which often escapes recognition by its disappearance before the onset of other symptoms. The local lesion is common in the white-skinned European and rare in the dark-skinned Tamil. In Sumatra the pseudo-typhus of Deli, transmitted by *T. deliensis* from infected rats, is also identical with tsutsugamushi; though the mortality is only 5 per cent. in the indigenous population, it may be as high as 40 per cent. in Europeans. Similarly, scrub typhus encountered in India, Ceylon, Burma, Indo-China, the Philippines, the Dutch East Indies, New Guinea and on the mainland of Australia in North Queensland is transmitted by larval mites, and the virus is identical with that of tsutsugamushi disease. A remarkable feature noted in New Guinea, as elsewhere, is the variable virulence of the virus, the mortality rate in different localities varying from 1 to 30 per cent. This variable virulence is probably dependent on different strains of the one virus, though the size of the infecting dose may also be a factor.

## TSUTSUGAMUSHI DISEASE

**Synonyms.**—Japanese River Fever; Mite Typhus; Scrub Typhus; Rural or Scrub Tropical Typhus; Pseudo-Typhoid of Deli; Sumatra Mite Fever.

**Definition.**—An acute disease of the typhus group characterised by fever of 2 to 3 weeks' duration, a primary sore or eschar associated with local adenitis, a maculo-papular rash, generalised lymphatic glandular enlargement, deafness and symptoms of basal pulmonary congestion. It is caused by *Rickettsia orientalis* and is transmitted from infected field mice (voles) or rats to man by the bite of certain larval mites of the genus *Trombicula*.

**Ætiology.**—In Japan the disease occurs commonly in the summer amongst harvesters handling the hemp crop in the Island of Nippon. Here the vole, *Microtus montebelloi*, is the reservoir host. Trombiculid mites pass through four stages in their development, but it is only the larval stage which can transmit infection to man. The rodent reservoirs in Sumatra, Malaya and New Guinea are rats, and, as in the case of voles in Japan, the red hexapod larvæ (100–200 $\mu$ ) are found inside the ears of their rodent hosts. The larval mite needs one feed on animal tissue-fluid for its metamorphosis, and is liable to get on to people walking through the jungle, lying on infected ground, or sitting on logs. Having attached itself to the skin and fed, the engorged larval mite drops off and passes through the nymph stage to become adult. The nymphs and adults feed exclusively on plant juices. The adults, which are only about 1 mm. long and 0.5 mm. wide, live in soil to the depth of a few inches, and presumably deposit their eggs on the ground, where a new larval generation hatches out. Larval mites live on the ground and in rotting leaves, but they may climb up a few inches on the stems of Kunai grass, etc., or even higher on to rotten logs when stimulated by the presence of man. Once the virus is acquired by a mite larva it can pass on continuously from the adult to the egg and larva, which transmits the disease at its next animal feed. It is important to demarcate accurately any area where the disease has been acquired, so that subsequent exposure of troops or civilians

to infection may be avoided. *T. akamushi* transmits in Japan, *T. deliensis* in Malaya and India and *T. fletcheri* in New Guinea.

There is no necessary relationship between scrub itch and scrub typhus, as the species of trombiculid mite, such as *T. minor*, which produces the former may not be a vector of the latter. Some hours after being bitten by uninfected mites, hypersensitive persons develop itchy papules, which may vesicate and later become infected with pyogenic bacteria. Large numbers of these close-set lesions may be observed round the waist, or on the legs, etc. If an infected mite inoculates rickettsiæ while biting, a primary sore or eschar is liable to result, due to multiplication of these organisms *in situ*.

**Pathology.**—The local eschar, with inflammatory enlargement of the regional lymph glands, petechial hæmorrhages involving the serous membranes and alimentary tract, bilateral pulmonary congestion, generalised adenitis, including the tracheo-bronchial and mesenteric lymph glands, a flabby heart, with or without dilatation of its cavities and degeneration of the kidneys and liver are typical findings at necropsy. The brain may show œdema, increase in the cerebrospinal fluid and congestion of the superficial cortical vessels. Occasionally thrombotic lesions, such as pulmonary infarction or femoral thrombosis, are encountered, but, unlike louse-borne typhus, widespread thrombosis of the peripheral blood vessels is rare, and rickettsiæ in the endothelial cells lining the blood vessels are exceedingly difficult to demonstrate. Histopathological findings include perivascular cell infiltration, extravasation of red blood corpuscles due to degeneration of the endothelial cells lining the small vessels and degenerative toxic changes in the parenchymatous cells of the spleen, liver and heart muscle.

**Symptoms.**—A small papule may be evident some 2 or 3 days after the attachment of the larval mite to the skin. This either subsides or may develop into a typical eschar. At the onset of the fever the eschar is a small rounded or oval sore 2 to 4 mm. in diameter, surrounded by a raised dusky areola 3 to 4 mm. in width. There is a firmly attached necrotic centre, which later develops into a black slough; this separates from the tenth day onwards, producing a punched-out ulcer. Healing occurs in 3 to 4 weeks, leaving a pitted scar which is occasionally pigmented. Eschars are demonstrable in about 60 per cent. of European cases; they are generally single but occasionally may be multiple, as many as 6 being recorded. The site of the eschar is largely determined by the type of clothing worn. With open shirt, shorts and stockings the lesion appears on the neck or the calf at the upper margin of the stocking. When trousers and gaiters are worn the legs are rarely affected, the common site being the arms and axillæ (30 per cent.), chest and neck (20 per cent.) and the thighs and buttocks (27 per cent.) (Williams, Sinclair and Jackson).

Fever commences some 5 to 14 days after the bite (incubation period). The onset is generally sudden, with a rise in temperature ( $99^{\circ}$  to  $102^{\circ}$  F.), malaise, headache, post-orbital pain, shivering, rigors, aching pains in the back and limbs and perhaps vomiting. Occasionally there is a period with mild malaise and headache for 2 or 3 days prior to the onset of fever.

In the typical case a high temperature is soon established— $103^{\circ}$  to  $104^{\circ}$  F. being usual and up to  $105^{\circ}$  F. not uncommon. A 4-hourly chart often reveals marked irregularities, the temperature being remittent, intermittent or continuous. In some, the temperature is continuous with little tendency to remittency; in others an intermittent type of temperature is common for the first 10 to 14 days, after which the temperature tends to become continuous and subsides by lysis on the fourteenth to seventeenth day. Injected conjunctivæ, a furred cracked tongue, anorexia and constipation are frequent; and diarrhœa and abdominal distension occur in a few instances. Characteristic features appearing near the end of the first week include (1) generalised enlargement of the lymphatic glands, (2) a maculo-papular eruption, (3) pulmonary features, (4) mental symptoms and (5) transient nerve deafness.

During the second and third weeks prostration and mental symptoms increase, the early euphoria being replaced by irritability, sleeplessness, delirium or apathy and drowsiness. The cough becomes increasingly troublesome, there is considerable loss of weight, tremor may be marked and the superficial abdominal reflexes and knee and ankle jerks are decreased or absent. The heart sounds soften and, in severe cases, the blood pressure tends to fall markedly, the skin assumes a dusky hue and the tissues over the ankles and sacrum may pit on pressure; occasionally there is incontinence of faeces and urine, with increased risk of bed sores developing. The patient may die from peripheral circulatory failure or coma in the third week, or the fever may subside by lysis with drenching sweats and steady improvement. Though the febrile stage of the disease does not generally exceed 3 weeks, severe cases do occur where fever continues for 4 to 6 weeks; in most of these there is some complication, such as an infected pulmonary infarct. In the average case the patient is normally well in 6 weeks and fit to resume his ordinary vocation within 3 months.

In dark-skinned Asiatics the eschar is not readily demonstrable and the rash may be so inconspicuous that it passes unnoticed. Mild suffusion of the eye, associated with photophobia, fever, mild cough, headache, deafness and slight enlargement of the glands may be the only noteworthy clinical features (Lewthwaite and Savaor).

In the *mild type* the onset and course of the fever are similar, but mental changes are inconspicuous, the blood pressure is well maintained, cyanosis and oedema of the feet are absent, and the pulmonary features are transient. Such patients are well at the end of 3 weeks and fit to work in 6 to 8 weeks.

In the *ambulatory type* symptoms are so mild that the patient does not feel sufficiently ill to take to bed; positive agglutination reactions are the only criterion of diagnosis in such cases.

*Special features.*—The characteristic eschar has already been described, but certain other features call for more detailed description.

(1) *Adenitis.*—By the fifth day there is often slight or moderate enlargement of the lymphatic glands, which are discrete, elastic and firm. The axillary, and superficial and deep inguinal glands are commonly affected, the cervical and epitrochlear glands less frequently. The most marked enlargement is found in the regional lymph glands draining the eschar, but even here tenderness is not marked unless secondary infection has supervened.

(2) *Rash.*—Some 50 to 70 per cent. of European patients develop a maculopapular rash, fading on pressure. Macules first appear on the chest and abdomen from the fifth to eighth day, soon become slightly raised, assuming a maculopapular appearance, and within 48 hours may spread to the face, neck, arms, palms of the hands, trunk, thighs, legs and soles of the feet. When fully developed these maculopapular lesions have a diameter of from 2 mm. to 1 cm. and a dull-red appearance; they commence to fade within 4 to 5 days and have usually disappeared by the fourteenth day of the disease. Macules may occasionally be observed on the soft palate. Sometimes the papular element may be lacking, and the small closely packed macules then simulate the rash of dengue or measles. In fatal cases the rash occasionally becomes petechial (Williams, Sinclair and Jackson).

*Pulmonary features.*—Cough is common early in the disease, and rales and rhonchi are frequently noted. Chest pain is not uncommon. Signs in the lungs appear from the seventh day onwards, but in milder infections these features are transient and do not progress as in the seriously ill, in whom dullness, diminished vesicular murmur, abundant crepitations, rales and rhonchi are audible over both lower lobes. These features are accompanied by the development of cyanosis of the lips and an increased respiratory rate to 40 or thereabouts. Mouth breathing is frequent, and there is an irritating cough, with tenacious white or blood-streaked frothy, non-

purulent sputum. In cases which recover, these abnormal chest signs begin to disappear at the end of the third week.

*Nervous system.*—Mental features are common in the seriously ill patient. During the first 4 days the mental state is generally normal, any change noted being towards euphoria or apathy. From the sixth to tenth day ill patients show more pronounced changes. In some the initial euphoria increases, and restless irritability, toxic confusion, insomnia and delirium supervene. Others become atonic, apathetic, drowsy and stuporous. Coma not infrequently precedes death. With clinical recovery, the mental state returns to normal.

Neurological features include nerve deafness, tremor, photophobia, tinnitus, *paræsthesia*, *hyperæsthesia*, *neuritic pains*, *depressed superficial and deep reflexes*, and urinary incontinence and retention. Nerve deafness, which is a characteristic feature, is generally bilateral. It appears about the fifth day and rarely lasts longer than a week, permanent deafness being very rare. Headache and neck stiffness may be associated with increased cerebrospinal fluid pressure.

The cerebrospinal fluid is often normal, but may show increased lymphocytes, increased protein and decreased chlorides. These changes are most commonly found about the tenth day, disappear with recovery and are not necessarily related to neurological complications.

*Cardio-vascular features.*—The pulse-rate is slower than would be anticipated from the temperature during the first week; it quickens to between 90 to 120 per minute during the second week. In non-fatal cases the pulse is regular in rhythm but may be dicrotic during the second and third week. With cessation of fever the heart-rate soon returns to normal, and during convalescence significant cardiac abnormalities are rare. From the second week onwards in severe cases the blood pressure tends to fall, the daily readings being 75–100 m.m. Hg. systolic and 35–60 m.m. Hg. diastolic. Fatal cases not infrequently die with peripheral cardio-vascular failure. After recovery it takes about 2 weeks for the blood pressure to become normal.

*Laboratory findings.*—The serum gives a positive agglutination to *Proteus* OXK suspensions, not to OX19 or OX2. The agglutinin commences to increase about the seventh day, reaching a maximum titre about the twentieth day. For this reason it is sound practice to examine the blood at weekly intervals, commencing during the first week and keeping some of the first serum for subsequent tests. In cases in which only one test is done, an arbitrary minimum diagnostic titre of 1/125 can be provisionally accepted as diagnostic of an active infection; but, as Felix points out, suspensions of *Proteus* OXK are more susceptible to non-specific "normal" agglutination by sera from man than are suspensions of OX19 and OX2, and for this reason additional caution is necessary in making a diagnosis on the basis of a low titre agglutination reaction.

The leucocyte count varies within fairly large limits, and neutropenia is not uncommon. During the first 9 days the count tends to be of low normal type, *i.e.* 4000 to 7000 cells per c.mm.; later it increases. The lymphocytes are on an average below 2000 per c.mm., but increase later in cases which recover; in fatal cases the count frequently remains below 2000 per c.mm. (Williams, Sinclair and Jackson).

Anæmia is not a marked feature. Hæmoglobin may be decreased by 2 to 3 g. per 100 ml., with an equivalent reduction in erythrocytes. Mild albuminuria is the rule, and in severe cases this increases and hyalo-granular casts appear.

*Complications.*—These include *parotitis*, *broncho-pneumonia*, *pleurisy* with effusion and infarction. Infarcts may become secondarily infected and lead to lung abscess. Femoral thrombosis may develop in the second or third week, and suppuration may occur in the course of the vein. Eye complications include conjunctival hæmorrhage, retinal hæmorrhage and rarely thrombosis of the retinal artery with

amblyopia. Epistaxis and bleeding from other mucous membranes rarely occur. Other vascular accidents include subdural hæmorrhage and intra-cerebral hæmorrhage with hemiparesis. Paresis and paralysis of different types may develop; these include ulnar paralysis, nerve deafness, facial paralysis, paralysis of scapulo-humeral type and paralysis of the phrenic nerve, with paradoxical movement of the diaphragm demonstrable by radiological examination. Cardiac complications are uncommon, but tachycardia of nervous origin may be observed in a proportion of convalescent patients. This soon disappears if no notice is taken of the condition, but if the attention of the patient be riveted on it by frequent cardiac examinations and over-anxiety on the part of the medical attendant a cardiac neurosis may result. During the War of 1939-1945 this danger was narrowly averted amongst the thousands of cases of scrub typhus contracted in the South-West Pacific.

**Diagnosis.**—This may prove difficult or impossible in the early stages of the disease unless an eschar be present. Local and generalised lymph gland enlargement, the appearance of the maculo-papular rash, and nerve deafness are of great diagnostic assistance if present. In most cases of doubt a positive Weil-Felix reaction in the second or third week of the disease will clinch the diagnosis. The differential diagnosis is largely a matter of geography; malaria, typhoid, paratyphoid, flea-typhus, leptospirosis, dengue, measles, broncho-pneumonia and cerebrospinal meningitis may require differentiation in many parts of the tropics.

**Prognosis.**—The case mortality rate in European troops averaged about 8 to 10 per cent., but varied from 1 to 50 per cent. It is higher in the older age groups. Big variations may be seen within the same country in people of the same race in the same year. Unfavourable features are increasing nervous symptoms, cyanosis, progressively rapid respiration, œdema, Cheyne-Stokes respiration, coma and cardiac and peripheral circulatory failure. Death is generally due to overwhelming toxæmia or respiratory complications.

**Treatment.**—**PROPHYLACTIC.**—This consists essentially in measures designed to destroy larval mites or avoid contact with them. Infected localities, if known, should be clearly demarcated and avoided wherever possible. If it is necessary to work in mite-infested country, anti-mite fluids, such as dibutyl and dimethyl phthalate, should be applied to the clothing, and blankets should be treated with anti-mite fluids where troops have to sleep in such country. No effective rickettsial vaccine is available for prophylactic use in man.

**CURATIVE.**—Expert nursing is all important, and if possible the patient is better nursed in Fowler's position. Strict rest in bed is necessary until the patient has been apyrexial for at least 10 days. Owing to the prolonged high temperature it is most advisable wherever possible, to treat patients in an air-conditioned ward. Hydrotherapy is important and frequent cool sponging is indicated. A fluid intake of 140 oz. daily is advisable. Eggs, milk, junket, ice-cream, fruit juices and nourishing carbohydrates are generally well taken, and vitamin reinforcement of the diet is often indicated. Intravenous injections of glucose and saline are necessary in a dehydrated patient whose water intake is unsatisfactory. Sedation is important, and phenobarbitone, Nembutal or morphine should be given to ensure sleep and rest when necessary.

Specific treatment with chlortetracycline, oxytetracycline or chloramphenicol is similar to that for flea typhus (p. 287).

Smadel and his colleagues reported that within 2 to 3 days of commencing treatment in Malaya the patient had a normal temperature, toxic symptoms had vanished and convalescence was established. In the first 90 cases, some of which were treated as late as the ninth day, no deaths occurred. The case mortality rate in Malaya is ordinarily 15 per cent. As patients die from the eleventh day onwards, the necessity for early diagnosis becomes increasingly important.

## TICK TYPHUS

Several strains of virus are probably concerned in the causation of tick-borne typhus. The reservoir hosts are rodents and dogs, and, as Megaw points out, the epidemiological and clinical features of the different tick-borne diseases have sufficient in common to justify their being dealt with together. The agglutination reaction to all the strains OX2, OX19 and OXK tends to be of low titre except in Rocky Mountain spotted fever where serum agglutinins to *Proteus* OX19 begin to appear about the eleventh day and rise in titre during convalescence.

Spotted fever of the Rocky Mountains was recognised long before any other types, and includes the milder Eastern type of spotted fever and the more severe São Paulo fever. The latter is conveyed from rats to man by the horse tick, *Amblyomma cajennense*, and has a mortality rate of 70 per cent.; it closely resembles the graver cases of Rocky Mountain spotted fever, and its virus also immunises animals against the latter disease. In U.S.A. the vector in the West is the wood-tick, *Dermacentor andersoni*, in the East the dog-tick, *Dermacentor variabilis*; and on the Gulf coast, *Amblyomma americanum*. The sera of dogs in infected localities may show a high complement fixation titre in infected areas against *Dermacentroxenus rickettsi*, and there appears to be a definite risk in "handling" dogs harbouring infected ticks. When the tick has a mammalian blood meal the rickettsiæ present in tick faeces may be reactivated and may penetrate the skin or be inhaled. Many cases of Rocky Mountain spotted fever show no evidence of tick bite and no local lesion and it is possible that people may be infected directly from tick faeces apart from tick bite.

Fièvre boutonneuse and the tick-bite fevers of Kenya and South Africa have much in common. Unlike Rocky Mountain spotted fever there is usually a sore at the site of the tick bite, and in experimental animals there is cross immunisation between boutonneuse and the South African virus. Fièvre boutonneuse occurs in most countries bordering on the Mediterranean, and is conveyed from dogs by the dog-tick, *Rhipicephalus sanguineus*. Clinically, it resembles the mild form of Rocky Mountain spotted fever, but the presence of a local eschar, the more nodular nature of the rash and the low mortality rate of 1 to 2 per cent. are outstanding differences.

"Q" fever, which is caused by *R. burneti*, gives rise to a mild typhus-like fever in man and inoculated guinea-pigs. In mice inoculated with human blood collected during the fever, rickettsiæ are found in the spleen and suspensions obtained from mouse tissue are agglutinated in high titre by human serum from infected cases. The Weil-Felix reaction with the serum, however, is negative to all the known strains of *Proteus*. In Australia the bandicoot is a natural reservoir of infection and infected ticks of the species, *Hæmaphysalis humerosa*, have been collected from these animals. "Q" virus has also been found in *D. andersoni* by Dyer, in Montana, where the inhabitants of certain villages acquire the disease. Guinea-pigs, injected with a vaccine which will protect against Rocky Mountain spotted fever, are not protected against "Q" fever. *R. burneti* has been shown to cause outbreaks of fever with pulmonary lesions simulating virus pneumonia, and it is not improbable that direct inhalation of rickettsiæ is the mode of infection in such cases (see p. 302).

## ROCKY MOUNTAIN TICK TYPHUS

**Synonyms.**—Rocky Mountain Spotted Fever; Spotted Fever of Eastern Type; Erythematous Typhus of São Paulo; Choix Fever; Pinta Fever; Tobia Fever.

**Definition.**—A non-epidemic severe typhus-like fever long recognised in the Rocky Mountains. It is generally unassociated with a local lesion or adenitis, and is transmitted to man from infected rodents by the bites of several different species of ticks including *D. andersoni*. The disease may have a high mortality.

**Ætiology.**—The disease primarily affects wild rodents, and, as shown by Wilson and Chowning (1904), is conveyed to man by ticks. Larval and nymph ticks transmit the virus from rodent to rodent, but human beings are usually infected by adult ticks of the species *D. andersoni*, *D. variabilis*, *A. americanum* and *A. cajennense*. Infected ticks transmit the infection to their offspring and serve not only as a vector but as a reservoir for rickettsiæ. The causal organism, *D. rickettsi*, was described by Ricketts (1909) in the blood of guinea-pigs and monkeys infected with Rocky Mountain spotted fever. *D. rickettsi* produces a well-marked scrotal reaction in inoculated guinea-pigs, and can be demonstrated in the fluid exudate of the tunica vaginalis prior to generalised dissemination in the blood stream.

Most infections are found in people whose occupations brings them in contact with ticks. Where town dwellers are affected, dogs probably are implicated. Most cases occur in April and May in the Rocky Mountains, and in the summer in the Eastern States of the U.S.A.

**Pathology.**—Pathological changes include petechial hæmorrhages involving the skin and serous membrane, enlargement of the spleen and lymph glands, and degenerative changes in the kidneys, liver and heart. The essential lesion is an acute infection of the small blood-vessels throughout the body, particularly in the skin and brain. Proliferation of the vascular endothelium often leads to thrombosis and possible secondary gangrene. *D. rickettsi* is found within the nuclei of mesothelial cells, not in the cytoplasm as with *R. prowazeki*.

**Symptoms.**—The incubation period is from 3 to 14 days. A local lesion at the site of the tick bite with adenitis is rare. The onset is generally sudden, with headache, lumbar and generalised pains, and sometimes sweating, rigors, anorexia, malaise and vomiting. The tongue is coated, the conjunctivæ injected and the temperature rises rapidly to 103° or 104° F., the maximum being reached in 3 or 4 days' time. By then, in severe cases, the face is becoming dusky and a rose-red macular or papular rash appears. Later the macules turn darker, cease to fade on pressure and may become obviously hæmorrhagic. The rash is first seen on the wrists and ankles; later it extends to the body generally, including the palms, soles and face. The fever lasts 2 or 3 weeks, and falls by rapid lysis. Constipation, restlessness and insomnia are usual, while severe cases may show stupor, delirium, coma and convulsions. Enlargement of the spleen is not uncommon, and may be an early feature. Later, there may be jaundice and hepatomegaly and, where the central nervous system is involved, altered reflexes, and Babinski's and Kernig's signs may be elicited. A leucocytosis of 15,000 to 20,000 per c.mm. is not infrequent, but leucopenia may occur; the lymphocytes are increased. Albuminuria is the rule in severe cases.

Apart from this average classical type there are abortive cases, with transient fever lasting 3 or 4 days; ambulatory cases, with scanty rash and fever lasting 7 to 10 days; and fulminating cases, which die with marked nervous symptoms either before the rash has appeared or with a hæmorrhagic type of eruption.

**Complications and Sequelæ.**—Convalescence tends to be prolonged, especially in severe cases. Bronchitis, pneumonia, femoral and other thromboses, parotitis, hæmaturia, epistaxis and melæna may complicate the picture. Iritis, nephritis, otitis media and gangrene of the fingers, toes, tonsils, prepuce and scrotum have been recorded.

**Diagnosis.**—The differential diagnosis includes epidemic and other forms of typhus, typhoid and the paratyphoid fevers, and cerebrospinal meningitis. Geographical considerations, the character of the rash and the serological and other laboratory findings are of importance. Positive serological reaction may be obtained with OX19 strains of *Proteus*, but more specific results have recently been obtained by means of complement fixation tests employing purified rickettsial suspensions as antigen.



**Prognosis.**—The mortality rate varies from 5 to 90 per cent. in different geographical areas. Apart from fulminating cases, the onset of profound nervous symptoms, severe cardio-vascular depression and a hæmorrhagic rash indicate a severe infection and imply a correspondingly grave prognosis. Age is of great importance, the higher age groups having a high mortality.

**Treatment.**—In endemic areas tick-proof clothing should be worn and the body carefully searched for ticks; iodine should be applied locally after their removal. A prophylactic vaccine prepared from a killed suspension of specific rickettsiæ should be given in endemic areas and repeated each year. Specific treatment with chlor-tetracycline, oxytetracycline or chloramphenicol (Chloromycetin) is similar to that described on p. 287.

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## LOUSE-BORNE TYPHUS FEVER

**Synonyms.**—Typhus Exanthematicus; Epidemic Typhus; Fleck Typhus; Jail or Camp Fever.

**Definition.**—An acute louse-borne infection due to *Rickettsia prowazeki* and characterised by continued fever, a maculo-papular eruption, nervous irritability and profound prostration. In favourable cases rapid defervescence occurs about the fourteenth day.

**Ætiology.**—The infection is conveyed by body lice, perhaps through their bites, but more probably by cutaneous inoculation of their excreta by scratching. Head lice are also possible vectors. The disease is one of a group transmitted by lice, rat fleas, ticks and larval mites, but differs from the others in that it has a human and not an animal reservoir. Typhus fever can also be transmitted sporadically by the rat flea, but in epidemics the body louse is the infecting agent. Most of the factors which conduce to the spread of typhus operate by their influence on the parasites by which the disease is conveyed. The lice pass directly from the sick to the healthy, or indirectly by means of garments, in the seams and folds of which they naturally live, or by bedclothes and mattresses. They migrate from the dead. Lice which have fed on infected persons can, after a few days, transmit the disease and remain infective for the rest of their short lives. Their eggs also contain the infective agent. Their dried *fæces* remain infective for many months and may possibly be air-borne as dust and inhaled. The conjunctivæ are also possible portals of entry. Infected lice die in about 11 days, but the rat flea remains alive and infectious for several months. Crowding of the sick together in dark, ill-ventilated rooms greatly favours the possibility of infection, whilst in the presence of free ventilation very close contact is necessary before the disease is contracted.

Typhus carriers are always verminous persons. Clothes which harbour infected lice have also transmitted the disease to distant parts. Typhus is a disease of cold and temperate climates; it occurs in those months when confinement within doors and overcrowding are most likely, but paradoxically the peak of prevalence in countries where it is endemic may occur in March, April and May. In hot climates bathing, scantiness of attire, free action of the skin and the lethal effect of high temperatures on lice are all factors which prevent its spread. But even here it may be found at high altitudes. Predisposing causes of epidemics are verminous infestation, overcrowding, mass movements of the population and, above all, starvation. Epidemics are particularly liable to occur in times of war and famine.

In Russia, Eastern Europe and Asia Minor the disease is very prevalent. An endemic form of typhus fever, due to *R. mooseri*, is of wide distribution. It is transmitted by the rat flea, *Xenopsylla cheopis*, and the rat is the reservoir of infection. This endemic or murine form has been observed in Africa, Greece, China, and North

and South America. The murine strain occasionally gives rise to epidemics, as, for instance, in Mexican typhus or tabardillo when the agent is louse-borne. Brill's disease, on the other hand, is an endemic form of typhus due to *R. protazecki* believed to have been imported into the towns of the North American Atlantic seaboard by immigrants from Central Europe.

Typhus attacks persons of all ages and both sexes. The greatest mortality is in those above middle age, at 50 years it may be 50 per cent., and between 75 and 80 years nearly 85 per cent.; attacks in the young are less severe and very much less fatal. The average mortality is 10 to 20 per cent. In populations where the disease is endemic attacks may be very mild, but when introduced into other places the same strain may prove excessively severe. In Brill's disease the mortality is less than 1 per cent. By some this low mortality is attributed to a previously acquired immunity or even to recrudescence of a latent infection. As a rule not only does louse-borne typhus protect against itself but also, it is stated, affords protection against the endemic flea-borne variety.

**Pathology.**—The naked-eye post-mortem appearances are those common to many acute infections and are not in themselves distinctive. Petechial hæmorrhages in the skin, serous and mucous membranes and bronchiolitis or a general catarrh of the air passages and hypostatic congestion of the lungs are common. Softening of the spleen and inflammatory lesions of the kidneys, heart and testes may occur. The absence of ulcerative lesions in the bowel affords a distinction from typhoid fever. Beyond occasional meningeal congestion the central nervous system appears normal. Zenker's degeneration of muscle may be found.

Microscopical examination reveals discrete nodules of endothelial proliferation widespread in small arteries of the conjunctivæ, the skin, the brain-stem and elsewhere. These foci are surrounded by a characteristic perivascular infiltration of large mononuclear and plasma cells. The lesions may initiate thromboses or by necrosis give rise to small hæmorrhages. They are known as typhus nodules.

Prime importance is attached to Rickettsia bodies (*R. protazecki*). These are small and pleomorphic, not more than 0.3 by 0.4 $\mu$  in size. They lie in the cytoplasm of cells, are Gram-negative and stain by Giemsa's stain. Rickettsia bodies are found sparingly in the blood on the seventh to the twelfth day of the disease, and also in infected lice and their excreta. Similar bodies occur in the typhus nodules and in the endothelial cells of the liver.

An agglutinative phenomenon, the Weil-Felix reaction, affords a valuable means of recognising typhus. The reaction is named after two observers who discovered in the urine of patients suffering from typhus an organism of the *Proteus* group which is agglutinated in high dilution by the serum of those infected. Two strains of the bacillus are concerned OX19 and OX2, and agglutinations have been obtained with dilutions of serum up to 1 in 30,000. Reactions in controls, if occurring at all, do not take place in dilutions exceeding 1 in 50 or, at most, 1 in 100. In half the cases of typhus the reaction is found by the fifth day, and in practically all by the tenth day, after which the titre rises for about a week. There is, however, no proof that either *Proteus* OX19 or OX2 is capable of producing typhus, nor does it confer immunity to the disease. An agglutination test with Rickettsia bodies has also been elaborated (*Weigl reaction*).

The Wassermann reaction is often positive in typhus if the blood is examined before the crisis, but becomes negative again in convalescence. In inoculated persons the titre of the Widal reaction for typhoid rises steadily. This is an anamnestic reaction.

**Symptoms.**—The incubation period is about 12 days with extremes of 5 to 21. The classical onset is sudden and ingravescence much more rapid than in typhoid. Distressing headache, giddiness, shivering or rigor and often vomiting mark the accession. Pains in the limbs and back may be severe and muscular prostration

evident from the first. Drenching sweats may occur. The face is flushed or dusky, the conjunctivæ injected, sometimes chemotic, and the pupils contracted. A characteristic nervous irritability leads to restlessness, photophobia and insomnia. The tongue is large and coated, but soon becomes dry. Appetite is lost, thirst is great and the bowels are generally constipated. The urine is high coloured and scanty, rich in urea and uric acid, but deficient in chlorides. Albumin may appear later and the diazo-reaction is very constant. Bronchitis and slight epistaxis may occur. The spleen may become palpable, but the abdomen is not tumid. Even thus early in the disease, especially in alcoholic subjects, marked delirium, mania or stupor may be present. The patient soon takes to his bed. The temperature may reach  $104^{\circ}$  F. by the first night; the acme, however, is generally attained on the third or fourth day. Associated with the fever is a somewhat rapid soft pulse. Marked rapidity of the respirations is also noticeable and may lead to an erroneous diagnosis of pneumonia.

The fever, which during the invasive stage may show remissions, after attaining its maximum, which may be as high as  $105^{\circ}$  or  $106^{\circ}$  F., undergoes little or no daily variation. At the end of the first week or a day or two later a sudden remission, which is rarely lasting, may occur (*pseudo-crisis*); from this period, however, the fever generally shows some abatement and a sudden or somewhat gradual defervescence sets in on the thirteenth to the seventeenth day of the disease.

The rash appears on the fourth or fifth day, first on the axillary folds, about the shoulders and on the sides of the chest and the abdomen. It avoids the face, and rarely invades the temples and forehead, nor does it appear on the palate, and seldom on the palms and soles, with these exceptions it may become general all over the body. It is most profuse on the trunk, especially on the back. The elements of which it consists are macules, papules and petechiæ. The macular elements of the rash generally appear before the papules. They are large, blotchy and dusky in tint. With them is associated a deep-seated erythema or "subcuticular mottling". This mottling is best seen about the shoulders and axillæ, but often extends to the back and front of the chest, the thighs and arms. The papules resemble the rose spots of typhoid, but are often ill-defined. At first they fade on pressure; later, unlike the spots in typhoid, they may show petechiæ, becoming dull red or brown and indelible. They do not appear in successive crops.

Petechiæ which resemble flea-bites may appear on the skin and in the conjunctivæ of the lower lids. Purpuric patches may form over pressure-points and terminate in gangrenous bed-sores. The purpura indicates a severe infection, the hæmorrhagic character of which may be confirmed by the occurrence of hæmatemesis, melæna or hæmaturia. Profusion of the rash in typhus is also an indication of a severe attack. In mild cases the eruption is scanty, and in children it is very evanescent. The application of a tourniquet will cause petechial hæmorrhages within the rash.

The polymorphonuclear cells of the blood, which may possibly at first be increased, include many immature forms. A lymphopenia in the early stages is later replaced by a lymphocytosis, and basophilic mononuclear cells, Turk cells and plasma cells become numerous.

The cerebrospinal fluid may show a slight lymphocytosis, and also give a low positive Weil-Felix reaction. The globulin is increased.

During the second week the patient in a grave infection may enter on the terminal stage of his disease. There is less complaint of headache; delirium, if present, is less violent and of a muttering rather than maniacal type. Delusions may occur. Prostration is extreme and sleeplessness pronounced. The face is dusky, sordes accumulate on the teeth. A curious mousy odour emanates from the body and dehydration becomes marked. Day by day the nervous depression increases and the patient lies helpless on his back with a tendency to sink down in the bed. The pupils are pin-point, the eyes half open and fixed (*coma vigil*). Although deaf and unnoticing,

he mutters hoarsely and incoherently and can be roused with some difficulty. The tongue is brown and tremulous or lies shrivelled in the floor of the mouth, it cannot be protruded. Tremors of tendons increase, and picking at the bedclothes is apt to occur. The pulse quickens and may reach 130 or 140 per minute. It is dicrotic or almost imperceptible. The heart's impulse is feeble and the first sound faint or inaudible. The blood pressure falls steadily. Acceleration of respiration is more than ever pronounced, 40 per minute not being unusual; the breathing becomes shallow, and hypostatic congestion of the lung bases sets in. The urine may be retained or passed into the bed. The blood urea rises rapidly, oliguria or anuria may occur and uræmia supervene. Bed-sores are apt to form. The patient may pass away in coma, or hyperpyrexia may precede death.

In favourable cases the symptoms are of less severity and on the fourteenth day, sometimes earlier, sometimes later, defervescence occurs. The condition rapidly improves; the temperature falls, sometimes abruptly, perhaps more frequently the fall is a little more gradual. Sleep ensues and the patient awakes from his stupor with a moist tongue and skin, a clearer intellect, polyuria and perhaps a slight critical diarrhœa. Inclination for food returns, but there is still extreme weakness. Some, failing to rally after the crisis, fall into a state of collapse.

In less severe cases, where the typhoid state has not been pronounced, the defervescence may occur rather earlier and recovery be much more rapid; this is especially the case with children, but, as a rule, convalescence is prolonged.

**VARIETIES.**—Typhus infection may occur in all degrees of intensity from extreme mildness to fulminant severity. The milder types are particularly seen among the natives of localities where the disease is endemic, and in children. They may appear in the guise of an influenza-like fever with headache, drowsiness and suffusion of the eyes, or as a broncho-pneumonia. Of the severe types, that known as *typhus siderans* or *blasting typhus* is the most striking. In this form death may occur within 2 or 3 days of the onset. A meningeal variety, accompanied by head retraction, ptosis, squint and other nervous symptoms, simulates meningitis, which may indeed be present. Some cases are characterised by fierce maniacal delirium. Typhus also may assume a frankly hæmorrhagic form, but this is uncommon. Relapse is almost unknown, and authentic second attacks are rare.

**Complications and Sequelæ.**—Bronchiolitis, broncho-pneumonia or hypostatic congestion of the lungs are the outstanding complications. Rarely laryngitis occurs and may lead to necrosis of the cartilages and œdema of the glottis. True lobar pneumonia is hardly ever seen. Diarrhœa is rarely troublesome; it may be accompanied by abdominal distension and even the passage of blood. Femoral thrombosis, similar to that of typhoid fever, is common. Septic or gangrenous infarcts may be formed in the lungs, and gangrene of the fingers, ears, nose or pudenda may occur. Suppurative parotitis is a marked feature of the disease, and the inflamed gland may become necrotic. Gangrenous bed-sores, too, may form with great rapidity and pyæmic complications ensue. When typhus is followed by hemiplegia or other form of paralysis, a vascular lesion should be suspected. Mania, melancholia and dementia are occasional sequelæ but generally clear up, although they may take several months to do so. Other complications are diffuse glomerular nephritis, cystitis, orchitis and jaundice. Pregnant women frequently abort.

**Diagnosis.**—For the Weil-Felix reaction a reliable smooth strain of *Proteus*, OX19, is requisite. A rising agglutination titre to this organism is most significant. Results with a titre of less than 1:200 should not be accepted as positive unless the titre has risen greatly since the onset. The agglutination may become negative in the third or fourth week of convalescence. Occasionally titres with proteus OX2 exceed those of OX19.

An ethereal extract of Cox's vaccine provides an antigen for complement, deviation and agglutination tests (Craigie).

As compared with *typhoid*, the onset in typhus is more sudden, prostration and nervous symptoms occur earlier and are more pronounced. The aspect is drunken, the face congested, the pupils contracted and the eyes suffused. Diarrhœa and abdominal symptoms are unusual. The eruption is more profuse and more widely distributed, and the rose spots, which are paler than those of typhoid, may show petechiæ. The termination of the fever is more abrupt. Blood cultures and agglutination tests, also the steady rise in the blood urea in typhus, are of great value in distinguishing the two diseases.

*Lobar pneumonia*, especially the apical form with meningeal symptoms, may be mistaken for typhus, but should be eliminated by repeated examination of the lungs and the presence of a marked polynuclear leucocytosis. The hypostatic pneumonia of typhus is bilateral and does not show frank signs of consolidation. Febrile herpes may occur in both diseases.

*Cerebrospinal meningitis* is distinguished by lumbar puncture and examination of the cerebrospinal fluid. *Encephalitis lethargica*, with fever, headache and delirium, must be distinguished by the absence of the characteristic rash of typhus, the negative Weil-Felix reaction, and the supervention of such signs as slight muscular rigidity, ptosis, ophthalmoplegia and a characteristic lethargy from which the patient can be roused. The cerebrospinal fluid may show a lymphocytosis, without globulin increase.

The *prodromal rashes of small-pox* have been mistaken for typhus. They are distinguished by their characters and distribution and later by appearance of the focal eruption. *Uremia* may complicate typhus but is sometimes mistaken for it. It is then distinguished by the absence of fever and rash and the condition of the urine. Difficulty occasionally arises with a fading *measles* rash, but unlike the rash of typhus this invades the face and a history of catarrhal symptoms may be obtained. The *spotted fever of the Rocky Mountains*, which is a tick typhus, closely resembles louse typhus.

In hot climates and on campaigns other possible sources of error in diagnosis are louse-borne relapsing fever, epidemics of which often coincide with those of typhus, sand-fly fever and malaria. Influenza may also lead to difficulty.

**Prognosis.**—The mortality, which is low in childhood and adolescence, then progressively increases (see p. 296). In aged patients, recovery is the exception. Clinical indications of gravity are persistent sleeplessness, marked subsultus, violent delirium or convulsions, evidence of a hæmorrhagic tendency, a profuse petechial rash and continued high fever or hyperpyrexia. Failing circulation is shown by rising pulse-rate, lividity, coldness of the extremities and hypostatic congestion of the lungs. Suppression of urine and uræmic symptoms are also of grave import. A blood urea of 90 mg. per 100 ml. is unfavourable, and it may rise to 200 mg. in fatal cases. Gangrenous bed-sores, extensive parotid suppuration, pyæmic symptoms and peripheral gangrene are of bad augury, as also is persistence of a leucocytosis of over 20,000. The disease is particularly deadly to alcoholics, and fat subjects.

**Treatment.**—**PROPHYLACTIC.**—Every effort must be made to get rid of lice. The patient should be stripped, the hair clipped short and the body shaved and thoroughly washed before admission to a ward. As the eggs of lice contain the virus and hatch in about 8 days, a second disinfestation at the end of 10 days may be desirable. The garments of attendants should be louse-proof, and attendants should also be immune or at all events below the age of 30 years. The clothing of those infected, and of contacts should not be shaken, it should be sterilised and their living rooms and their contents disinfected. The use of D.D.T. (dichlor-diphenyl-trichlorethane) has proved effective when diluted and dusted between clothes and skin, and also when used for impregnating the undergarments of those exposed to infection. Cases of typhus are best treated in isolation hospitals, and when the disease is epidemic good results are obtained by forbidding movements of the populace so that susceptibles are not introduced into infected areas and infection not carried to areas

hitherto free from it. Injection of the blood serum of convalescents is said to be a prophylactic, but has communicated the disease.

By cultivating the virus in lice and emulsifying their mid-guts in carbolic solution Weigl produced a protective vaccine. This contains dead rickettsiæ. Vaccines have since been prepared from infected mouse lung (Durand and Giroud), and from infected yolk-sacs (Cox). An alum-precipitated vaccine has been introduced by Osborn. Vaccines which consist of dead organisms do not appear to afford complete protection, but those containing living organisms have at times proved dangerous.

Quarantine or supervision of immediate contacts for at least 15 days is usually recommended.

**CURATIVE.**—This should be on the same lines as those adopted in typhoid fever. Free ventilation, tepid sponging night and morning, careful attention to the mouth and back, and the adoption of a fluid diet, consisting of milk, beef tea, fruit juices and plenty of water, are the essentials. The bowels are usually constipated and enemas should be used. The urine must be measured, suppression is dangerous and retention may lead to great restlessness with constant overflow. When the temperature rises above 103° or 104° F., tepid or cold sponging should be repeated. In hot climates, exposure to heat has a very deleterious effect. For sleeplessness, paraldehyde is the most useful hypnotic, but requires to be given in large doses. Wildly delicious patients need some form of restraint, and in these cases hyoscine should be injected if other means fail. Frequent rectal salines or the administration of glucose-saline solution intravenously, subcutaneously or by drip through Ryle's stomach tube are beneficial in toxæmia, dehydration and circulatory collapse. The tendency to collapse after the crisis should be remembered, and patients carefully watched at this period.

Both chlortetracycline and chloramphenicol have proved effective in the treatment of typhus fever. Improvement begins within 24 hours of administration, the temperature falls to normal usually by the third day and the rash begins to fade. This improvement is noted irrespective of the stage of the illness at which the drug is given. In view of the dangerous effects of chloramphenicol on the bone-marrow in some patients, chlortetracycline must be regarded as the drug of choice.

R. BODLEY SCOTT.

## TRENCH FEVER

**Synonyms.**—Volhynia Fever; Meuse Fever; Five-Day or Quintan Fever.

**Definition.**—Trench fever is a specific infectious disease, probably caused by *Rickettsia quintana*, transmitted from man to man by the body louse, *Pediculus corporis*. Clinically it is characterised by recurrent pyrexia, headache, giddiness, severe pain in the back and limbs, conjunctival congestion, sweating, leucocytosis and splenomegaly.

**Ætiology.**—The disease was first recognised as a specific entity during the War of 1914–1918, when it appeared on the European fighting fronts, Salonika, Egypt and Mesopotamia. Approximately 800,000 cases occurred amongst Allied troops in France during 4 years. No outbreak of this disease was reported during the War of 1939–1945. The inoculation of blood of infected patients into volunteers was found to be capable of causing the disease (McNee, Renshaw and Brunt). It was also proved that the blood may remain infective for 200 days. Later, it was discovered that lice which had been fed on febrile patients and were subsequently kept for 5 to 12 days at 26° to 30° C. could transmit the disease to volunteers. Once infected the lice remain infected for life. Large numbers of rickettsia bodies (*R. quintana*) were demonstrated in the mid-gut of lice fed on infected people (Töpfer). The disease is probably conveyed not by the bite of the infected louse but by its excreta being rubbed into skin abrasions.

**Pathology.**—As the disease never proved fatal no record of necropsies are avail-

able in man. Examination of the trench fever macules in skin obtained at biopsy has shown (1) hyperæmia, (2) œdema and (3) perivascular lymphocytic infiltration; unlike epidemic typhus, there was neither necrosis of the endothelial cells lining the vessels nor hyaline thrombosis.

**Symptoms.**—The incubation period varies from 10 to 30 days. The onset is generally sudden, with headache, giddiness, pain in the shins, back and behind the eyeballs, and a rapidly rising temperature ( $103^{\circ}$  to  $104^{\circ}$  F.). Chills and sweating are common. The conjunctivæ may be congested and the general appearance of the patient during the acute stage reflects extreme pain and discomfort. He is restless and changes his position constantly in a vain effort to get relief. Frontal or retro-orbital headache is often severe and persistent; if it be retro-occipital in type it may be accompanied by stiffness of the neck. The pain in the limbs may be of a dull aching or gnawing character, or of an acute stabbing type. Such pains are felt in the bones, especially the tibiæ, last many hours and are worse at night. At first the pain is generalised, but after a few days it becomes more localised in the loins and lower limbs. It is generally symmetrical, and may vary in situation from day to day. Associated with pain there may be intense superficial tenderness—especially over the shins—so that even the weight of the bedclothes cannot be borne.

Splenic enlargement occurs in 70 to 80 per cent. of cases. Splenomegaly may be associated with tenderness and sometimes with rigidity of the muscles in the left hypochondrium. If palpable, the edge is firm. In the early stages the spleen increases in size during febrile relapses and decreases during the afebrile periods; later, its dimensions remain more constant. Though profuse sweating is uncommon, a peculiar feature is the rapid alternations of shivering and sweating; several such attacks may occur within 24 hours. Vomiting and diarrhœa have been described but are rare; constipation is the rule. Red macules, fading on pressure and lasting from 6 to 48 hours, are frequently seen in the first few days of fever and at times during relapses. They appear in crops on the chest, abdomen and back, are at first a rose red and later a dull-red colour and measure 4 to 8 mm. in diameter. Herpes labialis is not infrequent.

Unlike typhus, the mental condition remains normal. The tendon reflexes are often exaggerated, and during fever lateral nystagmus may be induced by moving the eyes. A moderate neutrophil leucocytosis precedes and accompanies the fever. The total count rarely exceeds 20,000 leucocytes per c.mm., and there is a marked left shift. Urinary symptoms include frequency and polyuria in the post-febrile stage; the urine may contain a trace of albumin.

Widely different types of temperature chart are encountered. The total duration of fever varies from a few days to several weeks, and in most instances irregularities in the temperature chart are common. When the disease was first encountered in France short types predominated, later the disease became more severe and more prolonged pyrexia was more common. Various types include: (1) A short bout of fever lasting about 3 days. (2) A similar short febrile attack followed by a period of apyrexia and a febrile relapse on the sixth, seventh and eighth day. Irregular fever sometimes followed. (3) The primary fever running more or less into the relapse and producing a saddle-back type of chart. Again irregular fever might follow. (4) A definitely intermittent type of fever manifesting regular periodicity and sometimes lasting many weeks.

**Complications.**—In patients with prolonged pyrexia, pain and sleeplessness lead in certain instances to mental depression, neurasthenia and so-called disordered action of the heart (D.A.H.). The latter condition, which is really a cardiac neurosis, was erroneously attributed to organic disease of the heart during the War of 1914–1918.

**Diagnosis.**—During the early febrile stage trench fever may be mistaken for influenza, dengue, typhoid, paratyphoid, typhus, malaria, relapsing fever, undulant fever, rat-bite fever and leptospirosis. Laboratory investigations will help to exclude

many of the above-mentioned diseases. A 5 to 6-day periodicity in the temperature should suggest the diagnosis.

**Prognosis.**—As indicated under Symptoms, the course of the disease is very variable. The mortality is practically nil.

**Treatment.**—Prevention consists in delousing the individual, thoroughly disinfecting the clothing and the use of D.D.T. No specific drugs were available, and treatment was mainly symptomatic in the War of 1914–1918. No opportunity has been afforded for testing the action of chloramphenicol.

N. HAMILTON FAIRLEY.

## “Q” FEVER

**Definition.**—An acute febrile illness caused by *Rickettsia burneti*, characterised by sudden onset, general symptoms including headache, and usually the development of interstitial pneumonitis. There is no rash and agglutinins to *Proteus* organisms do not develop.

**Ætiology.**—The causative organism, *R. burneti*, is small and pleomorphic. It is present in the blood during the febrile period. It may also be recovered from sputum, urine or C.S.F. or from tissues, especially spleen, obtained at necropsy.

“Q” fever is believed to be an enzootic of animals transmitted naturally by certain ticks. It is commonly transmitted to domestic stock, including cattle. Ticks infesting livestock easily become infected with *R. burneti* which appears in their faeces. The causal organism is resistant to desiccation and is conveyed to man most commonly by inhalation of infected dust. Infection may also occur through handling infected tissues, secretions, etc. The disease is thus found mainly in persons concerned in handling of livestock or in those exposed to dirty, dusty conditions associated with livestock. Infection may result from drinking raw milk. It occurs easily in laboratory workers handling *R. burneti*.

“Q” fever, with pulmonary involvement, can be reproduced in man by inhalation or intranasal instillation of infective material containing *R. burneti*. Intradermal or intramuscular inoculation of the organism may give rise to fever and rickettsæmia but without pulmonary signs.

“Q” fever appears sporadically or in explosive outbreaks. It was first described in 1935 in Australia. It is now known to occur in many parts of the world, including England, Spain, Italy, Greece, the Middle East, tropical and South Africa and the United States of America. During the War of 1939–1945 localised “epidemics” occurred amongst troops stationed in the Mediterranean littoral.

**Pathology.**—*R. burneti* can readily infect many wild and domesticated animals and several species of ticks; transovarial transmission has been described in the latter.

Isolation of the organisms in a suspected case of “Q” fever is usually carried out by intraperitoneal inoculation of blood or urine into guinea-pigs. Pathological changes in infected animals include moderate enlargement and engorgement of the spleen and small granulomatous lesions in many organs.

In man, *post-mortem* findings have been described in very few cases. The principal lesions are found in the lungs, especially in the basal zones, in which there are patchy consolidation and thickening of the alveolar walls and perivascular tissues due to accumulations of macrophages and round cells. Polymorphs and red cells occur in minimal numbers. There may be small scattered areas of necrosis and breaking down of alveolar septa. Alveoli, bronchioli and small bronchi are filled with exudate containing large numbers of degenerate macrophages. Foci of round-cell and macrophage accumulations have been reported in the testes, kidneys and other organs, and similar lesions involving the microglia in the brain. Intracellular and extracellular rickettsæ have been identified by Whittick in smears of lung, spleen, testes and brain.



**Symptoms and Signs.**—The incubation period is given by Smadel as a mean of 19 days. The onset is usually sudden. There is a wide variation in severity. The clinical picture may show nothing beyond a mild fever lasting only a day or two. In most cases, however, the temperature rises rapidly at first to moderate heights, but may reach 103° to 105° F. after 1 or 2 days. The fever is remittent and swinging. It lasts from 1 to 10 days or longer, the average duration being from a few days to 3 weeks. In some cases, especially in middle-aged individuals, the fever persists for several weeks. General symptoms may develop at the onset and persist through the febrile period. Headache and general muscular pains are often severe. Subjective feelings of cold and occasional shivering may occur, but rigor is unusual. Nocturnal sweating and insomnia are common in some outbreaks. Anorexia and nausea are the rule. The upper respiratory tract is not usually involved, but a slight dry cough may develop after the fourth day, often accompanied by pain in the chest, which may be localised to one area. The sputum is usually mucoid or mucopurulent and may be blood-streaked; occasional small hæmoptyses have been reported. In some patients dyspnoea may be the dominant picture, and there may be cyanosis. Examination of the chest at this stage may reveal localised reduction in air entry, commonly in one or both bases, with occasional crepitations and scattered rales. In seriously ill patients there may be obvious signs of consolidation in one or both bases. The physical signs of lung involvement, however, may vary considerably from day to day and are often evanescent, but evidence of pulmonary changes can usually be demonstrated by radiography. Radiographic changes are said to occur in practically all naturally infected patients. The pattern is indistinguishable from that of primary atypical pneumonia. It develops about the fourth day, when signs of consolidation appear, involving small areas of one or more lobes. The shadows present a homogeneous "ground-glass" appearance. The lesions may progress for a few days and then become stationary, disappearing only slowly. They frequently persist well into convalescence.

Evidence of changes in organs other than the lungs and the spleen is uncommon. In those cases in which the febrile episode continues for weeks, however, signs of liver involvement, including jaundice, may develop.

Relapses occur weeks or months after the initial attack in a small percentage of cases, with recurrence of fever and pulmonary signs and symptoms.

**Course.**—Complications rarely develop. Delirium and signs of acute meningo-encephalitis have been reported. Orchitis has also been described during a severe attack. Some loss of weight occurs during the febrile period and there is considerable weakness, which may persist for weeks after treatment. The appetite improves rapidly and the temperature returns to normal.

Fatal issue is rare. Deaths have been reported in a few natural infections and in a laboratory worker.

**Diagnosis.**—Clinical diagnosis is difficult. A knowledge of the patient's employment, especially in regard to contact with livestock is essential. The early stages of "Q" fever closely resemble those of many other acute febrile illnesses, and in the stage of pulmonary involvement the diagnosis of pneumonia or atypical pneumonia is commonly made. Failure of the pulmonary condition to respond to sulphonamides or penicillin is often the first clue to the real condition. In some areas psittacosis and coccidioidomycosis must be differentiated. Diagnosis depends finally on the recovery of the organism or the results of serological examinations.

*R. burneti* can be recovered during the febrile stage of the illness by intraperitoneal inoculation of blood or urine into guinea-pigs. The organism is eventually identified in spleen smears from the infected animals. Because of the considerable danger of accidental infection, isolation of the organism should not be attempted except under the proper laboratory conditions.

Diagnosis is usually made by examination of the serum for agglutinins and

complement-fixing bodies. Agglutinins appear by the end of the second week and can be identified in most cases by the end of the fourth week. Complement-fixing bodies may be present by the seventh day and are at a high titre by the end of the third or fourth week.

The antibody content of the serum in a given patient should be ascertained early and late in the illness. Diagnosis should be made in the presence of a rising titre of antibodies. Titres of 1:8 for agglutination and 1:20 for complement fixation are regarded as significant, but considerably higher titres are usually found at a late stage, *i.e.*, weeks and even months after the onset.

No cross reactions with other members of the rickettsial group occur; serum from a case of "Q" fever will not agglutinate *Proteus* suspensions and do not contain cold agglutinins.

**Treatment.**—Prophylaxis is best achieved by immunisation (with formalised vaccine prepared from infected yolk-sac tissue) of individuals likely to be exposed to infection in stock yards, dairies, slaughter-houses, etc. Pasteurisation or boiling of milk is necessary in areas known to be infected: the former process may not be efficient. Transmission from patient to patient in a ward is unlikely so long as sterilisation of sputum and excreta is carried out. Quarantine and isolation are unnecessary.

Sulphonamides, penicillin and streptomycin have no appreciable effect on the course of the illness.

Chlortetracycline, chloramphenicol and oxytetracycline are effective. The illness itself is so variable in duration and severity, however, that it is difficult to judge the real value of chemotherapeutic treatment.

Chloramphenicol has been given orally in doses of 250 mg. 4-hourly, up to a total of 6.0 g. Smadel recommends oral administration of chlortetracycline or oxytetracycline in divided doses in a total dosage of 3 g. to 4 g. daily. Treatment is continued for some days after the fever has subsided.

Treatment with these antibiotics usually results in the fall of temperature to normal in a day or two and rapid resolution of the pulmonary signs and radiological pattern. A few cases may relapse shortly after treatment is stopped. These must be immediately re-treated with similar dosage régimes.

BRIAN MAEGRAITH.

## G. INFECTIOUS DISEASES OF DOUBTFUL OR UNKNOWN ÆTIOLOGY

### FOURTH DISEASE

**Synonym.**—Filatow-Dukes Disease.

Filatow and, later, Clement Dukes described an infectious disease which they considered distinct from scarlet fever and rubella.

It is most prevalent in spring and summer. Previous attacks of scarlet fever and of rubella afford no protection. Premonitory symptoms are absent or trivial, the first sign usually being a rosy red rash, slightly raised, which covers the whole body in a few hours. The temperature may range from normal to 103° or even 104° F. The fauces are red, the tongue clean or slightly furred and the pulse only accelerated in proportion to the temperature. The posterior cervical, axillary and inguinal lymph glands are enlarged to the size of peas, hard and somewhat tender. The conjunctivæ are pink. Desquamation may ensue. The incubation period is between 9 and 21 days, and infectivity lasts for 2 or 3 weeks. Most authorities either reserve judgment or refuse to recognise such a disease, alleging that some of the cases are rubella and some mild scarlet fever. Glandular fever is also a possibility.

The blood changes are distinctive but may be either transient or delayed. After a fleeting polymorphonuclear leucocytosis or, rarely, a neutropenia, there is a characteristic increase in the numbers of the mononuclear non-granular cells. These may form 40 to 90 per cent. of the total leucocytes instead of the normal 20 per cent. The cells are not of uniform type, as in acute leukaemias. Aberrant cells, which may in some respects resemble either large primitive lymphocytes, or large mononuclear, or plasma cells, preponderate. There is general agreement that these cells are of the lymphoid series; they are sometimes seen in other diseases, but their presence in any number is diagnostic of glandular fever. The small lymphocytes may be diminished in number. The total leucocyte count is rarely more than 12,000 to 18,000, but may be 30,000 or more; occasionally there is leucopenia throughout the disease. The red cell count is not diminished.

Heterophile antibodies, which agglutinate the red corpuscles of sheep, appear in the blood serum. This is the Paul-Bunnell reaction. It becomes positive with the appearance of the swollen glands. A titre of 1 in 100, or possibly less, is diagnostic of glandular fever. Appearing about the fifth day, it may persist for 1 to 4 weeks. Sometimes its appearance is delayed and repetition of the test is necessary. Its constancy is doubted by some observers. The distinctive antibodies are absorbed by ox red cells but not by guinea-pig kidney. A similar reaction which may occur after the injection of horse serum is distinguished by absorption by both agents. A differential test, positive in a titre of 1 in 40, combines absorption and agglutination procedures.

The lymphadenitis is characterised by vascular congestion and by hyperplasia of the reticulo-endothelium and germ-centres which may be packed with cells like those in the blood. Similar cells occur in the spleen where they pack the sinuses, infiltrate the trabeculae and ensheath the small arteries. They also penetrate the bone-marrow.

The febrile stage of the disease may last for 10 days or a month, and exacerbations of fever, with involvement of fresh glandular groups, may occur. The glandular swellings subside more slowly than the fever. A subacute or relapsing type with sweats and irregular pyrexia, simulating Hodgkin's disease, has been described. The mononucleosis may be very transitory, or may persist for some time. Convalescence is slow.

In some cases, mostly adult, glandular fever may differ considerably from the disease as described above. There is a febrile course, very suggestive of enteric infection, with malaise, muscular pains, headache and perhaps epistaxis, but no marked soreness of the throat. Shivering, or rigor, may occur. Towards the end of the first or second week of fever, a scanty eruption of macules or of papules, somewhat like those of typhoid fever, may appear on the trunk and perhaps the limbs. The diagnosis is established when glandular enlargement, usually less pronounced in this type, supervenes in the third week or later, and the fever assumes a remittent form. At this stage a relative or absolute mononucleosis is most likely to be discovered, and may be fleeting or very protracted. A membranous faucial inflammation may possibly now be found. The spleen may enlarge. Relapses may occur, and the fever has been known to persist for many months, but recovery is still the rule. This variety is known as the *typhoid type*.

In some cases of glandular fever the Wassermann, or Kahn, reaction becomes temporarily positive. A misleading agglutination with typhoid "O" antigen in low titres may also appear.

Very rarely petechial eruptions accompany glandular fever, the bleeding-time is increased, and platelet deficiency is present. This constitutes a rare *purpuric type*.

A striking feature of outbreaks of glandular fever is the occurrence of symptomless infections without overt clinical signs, the blood picture being typical and the Paul-Bunnell test positive.

**Complications.**—Suppuration in the glands is very rare. Otitis, retropharyngeal

abscess and laryngitis have been met with. A temporary albuminuria may occur and in some 6 per cent. of the cases a benign hæmorrhagic nephritis. A more serious complication is the spontaneous rupture of a swollen, infiltrated and softened spleen which has been recorded on rare occasions. Sometimes atypical pneumonia or glycosuria occurs. Serous or lymphocytic meningitis is exceptional, as also are cerebral palsies and lesions of certain peripheral nerves. Myocarditis, sometimes with disturbance of the conducting system, is an occasional sequel.

**Diagnosis.**—The clinical course is often so characteristic and the cervical adenitis so disproportionate to the faucial inflammation that suspicion of glandular fever should be aroused. In the more prolonged febrile form, fevers of the enteric group can be excluded by the blood count and the usual bacteriological and serological tests. In the membranous variety, diphtheria is excluded by absence of the Klebs-Loeffler bacillus and of acute toxæmic symptoms, despite persistent membrane.

Resemblance to rubella is sometimes close, but the differences in the blood films, and the Paul-Bunnell test will decide. Sore throat, adenitis and a maculo-papular rash may suggest secondary syphilis, and the possibility of a positive Wassermann reaction causes further confusion. The paroxysmal cough and leucocytosis may simulate whooping-cough but the *Bordet-Gengou bacillus* is absent, and the Paul-Bunnell test positive. Swelling of the salivary glands and even Mikulicz's syndrome have been reported in rare instances. In such cases, if authentic, mumps may be simulated. Vincent's angina may complicate glandular fever, but the occurrence of Vincent's organisms is now regarded as fortuitous.

Acute leukaemia at its onset constitutes a very real difficulty, but the leucocytosis is usually far in excess of that of glandular fever and the cell type more uniform. The diversity of cells seen in glandular fever is lacking, anæmia is progressive and the issue fatal. Rarely lymphatic leukaemia of a very chronic type, with bouts of fever, adenitis, which is but slight, and moderate lymphocytosis is mistaken for the usual tardy convalescence from glandular fever. *Hodgkin's disease* is a much more chronic and progressive affection, here lymphocytosis rarely occurs; biopsy of a gland is the only certain diagnostic criterion. In acute infectious lymphocytosis the increase is in the small lymphocytes, and although an adenitis occurs, the Paul-Bunnell test remains negative. Tuberculous adenitis has a greater chronicity; peri-adenitis and suppuration with other signs of tuberculosis may be present. Septic adenitis induces a polymorphonuclear leucocytosis, and may suppurate. Agranulocytic angina is characterised by a low leucocyte count due to the disappearance of all granular cells. The differentiation of glandular fever with abdominal symptoms from appendicitis is based on enlargement of glands, spleen and liver, the blood picture and the positive Paul-Bunnell test.

**Treatment.**—This is symptomatic. In the anginose form with severe symptoms neosarsenamine intravenously has a decided palliative effect. In protracted cases, injection of the blood serum of a convalescent may bring the disease to a termination. Excision of glands is unnecessary and should be avoided. Isolation for 7 days after the subsidence of the fever and glandular swellings is sufficient in the acute cases.

## ERYTHEMA NODOSUM

**Ætiology.**—Although this disease is a definite and easily recognisable clinical entity, it is still uncertain where it should be placed, when considered in relation to nosology or to ætiology. Formerly the favoured view was that the disease is a manifestation of acute rheumatism, but of this there is little or no evidence. It is now generally regarded as an allergic tissue response to various bacterial allergens. In some countries, especially those of Scandinavia, tuberculosis is the most frequent

underlying cause, in children it has been shown to make its appearance shortly after primary infection. In adults and adolescents it is more often a sequel of hæmolytic streptococcal infection of the naso-pharynx. A similar syndrome occurs in an early stage of Boeck's sarcoid and lesions, only distinguished with difficulty, are found in chronic meningococcal and chronic gonococcal septicæmia. A similar disorder has been recorded as a reaction to various drugs, including the iodides and the sulphonamides.

It occurs more often in females than in males (according to Mackenzie, in the proportion of 5 to 1), and the majority of cases are found between the ages of 10 and 30 years. There is no seasonal incidence. It is much more common in hospital than in private practice; this and some other observations suggest that bad feeding or insatiable conditions may contribute to the incidence of the affection.

**Pathology.**—There has been demonstrated a widespread arteriolitis in the subcutaneous fat, resolving without suppuration or residual fibrosis.

**Symptoms.**—The symptoms consist of: (i) the local lesions, and (ii) certain constitutional changes.

(i) The local lesions are bilateral and occur chiefly upon the lower limbs; indeed, in the great majority of the cases they are confined to these. When they appear on the arms they are most often found only in this situation, the patient is more often than not an adult and the general symptoms are less like rheumatic manifestations than is the case in the more common variety of the disease. The lesions are round or oval swellings, usually confined to the extensor aspect of the limbs, affecting the shin regions chiefly, and varying in size from a large pea to half an orange. There may be two or three only on each leg, or, in severe cases, the greater part of the extensor surface may be covered by them. They involve the subcutaneous tissue as well as the skin. They are very tender to touch. On their first appearance they are deep red in colour, later they become purple in hue, and still later they often show a definite ecchymotic appearance—giving rise to the name *dermatitis contusiformis*. In bad cases there is a good deal of associated œdema of the surrounding tissues.

(ii) The general symptoms include a mild grade of fever (not constantly present), joint pains, malaise and sore throat. But many cases occur in which the local skin condition, with pain and tenderness, covers the whole of the symptomatology. Constipation is common, and is sometimes severe. Radiographic examination of the chest will show in a proportion of cases some enlargement of the mediastinal glands, these are probably tuberculous or due to sarcoidosis. There is an initial leucocytosis and the erythrocyte sedimentation rate is raised, often considerably.

The course of the disease is from 2 to 3 weeks, but some mild cases get well within a week.

**Diagnosis.**—The diagnosis is not difficult. The lesions of Bazin's disease, though they occur on the legs much more than on the arms (as in erythema nodosum), though the sex and age are the same and though the association with tuberculosis is definite, are chronic and relapsing in character, and ulceration usually occurs; they tend to be on the posterior aspect astride the tendo Achillis.

**Treatment.**—Rest in bed, with the legs elevated, and general hygienic conditions, suffice to bring about spontaneous recovery in all cases. No drug has credit for cutting short the course of the disease. As a local application lead lotion is perhaps the most soothing.

R. BODLEY SCOTT.

## PINK DISEASE ~

**Synonyms.**—Infantile Acrodynia; Erythrœdema; Vegetative Neurosis.

**History.**—The disease was first accurately described by Swift (Australia) in 1914, but Selter (Germany) had reported similar cases in 1903, and Swift records that he certainly saw examples of the disease when he was a resident at the Hospital for Sick

Children, Great Ormond Street, in 1885. Feer (Zürich) is generally accepted in Europe as having described cases about the same time as Swift.

**Ætiology.**—The clinical syndrome is generally ascribed to the effects of a widely diffused toxin which shows a predilection for the autonomic nervous system. It frequently follows an acute infection of the upper respiratory tract and less often gastro-enteritis, either affording a possible portal of entry of a virus. Although not obviously infectious from case to case, small epidemics in localised areas have occurred in various parts of the world. This and a tendency to a seasonal incidence in spring and autumn offer obvious analogies with acute anterior poliomyelitis; and Mayerhofer has described cases following this disease. Another theory favours a vitamin or other deficiency, but usually affected children have been well fed. Mercury poisoning has been blamed, especially in the U.S.A., following the use of teething powders containing calomel, but very many babies are given such powders and do not develop pink disease. For this reason allergy has been invoked to explain individual susceptibility, possibly to a wide variety of toxic substances. Recent claims in Australia for adrenal-cortical insufficiency (and cure by common salt) have not been confirmed. The balance of opinion still seems to favour infection, probably by a virus, as the most likely cause. The disease occurs more especially in the temperate zones, affects the sexes equally and is almost limited to the period covered by the time of the primary dentition.

**Pathology.**—Apart from various findings due to secondary infections, the specific morbid pathology of the disease is said to include minor microscopical changes in medulla, cord and peripheral nerves. These consist of round-celled infiltration, demyelination and œdema. Some authorities maintain that even these changes are due to a non-specific terminal infection, or to secondary nutritional depletion.

**Symptoms.**—After a vague febrile onset, as intimated above, the infant fails to recover its previous vigour, and remains essentially miserable, with insomnia, muscular hypotonia, increasing loss of appetite and usually loss of weight. After a week or so some degree of stomatitis is commonly found, the child dribbles a lot, and just when the whole picture has been confidently ascribed to the effects of dentition the characteristic rash makes its appearance. This consists of three main features: a sweat rash, which may be present all over the trunk and proximal portions of the limbs; a curious "raw beef", puffy, non-pitting œdema of the hands, feet and frequently of the nose; and eventually various degrees of furunculosis and pyoderma. The condition of the mouth deteriorates, teeth may be shed (and swallowed), photophobia is often marked and the child "burrows" in misery in the bedclothes, constantly scratching and rubbing the hands and feet together. In severe cases the fingers and toes may be seriously bitten and the hair plucked out. Perspiration of a cold, clammy type is present and produces a "mousy" odour. Wasting and hypotonia become extreme, the child makes no effort to stand or walk and prolapse of the rectum may occur. Signs of affection of the nervous system are shown by a persistent tachycardia—which is constant and varies in degree according to the severity and state of the disease—the tendon reflexes are sometimes diminished or lost, and it may be possible to demonstrate a diminished sensitivity to pin-prick. The disease is usually afebrile save for the effects of complications, the blood pressure is said to be raised, although the determination of this is a matter of some difficulty, and there is frequently a leucocytosis. Excessive excretion of mercury in the urine has been found by those favouring this form of toxic substance as a cause but there are chemical pitfalls here.

**Complications.**—The upper respiratory tract infection may spread to affect the ears and, more seriously, to produce broncho-pneumonia, which is always a menace because of the risk of aspiration with an infected mouth. Pyelitis is not uncommon. Various local infections of the skin are almost invariable in a case of ordinary severity. Sequelæ, however, are unknown and relapses seldom occur.

**Diagnosis.**—There is no mistaking the disease once it is fully developed, and it obviously should be suspected whenever a young child appears to be seriously miserable for weeks at a time. Cases have been described with most of the classical symptoms, but without the rash or other skin changes. Tachycardia occurs in all cases, and unless the pulse-rate is 140 or more a diagnosis of pink disease should not be made with confidence.

**Prognosis.**—In the absence of serious complications this is invariably good, and one attack confers immunity. Death is usually the result of some serious complication but occasionally is sudden after a period of increasing rate and irregularity of the pulse. It is suggested that in such cases the end is due to ventricular fibrillation.

**Course.**—The whole clinical picture may be spread over 3 to 9 months, with some variation in the severity of the symptoms.

**Treatment.**—Since the exact causation is unknown, preventive measures are impossible, and most of the treatment has perforce to be symptomatic. Good nursing is essential but hospitalisation is undesirable although often unavoidable for a period as the patient's mother is almost invariably worn out. Isolation in a cubicle is advisable. If weather permits the child's cot should be in the open air as much as possible, day and night. Silk or cotton clothing, frequently changed, is best, the eyes should be protected from glare and some restraint may be necessary to prevent quite serious self-infliction of damage to the skin. The diet should be adequate, well-balanced, mostly liquid and offered cold, frequently and in small quantities. The troublesome anorexia can only be dealt with by skilful nursing. Deference to the deficiency theory of origin would indicate the administration of vitamin concentrates A, B, C and D, raw liver and some yeast preparation, such as Yestamin. Good results have been claimed for the injection of vitamin B<sub>1</sub> in massive doses, such as 1000 international units once a week. This has the merit of being a convenient way of treating an out-patient at a hospital. Whole vitamin B complex has also been used as well as individual constituents of the vitamin B series. Bellergal (1 to 3 tablets daily for several days) is believed to counteract the effects of the disease upon the autonomic nervous system. Dimercaprol (B.A.L.) has been used by those favouring the poisoning by mercury theory. Some sedative is essential and a mixture of chloral and bromide, according to the age, is probably the most suitable and should be used freely. For the skin a tepid bath once or twice daily, followed by a methylated spirit rub and copious powdering with a fine talc (not starch) powder, will help to promote comfort. The irritation may be slightly allayed by calamine lotion or the use of menthol in paraffin (1 per cent.) dabbed on at night. The mouth requires great care. Giving the child swabs soaked in hydrogen peroxide may be recommended, and actual inflammatory lesions should be dabbed with methyl violet solution (0.5 per cent. in water). Chemotherapy is of great value in most of the septic complications. During convalescence an iron tonic and a change to the seaside help to promote complete cure.

ALAN MONCRIEFF.

## “NON-SPECIFIC” OR ABACTERIAL INFECTION OF THE GENITAL TRACT

**Ætiology and Prevalence.**—This condition, of which the cause is unknown, is undoubtedly a venereal disease, although it may be confused with other and less common forms of urethritis which are non-venereal. In prevalence it is second only to gonorrhœa among the venereal infections. The figures from the public clinics of England and Wales for 1952 show 11,552 cases of “non-specific” urethritis in the male as compared with 15,510 cases of gonorrhœa. The infection often proves highly resistant to treatment and not infrequently persists indefinitely in latent form with the possibility of frequent clinical relapses. In some cases there are complications which may be local or metastatic.

**Clinical Course.**—*In the male.*—In most cases the condition commences as a low-grade urethritis with onset from 10 days to 4 weeks after intercourse, presenting with mucopurulent urethral discharge which is often scanty. Smears of the urethral discharge show pus cells and epithelial cells but no organisms; cultures grow no organisms or a few contaminants. One aspect of the urethritis in the male requires special mention. The urethral secretion is frequently so slight that the patient does not notice it. This may well account for the long incubation periods which are sometimes described, for the condition may be present for some time before it attracts attention. The true incubation period is probably about 10 to 14 days. It seems quite clear that in other cases the patient remains quite unaware of his condition which may come to light in the course of routine examination for some other reason, or through the development of a complication. Patients with asymptomatic infection may show no signs of the infection at the time of examination. In order to recognise the signs it may be necessary to examine the patients in the early morning before the first urine has been passed; if the urine has been held for 8 hours or more there is almost certain to be some secretion within the meatus and the urine will contain pus threads. Patients with asymptomatic infection are infectious to others by sexual intercourse and may at any time develop some complication.

*In the female.*—The consorts of men with "non-specific" urethritis nearly always show some evidence of infection which is presumed to be due to the same cause. Quite often there are no symptoms but if symptoms are present they are usually due to associated trichomonal vaginitis. The infection causes urethritis, cervicitis and, perhaps, proctitis. The diagnosis is difficult to make in the female because the evidence of urethritis is usually slight and the cervicitis has no characteristic features.

**Complications.**—The local complications in the male and female are the same as those which affect patients suffering from gonorrhœa (see pp. 66, 67) but they tend to be less acute. In particular ascending infection with inflammation of the uterine adnexa occurs in many cases in the female and recrudescence and relapse of tubal inflammation are very common. Sterility is a possible sequela. Metastatic complications are rare in the female.

**Arthritis** is the commonest metastatic complication. Polyarthritis is the rule, but occasionally only one joint is affected. The onset may be acute or subacute and where it is acute it is indistinguishable from that which may follow gonococcal urethritis. The joints of the lower limbs are most often affected, especially the knees, ankles and metatarso-phalangeal joints, but any joints may be involved. The development of arthritis is associated with pyrexia of varying degree. The temperature is usually above 100° F.; in severe cases it swings from 100° to 103° F. or more and the patient appears very ill and becomes cachectic. Tachycardia with pulse-rate of from 120 to 150 to the minute is found in some cases. The erythrocyte sedimentation rate is much raised being more than 100 mm. in 1 hour (Westergren) in many of the cases. In less severe cases with recurring attacks constitutional symptoms may be slight or absent. The attack of arthritis is usually self-limited and is likely to subside spontaneously after periods which vary from 1 to 12 months. Even in severe cases ultimate clinical recovery may be complete. Recovery may be permanent, but some patients are very prone to recurrent attacks of arthritis, and ultimately chronic arthritis or residual deformities may result. In the main the late effects are of three kinds:

(1) Multiple attacks without residual joint damage.—The later episodes of arthritis are sometimes related to sexual intercourse or to fresh attacks, or relapses, of urethritis; sometimes they occur without evident precipitating cause. The intervals between recurrences are highly variable and years may intervene. Each recurring episode of arthritis usually lasts up to 2 months. As with the initial attacks the distribution of the arthritis is not necessarily characteristic, for, although the knees and feet are usually affected, some patients show more generalised polyarthritis with involvement of small joints of the hands and wrists.



(2) Residual deformities of the feet.—The commonest of these is the painful calcaneal spur in association with the posterior attachment of the plantar fascia. Pes planus is sometimes a residual deformity; in other cases pes cavus occurs and may be associated with fixed dorsiflexion of all toes at the metatarso-phalangeal joints, giving multiple hammer-toe deformities. The hammer toes, and also lateral deviation of the toes at the metatarso-phalangeal joints may occur without pes cavus.

(3) Ankylosing spondylitis.—The usual course is an initial polyarthritis followed later by spinal stiffness. In the early stages low back pain is associated with radiographic blurring of the sacro-iliac joint and it is only later that the poker-back and bamboo spine develops.

Acute attacks of arthritis may be associated with crusted lesions on the soles of the feet, or perhaps widespread over the body, known as *keratoderma blenorrhagica* and with erythematous and desquamatory areas on mucous membranes, particularly on the glans penis and in the preputial sac, where the condition is called *balanitis circinata*.

Iritis also occurs as the result of this infection. It is occasionally found in the course of an attack of arthritis, but more commonly appears independently, perhaps after the lapse of months or years from the original infection. It shows a strong tendency to repeated relapses.

Conjunctivitis.—Inflammation of the conjunctiva as the result of direct contamination probably occurs in some cases, notably in the newly-born. More commonly, however, the infection is blood-borne and then nearly always involves both eyes. It is usually mild but occasionally severe, and tends to resolve quickly, although relapses are not uncommon in severe cases.

The triple syndrome of primary non-gonococcal urethritis of venereal origin, polyarthritis and bilateral conjunctivitis is comparatively uncommon. It is very rare among women. For inadequate reasons it is often called *Reiter's syndrome*. There appears to be an almost identical syndrome associated with dysentery, in which the primary focus of infection is in the bowel and not the urethra, but this is not known to occur in this country. Reiter, in 1916, described a single case of what was probably the dysenteric syndrome. The syndrome associated with venereal urethritis was fully described by Benjamin Brodie in 1818, and by others during the intervening period.

Treatment.—The urethritis is apt to be resistant to treatment and is prone to relapse after apparently successful treatment. Some cases respond to sulphonamides by mouth, and some to streptomycin given intramuscularly in dosage of 1 to 2 g. daily for 5 days. In general, however, the results of such treatment have been disappointing. Lyall (1953) recently claimed excellent results by combining these two drugs. He gave 1 g. of streptomycin intramuscularly followed by 6 g. of sulphathiazole daily for 5 days. The newer antibiotics all have some effect. According to Harkness (1953) the best results are obtained with oxytetracycline by mouth. He gave 500 mg. 6-hourly for 4 days and claimed success in 86.5 per cent. of cases, as compared with 63 per cent. after similar dosage of chlortetracycline and 36 per cent. with chloramphenicol.

Assessment of the value of any form of treatment for arthritis due to this cause is difficult. Any treatment which continues over 3 to 4 weeks will often coincide with spontaneous remission. The various antibiotics and sulphonamides appear to be ineffective. Artificial fever therapy produces temporary improvement, perhaps due to adrenal stimulation. Both corticotrophin and cortisone in sufficient dosage are capable of suppressing temporarily the various arthritic, ocular and cutaneous manifestations of the disease. The amount of hormone required appears to be proportionate to the severity of the inflammatory process. It may be that these hormones will provide a rational method of management of these cases by maintaining suppression of symptoms and signs of the condition until spontaneous remission occurs.

AMBROSE KING.

## TROPICAL EOSINOPHILIA

**Synonyms.**—Tropical Pulmonary Eosinophilia; Eosinophilic Lung; Tropical Eosinophilic Asthma.

**Definition.**—An acute or relapsing condition associated with loss of weight, cough and pulmonary signs and symptoms resembling asthma. Pulmonary radiograms usually show a picture of increased transverse striations and discrete soft mottling, sometimes closely resembling tuberculosis. Most cases respond rapidly to arsenical therapy.

**Ætiology.**—The cause is unknown. Present opinion inclines to viral infection. Worm infestations and pulmonary invasion by mites were at one time suspected as possible causal factors, but are now excluded. The condition occurs mostly in hot, moist coastal regions. There is no seasonal incidence. It was first observed in the indigenous population of India and has since been reported in most Asiatic races and in increasing numbers of Europeans living in India, the Far East and Africa.

It occurs most commonly in the age group 21 to 40 years, except in some parts of India, where children are most frequently affected. It has been reported in children under 6 years of age and in adults over 60 years of age. Sex and occupation do not seem to be ætiological factors.

**Pathology.**—The condition is not fatal. The only morbid anatomical evidence available was obtained from patients who died of some other cause. In these cases, pulmonary changes resembled those of viral pneumonitis, as indicated by the radiographic picture. There is usually a considerable leucocytosis and always an increase in absolute numbers of eosinophils. Details of the blood picture are given below. Sternal marrow smears show an increase in eosinophilic elements.

Smears of sputum show epithelial cells and clumps of eosinophils. The bacteriological content is non-specific. Mites belonging to the family *Tyroglyphidae* may sometimes be found in centrifuged deposits of sputum digested in 4 per cent. sodium hydroxide. They are not specific to the syndrome.

**Symptoms and Signs.**—The clinical picture varies considerably from patient to patient.

**Pulmonary signs and symptoms.**—The commonest complaint is coughing, usually in nocturnal paroxysms lasting from a few minutes to an hour. There may be little or no coughing during the day.

Paroxysms often occur several times during the night and may be of considerable violence, forcing the patient to sit up in bed in acute respiratory distress closely resembling an asthmatic attack, except that bronchial spasm is not always present and the dyspnoea is not always expiratory in type. *Status asthmaticus* has been reported.

A sense of constriction of the chest is common during and for some time after a coughing paroxysm. There may also be some aching pain in the sternal region or epigastrium, persisting for some time after the coughing.

Coughing is accompanied and succeeded by expectoration of mucoid or mucopurulent sputum, sometimes in considerable quantities. The sputum may be streaked with bright blood; occasionally there may be small hæmoptyses, especially immediately after a paroxysm. In some cases sputum may be coughed up throughout the illness; in others it appears only during and for a short time after the coughing paroxysm.

Chest signs may be minimal or absent, even when the clinical picture is severe. In most cases, however, during coughing and for some time afterwards, scattered sibilant or sonorous rhonchi and occasionally coarse crepitations may be heard in both lungs, especially over the bases. Signs of emphysema are common.

Sweating is usual during or shortly after the paroxysm and is sometimes profuse.

The paroxysms of coughing lead to disturbance of sleep, severe insomnia and progressive fatigue. Most patients rapidly lose weight.

**Pulmonary radiograms.**—In all active cases, there are pulmonary radiographic changes. The hilar shadows are usually irregularly enlarged and blurred. The lung fields are transversely crossed with fine irregular branching striations best seen in the mid-zonal regions. Mottled shadows present as discrete, soft, rounded and sometimes ill-defined areas up to 3 cm. in diameter. There may be few or many and the numbers of spots present vary considerably from patient to patient.

The radiological pattern is usually bilateral and most commonly basal in distribution. The apices are usually clear but are occasionally involved. Unilateral changes have been reported. There may be no mottling. Very occasionally the latter may be the only sign. Patchy emphysematous changes are very common in longstanding cases.

The transverse striation and mottling usually disappear after successful treatment and return during relapses.

The appearance of the shadows varies from time to time and it is not always easy to correlate the pulmonary radiographic picture with the prevailing clinical respiratory picture or eosinophilia. On the whole, the shadows are more prominent in early acute cases. There may sometimes be associated areas of consolidation or basal pleural thickening.

**The blood.**—The white cell count ranges between 10,000 and 100,000 cells or more per c.mm. Eosinophils constitute 25 per cent. or more of the total cells; counts of 80 per cent. or higher are common in acute cases. Other cells are usually present in normal numbers.

The white cell count and numbers of eosinophils vary considerably from time to time in a given patient. Intercurrent infection may affect the picture by temporarily raising the number of polymorphs and reducing the eosinophils. The eosinophils are normal in appearance. The sedimentation rate is increased: *i.e.*, of the order of 20 to 60 mm. per hour. It returns slowly to normal after treatment.

**Other presenting signs.**—Some patients do not complain of coughing or other respiratory disturbances. In these, the chief complaints are likely to be progressive lassitude and loss of weight, and sometimes inexplicable nocturnal sweating.

The patient is usually thin and may be emaciated. He is usually anorexic. Insomnia, especially when associated with nocturnal paroxysms of coughing, may lead to a desperate desire for rest and sleep. It is sometimes this helpless feeling of weariness that drives the patient to the doctor.

There may be an irregular low-grade intermittent fever in acute cases, the peaks of fever occurring in the evening. Many cases, however, even when suffering from severe pulmonary disturbances, remain afebrile. There are no circulatory disturbances. The heart is unaffected and the pulse-rate is normal, except during paroxysms when it may be fast. The lymph glands and spleen are not enlarged.

**Course.**—The condition is not fatal. It may last for years, with alternating periods of exacerbation and remission. Signs and symptoms usually develop gradually over months and sometimes years. On the other hand in some cases the development may be rapid.

Spontaneous recovery is common after a few months or years. Recurrences are rare after more than 2 years of quiescence.

Response to treatment is usually rapid. Recurrences are common but respond well to further treatment. A few cases are refractory to treatment but even these tend to recover eventually.

**Diagnosis.**—The diagnosis may be obvious from the clinical picture of nocturnal coughing paroxysms and the high eosinophil count. The lung signs, especially when associated with evening fever and sweating, may be easily confused with those of tuberculosis. Points of difference are the usual absence of apical signs and the common

mid-zonal and basal distribution of signs in the eosinophilic case, and the characteristic combination of striation and mottling in the pulmonary radiogram. The mottling in tuberculosis is usually distributed more widely over the lung fields and the individual shadows are harder and more clearly defined.

Difficulty may be experienced in distinguishing tropical eosinophilia from bronchitis and bronchiectasis or from allergic bronchial asthma. In the latter case, the patient suffers from expiratory dyspnoea and coughs after relief; in tropical eosinophilia there is often no expiratory distress and cough occurs during, as well as after, the paroxysm.

The radiographic picture may be mistaken for that of Loeffler's syndrome in which, however, the lung changes are transitory and the upper respiratory tract is usually involved.

The eosinophil count is the conclusive point in diagnosis. In the diagnosis of the individual case, the number of eosinophils per c.mm. should exceed 3,000, and the total white count 10,000 cells per c.mm. Figures of this order associated with pulmonary symptoms confirm the diagnosis. It must be remembered, however, when dealing with members of the indigenous population in tropical countries, that white cell counts of 10,000 with an eosinophilia of 10 to 12 per cent. are quite common. When eosinophilia occurs in asthma, hay fever, etc., it is never of the order seen in tropical eosinophilia. This is true of most parasitic infections which should be identified by discovery of the causative agent. A few worm infestations may produce a very high eosinophil count and may also be temporarily associated with pulmonary signs and symptoms. It is therefore most important to exclude these infestations as far as possible. Loeffler's syndrome is characterised by the presence of a very high percentage of eosinophils in a relatively low total white count.

**Treatment.**—Most cases react rapidly to arsenicals. The best results are obtained by parenteral treatment. Dosages of representative drugs are given below:

*Novarsenobillon*: 300 to 600 mg. given intravenously. One dose at weekly intervals for 6 to 8 weeks.

*Acetylarsan*: 3 to 5 ml. intramuscularly once weekly for 6 to 8 weeks. (Each ml. contains 20 mg. arsenic.)

*Stovarsol*: Gr. 4 twice or thrice daily for 7 to 10 days.

*Chlortetracycline* may be given to the few cases which do not respond to arsenicals.

*Dosage*: 500 mg. orally three times daily for 7 to 10 days.

There may be exacerbation of symptoms, with fever and increase of eosinophils after the first or second injection of arsenicals, or after the first few days on chlortetracycline. In some cases painful nodular swellings resembling those of erythema nodosum may appear at about the same time, especially on the limbs. Treatment should be continued in spite of these reactions.

In the majority of cases treatment with arsenicals is followed by almost immediate response. There is a rapid fall of total white cell numbers due to reduction in eosinophils. Normal white counts may be reached in 6 weeks from the beginning of treatment, but the eosinophils may remain at 10 to 15 or even 20 per cent. for some time longer. In treatment with chlortetracycline no improvement may be noted at all for the first week. After this, progress is rapid.

The radiographic pattern in early cases responds remarkably, often disappearing within a month. This effect is of considerable diagnostic importance.

Relapses, with return of clinical signs, the high white cell count, eosinophilia and radiographic pattern, occur in about 10 per cent. of cases within 2 years of treatment. Most relapses respond rapidly to arsenical therapy or chlortetracycline.

A few cases may continue to relapse after several courses of treatment. Even in these cases, however, recovery may be anticipated after a few years.

BRIAN MACGRAITH.

## SECTION III

### DISEASES DUE TO METAZOA

#### A. DISEASES DUE TO TREMATODES OR FLUKES (DISTOMIASIS)

##### PARAMPHISTOMIASIS

**Definition.**—An invasion of man with amphistome flukes of the family *Paramphistomidae*. Two of these parasites are known. *Watsonius watsoni* (*Cladorehis watsoni*).—L. 8 to 10 mm.  $\times$  4 to 5 mm.; Ova, 120 to 130  $\times$  75 to 80  $\mu$ . The parasite has a reddish-yellow colour when fresh and inhabits the duodenum and upper part of the small intestine. *Gastrodiscus hominis*.—L. 5 to 8 mm.  $\times$  3 to 4 mm.; Ova, 150  $\times$  72  $\mu$ . The parasite has a large posterior disc by which it attaches itself to the mucous membrane of the bowel; it occurs in the cæcum and colon.

**Symptoms.**—Diarrhœa, with loose bilious stools in the case of the former parasite, and intestinal disturbances with diarrhœa in the latter. The eggs of both parasites are found in the fæces.

**Treatment.**—Carbon tetrachloride (3 ml.) is probably specific.

##### FASCIOLIASIS

**Definition.**—An invasion of man and other animals with flukes of the family *Fasciolidae*. Several of these are known.

(1) *Fasciola hepatica* (*Distoma hepaticum*), the common liver fluke inhabiting the bile ducts of sheep and other mammals. L. 20 to 30 mm.  $\times$  8 to 13 mm. The ova are operculated and oval, measuring 130 to 145  $\times$  70 to 90  $\mu$ . From them miracidia emerge which develop into sporocysts, rediæ and cercariæ in snails of the species *Lamnea truncatula*; later the cercariæ encyst on grass stems and are subsequently eaten.

**Symptoms.**—Man is occasionally infected; light infections may be discovered accidentally during stool examinations, while severe cases may succumb to secondary cholangitis and liver abscess. In sheep the disease produces liver rot, which may be fatal.

**Treatment.**—Good results are reported following a course of emetine injections. Carbon tetrachloride is effective in sheep and has been favourably reported on in human cases; it is contraindicated where there is calcium deficiency.

(2) *Fasciolopsis buski* (*Distoma crassum*).—L. 30 to 70 mm.  $\times$  12 to 14 mm.; Ova, 120 to 130  $\times$  77 to 80  $\mu$ .—This giant fluke is found in China, Borneo, Malaya, Assam, Bengal and other regions in the East: it inhabits the small intestine, particularly the duodenum, producing focal lesions. The immature eggs are voided in the fæces, the miracidium matures in 3 to 7 weeks and escapes through the operculum. It enters certain snails (*Planorbis canosus*, *Segmentina nitidella*, etc.) and develops into sporocysts and rediæ which generate cercariæ; the latter encyst on water plants—water caltrop and water chestnut—man becoming infected by eating the corms. The cercariæ excyst in the duodenum and mature.

**Symptoms.**—The incubation period is 3 months. Initial symptoms include hypogastric pain, acid dyspepsia relieved by food, and diarrhœa. Later, asthenia, œdema of the face and extremities, ascites and dry, harsh skin develop.

**Diagnosis.**—The condition may simulate gastric ulcer or typhoid, and is diagnosed by finding the ova in the stools.

**Treatment.**—PROPHYLACTIC.—Consists of cooking water caltrops and water chestnuts and sterilisation of night soil.

**CURATIVE.**—Carbon tetrachloride (3 ml.), hexylresorcinol (1 g.), betanaphthol (gr. 5 to 10) and emetine are said to be specifics.

## PARAGONIMIASIS

*Paragonimus westermanni* (*Distoma westermanni*; *D. ringeri*)

**Definition.**—An invasion of the pulmonary tissues by the lung fluke, a member of the family *Troglorematidae*.

**Ætiology.**—Paragonimiasis occurs endemically in the Far East, especially Formosa, Japan, Korea and China. The adult flukes (7.5 to 12 mm.  $\times$  4 to 6 mm.) form cysts in the lung, where the broad, oval, immature, operculated ova (80 to 118  $\times$  50 to 70  $\mu$ ) escape via the bronchi and appear in the rusty brown sputum: they are also found in the faeces (40 per cent.). After attaining maturity the miracidium emerges, and invades a melaniid snail, especially *Melania libertina*, where it forms sporocysts, rediæ and, later, cercariæ which encyst in the gills, liver and muscles of certain freshwater crabs or cray fish—*Potamon obtusipes*, etc. If eaten by man the adolescaria emerges in the duodenum and migrates via the peritoneal cavity and diaphragm into the lung.

**Pathology.**—Host reaction results in cyst formation around the fluke, which generally communicates with adjacent bronchi, into which the eggs and anchovy-sauce cyst content are discharged. Pulmonary lesions consist of fibrosis, cystic dilatation of the bronchi, broncho-pneumonia and tubercle-like abscesses. Similar cysts may involve the intestinal mucosa, bile ducts, peritoneum, pleura, brain, spleen and liver.

**Symptoms.**—These are divided as follows: (1) *General*, which include adenitis and skin ulcerations; (2) *Thoracic*, characterised by cough, brownish or reddish purulent sputum, and hæmoptysis with physical signs of broncho-pneumonia, pleural effusions or bronchiectasis; (3) *Abdominal*, with involvement of the liver, spleen, pancreas or intestine: if the latter, there is diarrhœa with eggs in the faeces; (4) *Cerebral*, with Jacksonian epilepsy, hemiplegia, monoplegia, aphasia and eye symptoms. Headaches, loss of memory and insomnia may be present.

**Diagnosis.**—This is made by finding ova in the sputum or faeces. The complement-fixation reaction may be of assistance: eosinophilia is also present.

**Prognosis.**—Brain cases are fatal, and the outlook is bad in all severe infections.

**Treatment.**—Abstinence from eating raw freshwater crab or cray fish prevents the disease. Emetine and tartar emetic temporarily relieve pulmonary symptoms, but cures are doubtful (Faust).

## CLONORCHIASIS

**Definition.**—An invasion of the bile ducts of man and other mammals with trematode parasites of the family *Opisthorchidae*, occurring in Japan, Korea, China, etc.

**Ætiology.**—*Clonorchis sinensis* (*Distoma sinense*; *Opisthorchis sinensis*, etc.) is a spatulate fluke, measuring 10 to 20 mm.  $\times$  2 to 5 mm. Its yellowish-brown ova are oval, possess a well-marked operculum and measure from 27.3 to 35.1  $\times$  11.7 to 19.5  $\mu$ . Viable eggs are ingested by certain bithyniid snails (*Parafossarulus striatulus*, *Bithynia fuchsiana*), and the miracidia, penetrating the soft parts, form sporocysts, rediæ and

finally cercariæ, which escape, and encyst in the flesh of certain freshwater fish of the family *Percidæ*, *Gobiidæ* and *Anabantidæ*. When the mammalian host eats infected fish the adolesearia escapes in the duodenum and directly invades the bile ducts, especially the left, owing to its straighter course.

**Pathology.**—Initially infection leads to primary proliferation of the biliary epithelium and thickening of the duct wall; later this becomes greatly thickened, and finally cirrhosis of the liver with destruction of the parenchyma results (Faust). The pancreatic duct is sometimes involved.

**Symptoms.**—Mild cases may be symptomless, but the heavier infections show anorexia, epigastric pain, hepatomegaly, diarrhoea, wasting, jaundice, œdema and ascites.

**Diagnosis.**—This is made by finding the eggs in the fæces.

**Prognosis.**—This is dependent on the intensity of the infection; heavily infected cases occasionally die, but mild and moderate ones invariably survive unless some intercurrent disease develops.

**Treatment.**—Prevention lies in the cooking of freshwater fish before consumption. Tartar emetic intravenously possibly reduces the number of worms, while gentian, crystal and methyl violet reduce the intensity of infection as measured by the egg-cell count. Gentian violet is given as a keratin-coated pill ( $2\frac{1}{2}$  grains) thrice daily after meals for 10 days; for intravenous use 40 ml. of an 0.5 to 1.0 per cent. solution is injected every other day; not more than 6 g. is advised (Faust).

When the liver is enlarged and tender, bile drainage may be accelerated by concentrated magnesium sulphate fed through a duodenal tube left *in situ* for several days. It decreases intra-biliary pressure and absorption of toxic material, but does not cure.

## HETEROPHYIASIS

**Definition.**—Infection with flukes of the family *Heterophyidæ*. Three genera occur in man.

(1) *Heterophyes heterophyes* (*Distoma heterophyes*, etc.).—A minute intestinal fluke infesting man, the dog, cat, etc., in Egypt, measuring  $1.0$  to  $1.7 \times 0.3$  to  $0.4$  mm. The oval, light-brown, operculated ova measure  $28$  to  $30 \times 15$  to  $17\mu$ . The first intermediate host is the brackish-water snail, *Pirenella conica*, and the cercariæ encyst in mullet (*Mugil cephalus*), the ingestion of which causes infection.

(2) *Heterophyes katsuradai* differs morphologically in the great size of its acetabulum, etc.

(3) *Metagonimus yokogawai*.—This pear-shaped fluke measures  $1$  to  $2.5 \times 0.4$  to  $0.75$  mm., while its eggs closely resemble *H. heterophyes*, measuring  $26.5$  to  $28 \times 15.5$  to  $17\mu$ . The life cycle passes through *Melania libertina* and allied molluscs, the cercariæ encysting in the edible fish, *Plectoglossus altivelis*.

(4) A number of other heterophyid flukes, including *Monorchotrema taichi*, *M. taihookui*, *Diorchitrema pseudocirrata* and *H. brevicæca*, have been recorded by Africa and Garcia from Manila.

**Pathology.**—The flukes become attached to the intestinal mucosa by their suckers, inducing mild inflammatory reactions and eosinophilia.

**Symptoms.**—Mild digestive disturbances and diarrhoea with blood in the stools may result in severe infections. Often the condition is symptomless, the diagnosis being made by finding ova in the fæces. In their cases in Manila, Africa and Garcia have described a condition of cardiac heterophyidiasis, resembling cardiac beriberi, associated with sclerosis of the mitral valves and fibrosis of the myocardium; heterophyid ova were demonstrated in the local lesions.

**Treatment.**—Carbon tetrachloride, betanaphthol and emetine injections are said to be efficacious in eradicating the infection. To find the parasites, the stools must be strained through muslin.

## SCHISTOSOMIASIS (BILHARZIASIS)

**Definition.**—Invasion of man with blood flukes of the family *Schistosomidae*. Three species are well known—*Schistosoma hæmatobium*, *S. mansoni* and *S. japonicum*. More rarely man may be affected by *S. bovis* and *S. matthei*. **Life cycle.**—The parasites inhabit the portal veins and their tributaries, depositing ova in the hollow viscera, whence they escape via the urine or fæces; on contact with water miracidia emerge, invade the appropriate molluscan intermediary, in which sporocysts and cercariæ develop (Miyairi and Leiper). The latter invade the skin and find their way to the portal system, where the schistosomulæ mature. The tuberculated male, originally a flattish fluke, has become rounded by inrolling of its edges to form the gynæcophoric canal, in which the threadlike female lies. Both sexes have an anterior, prehensile sucker and a posterior, suctorial sucker by which the worm maintains its position against the portal blood-stream.

*S. hæmatobium* (*Bilharzia hæmatobia*) occurs in Africa and parts of Western Asia, etc. (♂ 10 to 15 mm.  $\times$  0.8 to 1.0 mm.; ♀ 20 mm.  $\times$  0.25 mm.). The ova have a sharp terminal spine and measure 120 to 160  $\times$  40 to 60  $\mu$ . The intermediary hosts vary considerably, being *Bullinus contortus*, etc., in Egypt, *Physopsis africana* in Natal and Rhodesia, and *Planorbis metidjensis* in Portugal. *S. mansoni* is found in Africa, South America, etc. (♂ 10 to 12 mm.  $\times$  1.0 to 1.2 mm., ♀ 12 to 16  $\times$  0.16 mm.). The ova have a lateral spine and measure 140 to 165  $\times$  60 to 70  $\mu$ . The intermediary host is *P. boissyi* in Egypt, *P. pfeifferi* in West and East Africa and *P. guadeloupensis* in the West Indies and South America. *S. japonicum* is confined to the Far East—Japan, China, Formosa and the Philippines (♂ 12 to 20 mm.  $\times$  0.5 to 0.55 mm., ♀ 15 to 26 mm.  $\times$  0.3 mm.). The ova possess a lateral knob and measure 100 to 110  $\times$  55 to 65  $\mu$ . The intermediate hosts are *Katayama nosophora*, *K. formosana* and *Oncomelania hupensis*.

**Pathology.**—In *S. japonicum* and *S. mansoni* the worms are found in the portal system, especially its mesenteric branches, ova being deposited in large numbers in the colon and liver, and to a lesser degree in the small intestine, mesenteric glands, stomach, pancreas and rarely the spleen. In *S. hæmatobium* they wander still farther afield via the inferior hæmorrhoidal plexus into the pelvic plexuses of veins, especially the vesical, prostatic and uterine; eggs are deposited in the bladder, prostate, seminal vesicles, urethra, the lower third of the ureter, cervix and vagina. These plexuses communicate with the inferior vena cava; in consequence stray ova filter out into the lungs rather than the liver. Apart from toxic effects and suctional trauma produced by the schistosomes themselves, the egg deposits cause considerable local inflammatory reaction, at first giving rise to small pseudo-tubercles initially composed of giant cells, eosinophiles and round cells; later these disappear or are replaced by whorls of fibrous tissue in which degenerated and calcified eggs are found. The characteristic papillomata form as a combined result of irritative downgrowth of epithelium produced by toxic substances liberated from worms and ova, and submucous cellular accumulations pressing the mucosa upwards from below.

**Special pathology.**—*S. japonicum* and *S. mansoni* produce various colonic lesions, including round, yellowish, submucous, pseudo-tubercles, bilharzial colitis and papillomata, which may slough off, leaving round ulcers. All these lesions may be visible with the sigmoidoscope. In addition, marked fibroid thickening and contractions of the bowel wall, mesentery and omentum sometimes occur. Periportal cirrhosis of the liver, which may or may not be associated with bilharzial splenomegaly, is met with. Other lesions include rectal papillomata, prolapse of the rectum, perineal granulomata and ischio-rectal fistulæ. In *S. mansoni* egg deposits in the spinal cord may produce myelitis, and granuloma of the brain simulating cerebral tumour is recorded in *S. japonicum*. In *S. hæmatobium* vesical lesions are dominant, but in



addition there may be involvement of the ureters (lower third), chronic fibrosis of the prostate and seminal vesicles, bilharzial infiltration of the cervix, vagina and peri-urethral tissues with sinus formation, and granulomata of the penis and vulva. In the bladder the earliest lesions are minute petechiæ and round, yellowish, pseudo-tubercles studding its surface; later, papillomata and ulcers may develop, while chronic fibroid thickening and the so-called "sandy patches" are very characteristic of the chronic stages with calcified eggs. These lesions are demonstrable cystoscopically. Pulmonary fibrosis associated with egg deposits is not uncommon, but involvement of the colon and liver is minimal.

**Symptoms.**—Three stages can be recognised: (1) invasive; (2) toxic or anaphylactoid; (3) localised disease (a) early, (b) late.

(1) *Invasive*.—The entry of cercariæ may give rise to transient rash and local irritation lasting 24 to 48 hours (Kabure disease).

(2) *Toxic or anaphylactoid*.—Within 2 to 8 weeks a clinical syndrome may appear, characterised by urticaria and an intense eosinophile leucocytosis; in addition there may be rigors, abdominal pain, enlarged tender liver and spleen, dyspnœa, bronchitis, anorexia, diarrhœa and fever, lasting a few days to several weeks; the severe cases often simulate typhoid. This stage is most often described in *S. japonicum* (Katayama disease), but it also occurs in *S. mansoni* and *S. hematobium* infestations. Fulminating cases due to hyperinfection with *S. japonicum* may die from toxæmia before ova appear.

(3) *Localised disease*.—Local features dependent on egg deposition in the bladder or colon are not generally apparent for 3 to 9 months after infection. In *S. hematobium* early symptoms include scalding or frequent micturition, penile, perineal, suprapubic or loin discomfort or pain, and terminal hæmaturia, the blood being bright red and increased by exercise. At this stage the prostate may be congested and tender, cystoscopic examination shows the characteristic yellow, round pseudo-tubercles, and the urine contains leucocytes, erythrocytes and terminal-spined ova which may also appear in the feces (40 per cent.). For years intermittent hæmaturia may be the only clinical manifestation, the subsequent course depending on such complications as carcinoma, cystitis and renal involvement. In *S. mansoni* localised features may be absent or a chronic bilharzial dysentery may develop, characterised by colicky abdominal pain, the passage of blood and mucus, and tenesmus. Between attacks there is rectal discomfort, but the stools are solid, and coated with mucus, which may contain the characteristic lateral-spined ova. Later periportal cirrhosis and splenomegaly with ascites, etc., may supervene. In *S. japonicum* similar dysenteric symptoms are present. The chronic stage with cirrhosis and splenomegaly is characterised by weakness, emaciation, pallor, secondary anæmia, dilatation of the abdominal veins and finally ascites and liver insufficiency.

**Complications.**—In *S. hematobium* there may be chronic nephritis or hydro-nephrosis due to backward pressure, or septic cystitis with pyonephrosis or ascending pyelonephritis. Carcinoma of the bladder, penis or vulva may also ensue, while bilharzia papillomata and vesical calculi are not uncommon. In *S. japonicum* and *S. mansoni* hepatic cirrhosis with or without splenomegaly may supervene.

**Diagnosis.**—In the early toxic or anaphylactoid stage the diagnosis may be suggested by the intense eosinophilia and confirmed by the cercarial complements fixation reaction. In the localised stage the diagnosis is generally made by finding ova in the excreta, but the complement-fixation reaction and the cystoscopic or sigmoidoscopic findings often prove of considerable value. The small nodules or pseudo-tubercles seen in the bladder or pelvic colon and rectum during instrumental examination in the early stages of the disease are yellowish in colour while the ova are living and become whitish when they die and calcify. In examining for *S. mansoni* or *S. japonicum*, the mucus covering of the stool should be selected, and in *S. hematobium* the last few millilitres of urine passed; several examinations may be

necessary and eggs may be found in scrapings from the bowel wall obtained with a blunt curette during sigmoidoscopy, when ordinary fæcal examinations are negative.

Concentration of ova by sedimentation of the stools with 25 times their volume of 0.5 per cent. glycerin in water is sometimes helpful.

**Prognosis.**—The prognosis is bad only in patients continuously exposed to infection, or in late cases when hepatic or renal insufficiency, septic infection or carcinoma has supervened. Otherwise the results of treatment, with full courses of tartar emetic, are satisfactory; two or even three courses of treatment are sometimes necessary, especially in *S. japonicum* infestations.

**Treatment.**—**PROPHYLACTIC.**—This consists in curing the disease in man, in preventing excretal contamination of water, in destruction of snail vectors and in avoiding contact with infected water.

**CURATIVE.**—Three trivalent antimony compounds, tartar emetic, Anthiomaline and stibophen (Fouadin), as well as emetine hydrochloride, exert a specific lethal action on the adult schistosome. During treatment rest in bed is advisable, especially if complications exist, but in Egypt and other endemic areas generally ambulatory treatment is alone practicable.

(1) *Tartar emetic*, first successfully introduced by Christopherson, is given intravenously in 10 ml. of saline every second day, commencing with gr.  $\frac{1}{2}$  and increasing by gr.  $\frac{1}{2}$  until a maximum of gr. 2 is attained. The solution should be freshly prepared each day, and the total course for the adult should be at least gr. 30. The drug kills the schistosomes, and viable ova completely disappear from the excreta in about 10 to 14 days owing to the degenerative effects exerted on the yolk glands and ovaries of the female worms. Relapses are due to gradual recovery of the surviving female worms and restoration of their egg-laying function. Cough, vomiting and toxic muscular pains may follow its administration, but the drug is generally well tolerated except in cases complicated by hepatic cirrhosis, renal involvement, sepsis, etc. Great care must be taken not to inject any tartar-emetetic solution into the tissues, as severe inflammation and necrosis result. Recently, intensive mass treatment with sodium-antimonyl-tartrate has been advocated, a total dose of 12 mg. per kg. body weight being given in 6 intravenous injections in 2 days (Alves and Blair). This intensive course is not considered to effect sterilisation of the infection as frequently as the classical longer course.

(2) *Stibophen* (*Fouadin*) (antimony-pyrocatechol-disulphonate of sodium) should be given in an all-glass syringe in 6.3 per cent. solution; the ordinary course consists of 40 ml. administered in 9 intramuscular injections extending over a period of 15 days. Even when twice this amount of drug is given, i.e., 80 ml., the results are not as satisfactory as those obtained with tartar emetic. Another useful trivalent antimonial is Anthiomaline, given intramuscularly in doses of 2 ml. (0.01 g. metallic antimony) on alternate days for up to 20 doses. Results with this drug are not as good as with tartar emetic.

(3) *Emetine hydrochloride* in a dosage of gr.  $1\frac{1}{2}$  daily for 10 days is advocated intravenously (Tykalas). Though emetine undoubtedly kills schistosomes, this treatment is dangerous owing to toxic effects on the myocardium and is rarely used.

An entirely new drug known as Nilodan (Miracil D) is at present under clinical trial. Promising results have been reported. The drug is given orally in doses of 1 to 2 grammes twice daily for 3 days, the treatment being repeated after a month. Toxic effects include vertigo, epigastric pain, nausea and vomiting, colicky diarrhoea.

The usual medical and surgical measures should be employed for complications as they arise, and vesical and rectal polyps which do not resolve with specific therapy may need local treatment.

N. HAMILTON FAIRLEY.

## B. DISEASES DUE TO CESTODES

## TÆNIASIS—TAPE-WORMS

**Definition.**—Tæniasis is produced by different forms of tape-worms occurring either as adults in the intestine (intestinal tæniasis) or as the developmental stage in the muscles and other host tissues (somatic tæniasis).

## INTESTINAL TÆNIASIS

(1) *Tænia solium* (Linnaeus, 1758).—The pork tape-worm measures 2 to 3 metres in length. The head is globular and possesses four suckers, a rostellum and a double row of hooks. The uterus never has more than twelve lateral processes (diagnostic). The ova are spherical, 31 to 40 $\mu$  in diameter, having a thick-walled shell and an oncosphere with three pairs of hooklets. The cysticercus stage is passed in the pig (*Cysticercus cellulosæ*), and man becomes infected by eating undercooked "measly" pork. Pickling and smoking do not kill cysticerci.

(2) *Tænia saginata* (Goeze, 1782).—The beef tape-worm measures 3 to 4 metres in length. Its head is cubical with four suckers, but no armature; the uterus contains fifteen or more lateral processes, thus differentiating it from *T. solium*, though its oval eggs, measuring 33 to 40 $\times$ 20 to 30 $\mu$ , may be indistinguishable. The cysticercus stage is found in the ox (*Cysticercus bovis*) and man becomes infected by eating undercooked beef.

(3) *Dipylidium caninum* (Linnaeus, 1758).—A common tape-worm of the dog is occasionally found in man. Human infestation with *Tænia confusa*, *Tænia africana* and *Bertiella satyri* has been described on two or three occasions.

(4) *Hymenolepis nana*.—This dwarf tape-worm, which is common in Southern Europe, the Southern United States and India, inhabits the small intestine of man. It measures 2.5 to 4.0 cm. in length, has four hemispherical suckers and a short rostellum with a single row of hooks. The eggs measure 30 to 40 $\mu$  in diameter and contain an oncosphere. No intermediary host is required, as the eggs hatch out in the intestine. After penetrating the mucosa the embryos develop into cercocysts, return into the lumen of the bowel, become attached by their heads to the villi and develop into mature worms.

(5) *Diphyllobothrium latum* (Linnaeus, 1758) (*Tænia lata*, etc.).—The broad, fish tape-worm, some 2 to 10 metres long, possesses an almond-shaped head, but no armature. The immature eggs are oval, operculated and measure 70 $\times$ 45 $\mu$ . After 3 to 5 weeks' development in water the hexacanth embryo escapes and is ingested by some species of cyclops or allied crustacean in the body cavity of which it develops into a procercoid larva. Infected crustaceans must be swallowed by certain fish, i.e. before the plerocercoid larva develops. Man becomes infected by eating the undercooked, infected fish. Other species, such as *D. cordatum*, *D. parvum* and *D. houghtoni*, have been described on one or two occasions as has also *Diplogonoporus grandis* and *Braunia jassyensis*.

**Symptoms.**—Symptoms may be absent, or gastro-intestinal disturbance, such as anorexia, voracious appetite, dyspepsia, abdominal pain, colic and diarrhœa may result. Neurasthenia in adults, and headache, convulsions and strabismus are described in children. Occasionally *D. latum* is associated with severe megalocytic anemia.

**Diagnosis.**—The diagnosis is made by identifying the appropriate segments or ova in the excreta. Skin hypersensitiveness to tape-worm protein and eosinophilia may be present.

**Treatment.**—Felix mas and carbon tetrachloride are effective remedies for all the tape-worms, provided preliminary starvation and terminal purgation with salines be instituted. After a liquid diet, consisting of broths, orange juice, dextrose, etc., for 2 days, during which time the bowels are well opened, extractum filicis liquidum in 30 minim doses is given in gelatine capsules or emulsion at 8.0, 8.20, 8.40 and 9 a.m. Sodium or magnesium sulphate (gr. 240) is administered at 10 a.m., and all the motions subsequently passed must be carefully sieved and examined against a black background to identify the head; castor oil must never be used as it dissolves out filicic acid and leads to poisoning. If the head is not recovered, treatment may be repeated in 10 days' time, or 3 months' interval may be allowed, by which time segments will have generally reappeared if the worm has survived. Alternatively, carbon tetrachloride is given in capsules, the maximum adult dose being 3 ml.; this is followed by a saline purge 3 hours later. Some report that it is advantageous to combine oil of chenopodium (1 ml.) with carbon tetrachloride therapy, as in the treatment of ankylostomiasis. This is important where concomitant infection with ascaris is likely.

In intractable cases a duodenal tube may be passed and specific drugs run directly into the duodenum. If extractum filicis liquidum followed by magnesium sulphate fails to dislodge the head, this treatment may be followed within 48 hours by carbon tetrachloride similarly administered. This treatment, though severe, is generally highly successful.

Mepacrine in high dosage is sometimes effective. It should be given in doses of about 1 g. in the course of 1 or 2 hours.

The megalocytic anæmia associated with *D. latum* infestation responds satisfactorily to oral liver extract therapy, but recurs unless the worms be eradicated by specific drug treatment.

#### SOMATIC TÆNIASIS

(1) *Sparganum mansoni*.—This is the plerocercoid stage of *Diphyllbothrium mansoni* (Cobbold, 1882) which has a somewhat similar life-history to *D. latum*. The adult worm infests the intestine of the dog and cat, the ciliated embryo is ingested by *Cyclops leuckarti* where it develops into a proceroid larva. When swallowed by the second intermediate host, which may be a snake, bird or mammal, including man, the cyclops is digested, the liberated larva penetrates the stomach and, travelling under the peritoneum, reaches the deep somatic muscles, also the iliac fossa, lumbar region, pleura, urethra and eye, where it multiplies asexually by transverse fission, many spargana resulting from a single plerocercoid (Faust). Ingestion of spargana-infested tissues by the dog and cat results in intestinal diphyllbothriasis, but the adult stage does not develop in man.

**Symptoms.**—Pain, swelling and œdema of the subcutaneous tissues and muscles sometimes occur, and in ocular sparganosis, which is common in the Tonkin delta, inflammation with pain, redness, œdema, lacrimation and ptosis may result. Human infection in China often follows the direct transference of spargana from infected frogs which are applied locally in the treatment of ulcers, etc. (Joyeux and Houdemer).

**Diagnosis.**—This is made by finding the unbranched sparganum larvæ embedded by their scolices in a slimy matrix in the tissues.

**Treatment.**—Where possible the parasite is removed surgically.

(2) *Sparganum proliferum* (Ijuma, 1905).—This species affects man in Japan, innumerable spargana producing nodules and honeycombing of the tissues, and elephantiasis if the lymph channels be involved. The adult stage and life-cycle are unknown.

(3) *Tania solium*.—The cysticercus stage of *T. solium*, i.e. cysticercosis, is occasionally found in man who may or may not have harboured the adult parasite. The

cyst, which is generally surrounded by a fibrous-tissue capsule, consists of an opalescent bladder containing a single evaginated head with hooklets. Various tissues, including the brain and its ventricles, the liver, lungs, orbit and the somatic muscles, tongue and heart, may be involved. It occurs in Europe, Africa and Madagascar, and in soldiers returning from India and Egypt. Macarthur has found it to be a common source of epilepsy. Man probably acquires the disease by auto-infection, or eating uncooked food, such as lettuce, to which dried segments of *T. solium* are adherent.

**Symptoms.**—Subcutaneous nodules ( $\frac{1}{2} \times 2$  cm.), muscular weakness, cramp and pains may be encountered, also Jacksonian epilepsy, petit mal, various psychoses and occasionally focal lesions of different types, if the brain be involved (*Cysticercus cellulosæ*). The diagnosis is established by biopsy of a subcutaneous cyst, or a radiographic examination revealing calcified nodules in the muscles. Ophthalmoscopic examination may show retinal lesions, while eosinophilia and skin hypersensitiveness and positive complement-fixation reactions with *taenia* antigens may be found. Accessible cysts can be excised, but the prognosis is bad if the brain be involved. The most dangerous period is the sixth to the eighth year, when cerebral disturbances, associated with the death of the cysticerci in the brain, most frequently occur. Mental deterioration and death frequently result, but many of those developing cerebral cysts may recover. Fits should be controlled by phenobarbitone and bromide.

(4) *Taenia multiceps* (Leske, 1780).—*Cœnurus cerebralis*, the cystic stage of the canine tape-worm, *T. multiceps*, commonly affects the brain of goats and sheep; it has been recorded in man, producing epilepsy and aphasia.

(5) *Echinococcus granulosus* (Batch, 1786).—This small tape-worm (2.5 to 6 mm. in length) inhabits the intestines of dogs, jackals and wolves; it consists of a head with four suckers, a rostellum and hooklets and three or four segments, of which only the terminal one is gravid. In the intermediate hosts, which include sheep, cattle, pigs and man, hydatid disease is produced. Man becomes infested from swallowing water and uncooked vegetables, etc., contaminated with infected canine faeces, or by handling and fondling infected dogs. Hydatid disease is frequently contracted in childhood and is most common in sheep-breeding countries like Australia, New Zealand, the Argentine and South Africa; it also occurs in Iceland but is less frequently encountered in Europe.

After the egg is swallowed, the six-hooked embryo escapes from its shell, traverses the intestinal wall, invades the blood-vessels and metastasises generally in the liver, but less frequently in the lungs, brain, bones and muscles, etc., where it loses its hooks and forms a cyst, the wall of which consists of two layers, a laminated outer layer, the ectocyst, and a granular inner layer, the endocyst. As the cyst grows, it exerts mechanical pressure and toxic effects on adjacent host tissue, resulting in inflammatory reaction and the formation of a fibrous tissue capsule known as the adventitia. Endogenous budding from the granular layer of the cyst results in the formation of brood capsules, scolices and daughter and granddaughter cysts. Exogenous budding sometimes occurs, especially in bone, while atypical development in viscera like the liver may result in alveolar or multilocular types of hydatid. It is improbable that a second parasite, *E. multilocularis*, exists.

**Symptoms.**—The clinical picture is very varied. Cysts may be symptomless for many years until pressure effects are produced, or they may rupture or suppurate with the production of acute illness. Rupture into a vein may lead to sudden death from an embolus of daughter cysts, or to an anaphylactic syndrome characterised by injected conjunctivæ, lacrimation, vasomotor collapse, urticaria, œdema, respiratory distress and eosinophilia. Rupture into the peritoneal cavity may produce an acute abdominal crisis followed by peritoneal echinococcosis, secondary cysts developing from scattered scolices, or if the cyst rupture into a bronchus natural cure may ensue. Suppuration, especially of liver cysts, is not uncommon, while in some 30 per cent.

of cases their degeneration and death with subsequent calcification lead to natural cure. The inferior aspect of the right half of the liver is the commonest site affected, while the right lung is three times as often involved as the left. Brain cysts closely simulate cerebral tumour, while echinococcosis of bone, owing to its rapid exogenous growth, often leads to a fatal issue, especially when the pelvis and vertebral column are involved; a pressure myelitis may result.

**Diagnosis.**—A history of contact with dogs in childhood is important; hydatid thrill, if present, is pathognomonic. Collapsed cysts, membrane, scolices and hooklets may be coughed up or passed per rectum, while the aspiration of a clear watery fluid containing considerable amounts of sodium chloride and hydatid elements clinches the diagnosis. Aspiration, however, should never be carried out in lung cysts except on the operating-table owing to the danger of drowning from rupture into the bronchial tract. Radiographic examination is of considerable importance in localising liver and lung cysts, while the complement-fixation and precipitin reactions and the intradermal test have greatly increased the percentage of cases correctly diagnosed before operation. Eosinophilia may occur, especially if a cyst has recently ruptured.

**Treatment.**—No medical treatment is available except for the anaphylactic syndrome, when adrenaline (10 minims of 1 in 1000 solution) should be administered. As a rule, calcified cysts should not be operated on. After the injection of formalin to kill scolices in hepatic cysts the contents should be evacuated and the adventitia sewn up in smaller-sized cysts; suppurating and large cysts must be drained. Special care must be taken to prevent soiling of the peritoneum with the cyst contents in hepatic hydatid, as secondary peritoneal echinococcosis is liable to develop.

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## C. DISEASES DUE TO NEMATODES (ROUND-WORMS)

### STRONGYLOIDIASIS

*Strongyloides stercoralis* (Bavay, 1876).—A common tropical parasite of man, the female worms living in the jejunum and duodenum, and in massive infections invading the bile and pancreatic ducts, the stomach and colon.

**Ætiology.**—The eggs hatch out rhabditiform larvæ which appear in the fæces: rarely, where intense diarrhœa is present, the eggs ( $50$  to  $80 \times 30$  to  $34\mu$ ), which resemble ankylostome ova, may be found. The rhabditiform larvæ give rise either directly, or indirectly through a sexual circle, to filariform larvæ which invade the skin or mucosa and follow a similar route to ankylostomes proceeding via the lung to the intestine.

**Pathology.**—Intestinal catarrh or an enteritis, with extensive erosions of the mucosa, giving rise to a "beefsteak" appearance, may occur in heavy infections.

**Symptoms.**—Initial dermatitis and lung symptoms may be seen during the first few days. Mild infections show no symptoms; severer infections may present epigastric discomfort after meals, flatulence and diarrhœa which occasionally is very intractable. Occult blood may occur, urticaria and œdema sometimes develop at the site of entry of infective larvæ and dermal sensitivity can be demonstrated to strongyloid extracts (Fülleborn).

**Diagnosis.**—This is made by finding the rhabditiform larvæ in the stools, which should be mixed with water and strained through muslin. Hook-worm embryos have a longer pre-œsophageal mouth cavity and occur within the egg.

**Treatment.**—Gentian violet, introduced as a specific by De Langar, is given as a keratin-coated pill (gr. 1) thrice daily before food until a course of gr. 50 has been taken. In intractable cases, 25 ml. of a 1 per cent. aqueous solution can be administered through a duodenal tube. For the intravenous route 25 ml. of an 0.5 per cent. solution is recommended on alternate days for 10 days. Though favourably reported on, gentian violet treatment by no means always cures.

Allied helminths, including *Rhabditis pellio* (Schneider, 1886) and *Turbatrix aceti* (Müller, 1783), the common vinegar worm, have been reported in the vaginal exudate and urine of women.

## FILARIASIS

An invasion of man by members of the family *Filariidae*. Several species are known to infest man, *Filaria bancrofti* or *Wuchereria bancrofti*, *F. malayi* or *W. malayi*, *F. loa* or *Loa loa*, *F. perstans* or *Acanthocheiloneuma perstans* transmitted by *Culicoides austeni*, *F. ozzardi* or *Mansonella ozzardi*, the insect vector being *C. furens* and *Dipetalonema streptocerca* (Macfie and Corson, 1922) found commonly in the skin of natives on the Gold Coast and parts of Belgian Congo. Only the first three are of clinical importance.

(1) *F. bancrofti* (Cobbold, 1877).—This parasite has a widespread tropical distribution, being especially common in India, the West Indies, Porto Rico, Southern China and the Pacific Islands. The adults are like fine catgut (♂ 30 to 40 mm. long; ♀ 76 to 100 mm.  $\times$  0.2 mm.); they inhabit the lymphatics and periglandular lymphatic tissue, and produce embryos which subsequently invade the blood-stream, living in the lungs and thoracic blood-vessels by day and appearing in the peripheral blood only at night—nocturnal periodicity. The embryos are enclosed in a loose sheath and measure 230 to 320  $\times$  7.5 to 10  $\mu$ . As Manson first showed, the intermediate host is a mosquito (chiefly *Culex fatigans*), which sucks the embryos out of the blood at night; metamorphosis subsequently takes place in the thoracic muscles. The mature embryos are inoculated into man via the proboscis (Low). Development in the insect vector takes from 10 to 40 days, depending on the temperature, etc. In the Pacific two filaria zones are encountered. Filariasis in New Guinea and New Britain is of the usual nocturnal type and transmission is chiefly by *C. fatigans*. In islands east of 170° east longitude filaria is transmitted mainly by the day-biting mosquito, *Aedes scutellaris pseudoscutellaris*, and is non-periodic in type. This holds in the Samoan, Wallis, Friendly, Fijian, Ellice, Gilbert and Society island groups. Though there are no morphological differences between the adults and microfilariae of the nocturnal and non-periodic types of *F. bancrofti*, it is still possible they may represent different strains or subspecies.

**Pathology.**—The parent worms often produce little obvious damage, the infection then being recognised only by the presence of microfilariae in the blood. Pathological changes, associated with the presence of filaria worms, however, may be found in the tissues of such patients (O'Connor and Hulse), notwithstanding the absence of symptoms, while in others, especially when hyperinfection has extended over many years, the most gross and grotesque pathological manifestations may be found. The various changes in the lymphatics and lymph glands are partly of mechanical origin and partly attributable to the effects of helminthic toxins which induce lymphangitis with resulting lymph stasis and lymph oedema. Lymph oedema and inflammatory tissue reaction ensure an increased protein content of the tissue fluids; this stimulates growth and results in hyperplasia of the skin and subcutaneous tissues, ultimately leading to elephantiasis. Recurring lymphangitis and blocking of the lymphatics may result in death of adult worms, but even if this does not happen, obstruction of the lumina of the lymphatics proximal to the worms will prevent the escape of

microfilariae into the circulation. These are the probable reasons why microfilariae are no longer demonstrable in the blood of patients with elephantiasis.

**Symptoms.**—The incubation period is variable. Some 6 months to 2 years may elapse before early clinical features such as urticarial swellings, filarial nodules and thickened lymph cords, lymphangitis, adenitis, epididymo-orchitis, or lymph scrotum appear. Eosinophilia and skin hypersensitivity to *Dirofilaria immitis* antigen are generally present at this time, but no microfilariae are demonstrable in the blood. Excision of a nodule and subsequent microscopic examination may reveal adult worms. As in loa loa infestation, it may be 2 years before embryos are demonstrable, even when considerable quantities of blood are examined.

Lymphangitis is associated with rigors, high temperature, tender enlargement of the lymphatic glands, red lines in the course of the lymphatics and inflammatory swelling of the affected tissues. The "elephantoid" fever usually lasts 1 to 3 days; if the temperature persists longer superadded streptococcal infection should be suspected. The filarial nodules described by O'Connor originate as a local tissue reaction around dead filarial worms located in the lymphatics; from here red lines caused by inflamed lymphatic vessels may radiate down the limb. The lymphangitis is well defined and the skin and subcutaneous tissue are dull red, tense and oedematous.

Enlarged groin glands are common and if associated with a mass of varicose lymphatics (lymphatic varix) may be mistaken for a hernia. Microfilariae are often found in the aspirated lymph. If lymphangitis ensues there is much local inflammatory swelling, tenderness and pain. The axillary, epitrochlear and cervical glands occasionally become enlarged, especially in non-periodic filaria, while enlargement of the deep-seated glands—iliac, lumbar, mesenteric, retroperitoneal and thoracic—sometimes occurs. Living or calcified worms may be found in such glands, and secondary coccal infection is said sometimes to lead to fatal septicaemia. Involvement of the retroperitoneal lymphatics may cause abdominal pain, associated with tenderness and rigidity of the abdominal muscles, vomiting, hiccough and fever; death from streptococcal peritonitis may follow. Endemic funiculitis or lymphangitis of the spermatic cord is often associated with lymphangiectasia, and is characterised by acute tenderness and local inflammation of the scrotum and cord. Filarial epididymo-orchitis is also not uncommon. It produces fever, shivering and pain in the testicle, which rapidly enlarges and is associated with exudation of fluid into the tunica vaginalis. The swelling subsides in a few days, but permanent thickening and a filarial hydrocele or chylocele may result. Recurrences are common. Lymph scrotum is due to an inflammation of the scrotal lymphatics, which may become dilated and tortuous, and form small vesicles exuding lymph containing microfilariae. Recurrent attacks lead to elephantiasis. Chyluria results from obstruction and dilatation of the thoracic duct itself or of some of the chyle-carrying intestinal lymph vessels. Subsequent rupture of dilated lymphatics into the pelvis of the kidney, ureters or bladder leads to chyluria, or, if chyle escapes into the peritoneal cavity, to chylous ascites.

Elephantiasis results in people repeatedly exposed over long periods of time. The lower limbs are most frequently involved, next the scrotum and next the arms. Elephantiasis of the mammae, vulva and penis are rare. The condition is generally preceded by recurrent attacks of lymphangitis with fever and secondary dermatitis and cellulitis. Occasionally such a history is lacking. Different clinical types are described varying from slight uniform enlargement of the limbs with perceptible thickening of the skin, to gross enlargement with characteristic elephantoid appearance and deformity. The skin becomes coarse and thickened; later, indolent ulceration or abscesses may form, or a coarse warty appearance develops (Elephantiasis verrucosa). Finally the skin becomes leathery in consistency and thrown into rugae, while the hypertrophy of the subcutaneous tissues become so great that the patient is practically immobilised by mere increase in the weight of the lower limbs or scrotum.



Patients inflicted with this condition may live for many years, finally dying from intercurrent disease.

**Diagnosis.**—Prior to the appearance of embryos in the blood, eosinophilia associated with a positive intradermal skin test will suggest the diagnosis. If nodules are present, biopsy should be performed and examination made for the presence of adult filaria in tissue section. When searching for embryos, blood should be collected at the appropriate time (about 10 p.m. to 12 midnight in the nocturnal type and as much as 2 ml. of blood examined in thick films. The fact that the lymphangitis often originates in a nodule in the course of the lymphatic vessels and is of retrograde not the ordinary ascending type, should suggest a filarial origin.

Filarial elephantiasis should be distinguished from the familial type of elephantiasis known as Milroy's disease, and from elephantiasis secondary to recurrent streptococcal lymphangitis, or blockage associated with tuberculosis or carcinoma of the lymph glands or surgical excision.

**Treatment.**—Prophylaxis depends on mosquito destruction and the use of mosquito nets, etc. Certain trivalent and pentavalent organic antimony compounds have been favourably reported on in animal filariasis. Fouadin kills the microfilariae in dogs infected with *Dirofilaria immitis* but not the adult worms, and Neostam (stibamine glucoside) has recently been reported as curing filariasis (*Litomosoides carinii*) in the cotton rat by destroying the adult parasites. Favourable results have recently been reported in human filariasis (*F. bancrofti*) following intensive treatment with Neostibosan, 12 to 15 g. being given in 14 days (Culbertson). The drug acts on the adult worms not on microfilariae, which may take many months to disappear. The blood became entirely negative in two-thirds of the patients after 13 months. Unfortunately, severe toxic reactions developed in some instances and for this reason the treatment appears hardly justified.

Much more promising results have followed the use of the piperazines in the treatment of *F. bancrofti*. The drug of choice is Hetrazan (1-diethyl-carbamyl-4-methylpiperazine hydrochloride) which is given orally in a dosage of 2 mg. per kg. thrice daily for 11 to 22 days. Hetrazan has a pronounced effect on circulating microfilariae, patients showing a negative or markedly reduced counts as early as the second day of treatment. Patients followed up to 5 months have shown no recurrence and the available evidence suggests it also exerts a lethal action on the adult worms.

If secondary streptococcal infection has supervened, sulphonamide therapy or penicillin is indicated. Surgical intervention may be necessary for septic complications, such as filaria abscess and various elephantoid conditions. In elephantiasis of the legs elastic bandaging, massage and rest, with elevation of the limbs, are desirable. Elastic stockings should be washable, porous and made to fit, extending from the dorsum of the foot to above the knee.

(2) *Filaria malayi*.—The adult parasite resembles *W. bancrofti* but it is not as widespread. It occurs in India, Dutch East Indies, the Malay Peninsula, China and Indo-China. The microfilariae have a nocturnal periodicity and the insect vectors are certain species of *Mansonioides* and *Anopheles*. The microfilariae were first described by Brug (1929) but the adult worms were not discovered until 1940 by Rao and Mapleston who removed them from a cyst in the forearm of an Indian. The clinical aspects of this infection have not been closely studied. Elephantiasis, most commonly of the lower limbs, is associated with the infection. Treatment is the same as that for bancroftian filariasis.

(3) *Loa loa* (Cobbold, 1864).—Human infestations with this parasite occur in West Africa. The adults inhabit the subcutaneous and retroperitoneal tissues, while the sheathed embryos have a diurnal periodicity (9 a.m. to 9 p.m.); several years may elapse before embryos appear in the peripheral blood. Transmission is by certain species of mango-fly (*Chrysops dimidiata* and *C. silacea*) which feed in the daytime. Clinically the worms give rise to urticarial eruptions and puffy, painless, white swell-

ings the size of a hen's egg, lasting 2 to 3 days, known as Calabar swellings. These are due to an œdema of the subcutaneous tissue and probably represent an anaphylactoid reaction to helminthic products or toxins. Leucocytosis associated with a marked eosinophilia (20 to 60 per cent.) is characteristic, and dermal hypersensitiveness to dirofilarial extract is shown in almost every case. Positive complement-fixation reactions are also given with dirofilarial alcoholic extracts. Neuritic pains may also be complained of. Not infrequently the worms appear about the eye, and in their migration across the conjunctivæ give rise to transient conjunctivitis and lacrimation. Where visible, the worm should be surgically removed under local anæsthesia.

Treatment with Hetrazan is often effective. Because of the frequent severe reactions to treatment the drug should be given first in small doses and the dose increased in the first 3 or 4 days up to 2 mg. per kg., 3 times a day. Continue treatment for up to 21 days. The immediate reactions include urticaria, local irritation in regions where the worm is present, effusions into joints and irregular or generalised œdema.

## ONCHOCERCIASIS

*Onchocerca volvulus* (Leuckart, 1893).—This nematode, first found on the west coast of Africa, inhabits the subcutaneous or connective tissues of man, often giving rise to nodular, subcutaneous, cystic tumours, 1 to 10 cm. in diameter, over which the skin is generally movable, and in which lie entangled masses of worms and embryos encased in dense fibrous tissue. The swellings are particularly common around the elbows, knees, ribs, iliac crests and greater trochanters. Unsheathed microfilariae may occasionally be demonstrated in the skin, especially of the loin and thigh, as well as in the circulatory blood and subcutaneous lymph channels, even though no evidence of disease exists. Dermal lesions, including achromia, xeroderma and pseudo-ichthyosis, are attributed to embryos located in the skin (Laigret). Pruritus may be intense, especially at night. Onchocerca tumours of the head are not infrequently associated with ocular complications. Blindness may result from retinochoroiditis or punctate iritis when embryos are found in the anterior chamber. Blacklock has shown that transmission is by the buffalo gnat, *Simulium damnosum*. In East Africa it is also transmitted by *S. neavei*. Localised tumours may be removed under local anæsthesia.

The parasite called *Onchocerca cecutiens* (Brumpt, 1919) is found in Guatemala and Mexico. Its status as a distinct species has for some time been doubtful, and the recent work of Strong indicates it is the South American form of *O. volvulus*. It produces flat nodes (Guatemala nodules) up to 2 cm. in diameter, especially affecting the scalp and face, and an eruption known as "coastal erysipelas", associated with pain, tumefaction and fever, may result from secondary streptococcal infection of the skin due to scratching, the irritability being caused by microfilariae in the corium. More important are the ocular lesions caused by microfilariae, piercing the capsule of the nodules and invading the tissues of the eye, producing conjunctivitis, punctate iritis, keratitis and choroiditis. Blindness commonly follows (Strong). An eosinophile leucocytosis is the rule. Diagnosis is made by demonstrating the microfilariae in the milky fluid aspirated from the nodules, or in adjacent pieces of skin shaved off and teased up in saline at 37° C. for microscopical examination. Transmission is by three different species of *Simulium*, the coffee flies living at a height of 2500 to 5000 feet. The nodules should be excised whenever possible, especially those in the vicinity of the eyes. Some improvement in the ocular condition may follow this procedure.

Two drugs, i.e., suramin and Hetrazan, are at present employed with some success. Suramin gives somewhat the better results.

Suramin (Antrypol, Germanin).—For adults, 1.0 g. intravenously once every 5

days for 5 to 15 doses. Children in proportion. An initial dose of 0.2 g. is sometimes given to test for idiosyncrasy to the drug, which shows itself as proteinuria and oliguria with casts, appearing within 24 hours of dosage. Individuals reacting in this way should be given Hetrazan as an alternative. Toxic reactions related to the worm infestation also appear after 2 or 3 doses of suramin. They are similar to those described below, but usually less severe.

**Hetrazan.**—For adults, 2 mg. per kg. orally once on the first day, twice daily on the second day, thrice daily on the third and consecutive days up to the twenty-first day. Side-effects appear early after the first few doses and include burning of the eyes, congestion of conjunctival vessels, hard œdema of the face and ears and sometimes of the limbs. Skin lesions may become œdematous and pruritus is often severe. Antihistamine drugs relieve the reactions.

## DRACONTIASIS

*Dracunculus medinensis* (Linnaeus, 1758).—Guinea-worm disease is common in India, Persia and Africa. The adult female, measuring 40 to 120 cm.  $\times$  0.5 to 1.7 mm., inhabits the subcutaneous and intersutural tissues, and takes some 12 months to reach the skin where it secretes some toxin producing a blister which later ulcerates, and permits, on contact with water, the reflex discharge of embryos from the prolapsed uterus which perforates the base of the ulcer. The worm itself is often surrounded by a fibrous-tissue canal. Fedtschenko, in 1879, produced evidence that a cyclops was the intermediate host. Man becomes infected by swallowing these crustaceans in drinking water.

**Pathology.**—Three factors are responsible for pathological lesions, namely, the worm, the embryos and secondary bacterial invaders. The toxic substance responsible for blister formation may, if absorbed, lead to anaphylactoid symptoms. Premature ejaculation of embryos may produce subacute sterile abscess. Bacterial invaders, especially *Staphylococcus aureus*, *Bact. coli* and streptococci are responsible for acute abscess, cellulitis, bubo, synovitis, arthritis and septicæmia; these complications almost invariably result from the retraction into the tissues of a taut, elastic worm, broken during efforts to extract it.

**Symptoms.**—Prodromal symptoms consist of an itchy, urticarial eruption (40 per cent.) which may be associated with vasomotor collapse, vomiting, diarrhoea, dyspnoea and high eosinophilia, followed a few hours later by blister formation and ulceration (Fairley). The lower extremities are commonly involved (86.5 per cent.), and in decreasing frequency the arms, trunk, buttock and scrotum. Septic complications are frequent, and contracture of tendons and fibrous ankylosis of joints sometimes result. Neuritis and muscular rheumatism may be produced by calcified worms, which on radiographic examination show a pathognomonic, convoluted, moniliform shadow.

**Treatment.**—This depends on the stage at which the patient is seen. Anaphylactoid symptoms are best treated by injections of adrenaline (10 minims of a 1 in 1000 solution). A blister, if present, should be aspirated. Once an ulcer has formed it must be treated with antiseptic dressings and the worm subsequently extracted either by intermittent traction and massage, or by multiple incisions under local anaesthesia. The outline of the worm becomes more obvious if the tissues are sprayed with ethyl chloride. When the worm is closely convoluted the whole area may be excised *en masse*. The old method of gradual extraction by winding round a match and daily douching with water until the uterus is emptied still has its advocates. Localised abscess must be treated by passing a probe through the sinus and slitting up the canal in which the worm lies. Other complications are treated along general surgical lines.

# TRICHINIASIS

**Definition.**—A disease produced by the embryos of *Trichinella spiralis* (Owen, 1835) during their migration from the human intestine to the muscles.

**Ætiology.**—Infection is acquired by eating raw or underdone pork in which the larvæ have encysted. After the cyst walls have been dissolved by the gastric juice the embryos mature and breed in the small intestine. The gravid female bores into the mucosa, depositing hundreds of viviparous larvæ ( $100 \times 6\mu$ ) which reach the muscles from about the ninth to the fortieth day via the liver, lung and left heart. The adults are small ( $\delta$  1.4 to 1.6 mm.  $\times$  0.04 mm.;  $\varphi$  3 to 4 mm.  $\times$  0.6 mm.) and live only a few weeks, whereas encysted larvæ may survive for 25 years, though they often calcify within 6 months. Rats act as reservoir hosts.

**Symptoms.**—For the first week during the invasion period gastro-intestinal symptoms develop with nausea, vomiting, colic and diarrhœa with perhaps blood and mucus; then when migration of larvæ commences myositis of the tongue, laryngeal and intercostal muscles and the diaphragm occurs, giving rise to difficulty of swallowing, speech and respiration. The muscles of the jaws, arms, legs and abdomen may also be involved with stiffness and pain; the affected areas are exquisitely tender and hard to the touch. Oedema, especially of the face, urticaria, leucocytosis with high eosinophilia, prolonged remittent fever ( $102^{\circ}$  to  $104^{\circ}$  F.) and sweating are characteristic. Pulmonary features are common, and occasionally hæmoptysis occurs. Cachexia develops and, finally, during the period of larval encystment, the patient may succumb from toxæmia with respiratory disturbance and coma.

**Diagnosis.**—Early, the disease may be mistaken for ptomaine poisoning, enteritis or dysentery, and later for rheumatic fever or typhoid. The intense eosinophilia should arouse suspicion, while later biopsy of a piece of the affected muscle such as the deltoid at its tendinous insertion will often reveal precystic or encysted larvæ. Embryos may be found in the blood, especially from the twelfth to the twentieth day, by laking it with 10 volumes of 3 per cent. acetic acid and centrifuging the deposit. Intradermal and precipitin tests are often positive to an antigen manufactured from the embryos (Bachman). At a later stage, calcified cysts may sometimes be visualised by radiography.

**Prognosis.**—This largely depends on the intensity of the infection, the mortality rate varying in different outbreaks from 1 to 30 per cent. Convalescence is often slow and muscular atrophy may follow.

**Treatment.**—PROPHYLACTIC.—This depends on careful meat inspection, and adequate boiling of pork; curing by smoking and salting is ineffective. Special care should be taken at necropsy to prevent infection.

**CURATIVE.**—No specific treatment is known, but every effort should be made to expel the adult worms. Purgatives and glycerin, santonin, thymol and turpentine are employed for this purpose.

# ÆSOPHAGOSTOMIASIS

(1) *Æsophagostomum opisthomum* (Willach, 1891).—This nematode frequently affects certain anthropoid apes and monkeys in West Africa, and not uncommonly man in Northern Nigeria. The rhabditiform larvæ exsheathe in the cæcum, invade the bowel wall and give rise to inflammatory nodules in which they develop; later they erupt into the intestine and mature. Dysentery-like symptoms, with hæmorrhage and occasionally peritonitis and septicæmia, may result. The ova are indistinguishable from ankylostome eggs, but fortunately thymol, oil of chenopodium and carbon tetrachloride are specific for the adults (Faust).

(2) *Cesophagostomum stephanostomum* (Raillet and Henry, 1909).—The adult worms present minor differences, and in the only human case recorded, by Thomas in Manaus, Brazil, nodules were found in the ileum as well as in the colon.

## ANKYLOSTOMIASIS

**Synonyms.**—Uncinariasis; Hookworm Disease.

**Definition.**—Ankylostomiasis is caused by members of the family *Ankylostomidae*. Five species may affect man—*Ankylostoma duodenale* (Dubini, 1843), *Necator americanus* (Stiles, 1902), *A. malayanum* (Alessandrini, 1905), *A. braziliense* (Gomez de Faria, 1910) and the *A. caninum* (Ercolani, 1859). The first two species commonly affect man, the third and fourth rarely, while the larvae of the fifth may cause creeping eruption.

**Ætiology.**—*A. duodenale*.—Adults ♂ 8 to 10 mm.  $\times$  0.4 to 0.5 mm.; ♀ 12 to 18 mm.  $\times$  1 mm. Ova are elliptical, thin-shelled containing vitellus, segmented into 2 to 8 spherules, and measure 55 to 65  $\times$  32 to 45  $\mu$ . *N. americanus*.—Adults ♂ 7 to 9 mm.  $\times$  0.3 mm.; ♀ 9 to 12 mm.  $\times$  0.4 mm. The ova measure 64 to 75  $\times$  36 to 40  $\mu$ . The buccal armature of the two species differs. The capsule is smaller in *N. americanus*, and has an irregular border instead of the four ventral hook-like teeth of *A. duodenale*; there is also a pair of semilunar plates. All subsequent description applies to both these parasites.

When fæces containing ova are deposited on moist earth the rhabditiform larvae hatch out in 24 to 48 hours: later they moult twice, developing into filariform larvae which may remain viable for 3 to 4 months. On contact with human skin the latter bore their way into the blood-vessels, pass to the right heart and lungs whence they progress via the trachea, œsophagus and stomach to their natural habitat in the duodenum and small intestine; here they mature and breed, egg-laying commencing in about 5 weeks. The worms attach themselves firmly to the mucosa, feeding on blood and may cause local bleeding (especially *A. duodenale*), though the stools generally give a negative test for occult blood. At necropsy œdema of the legs and sacrum is common, and effusions and petechiæ may involve the serous sacs. The heart is dilated and shows marked fatty degeneration, as do also the liver and kidneys. The duodenum and jejunum may present petechial hæmorrhages, especially at points where the worms are attached.

**Symptoms.**—At onset the larvae may produce ankylostome dermatitis or ground itch, which clears up within 2 weeks unless secondary infection has occurred. In heavy infection symptoms may appear within 1 to 2 months. These are largely related to the anæmia which is microcytic and hypochromic in type; there is a low colour index, and an increased blood volume. The counts in a severe case would show erythrocytes = 1,000,000 to 2,500,000 per c.mm.; hæmoglobin = 10 to 25 per cent.; colour index = 0.5. Leucocytes are normal or slightly increased in number, and eosinophilia is characteristic. Mild cases may be symptomless, and it is uncommon for the well-fed European to develop anæmia unless hyperinfection be present. Anæmia generally occurs in patients living on a borderline diet, poor in animal protein and iron-containing foods. Those moderately infected may complain of

capacity for work and predisposing to secondary infections like pneumonia and dysentery. In Europe outbreaks have sometimes occurred in miners.

**Diagnosis.**—A microcytic, hypochromic anæmia, especially if associated with eosinophilia, should arouse suspicion in a tropical patient, and the stools should be immediately examined for ova, preferably by the Clayton-Lane flotation method.

**Prognosis.**—The mortality rate is low, even in natives, the chief danger being anæmia, which predisposes to intercurrent disease unless specific treatment be instituted. Hook-worm infection is especially serious in children owing to its effects on their mental and physical development. In the well-fed European the disease rarely produces serious manifestations.

**Treatment.**—**PROPHYLACTIC.**—This includes the treatment of carriers, the substitution of latrines for promiscuous defæcation, the proper disposal of night soil, the treatment of contaminated ground and the wearing of good shoes and boots. Sanitation in mines must be satisfactory.

**CURATIVE.**—There are three specific drugs which are widely used in the treatment of ankylostomiasis: (1) tetrachlorethylene; (2) carbon tetrachloride and (3) oil of chenopodium. Either tetrachlorethylene or carbon tetrachloride can with advantage be combined with oil of chenopodium, and this should be done whenever possible. After saline purgation, the object of which is to get rid of both drug and parasites, the stools should be examined and the number of worms recorded if time permits. In 7 to 10 days' time the stools are re-examined; if ova have reappeared another course of treatment may be considered advisable.

(1) *Tetrachlorethylene.*—Adult dosage 2 to 3 ml. This drug is effective against *A. duodenale*, *N. americanus* and *Enterobius vermicularis*. It is the safest and cheapest anthelmintic, and is given in a single dose, either in gelatine capsule or shaken up with  $\frac{1}{2}$  to 1 oz. of magnesium sulphate in water; 1 ml. of oil of chenopodium should be added or administered in a gelatine capsule. These are given in the early morning on an empty stomach. No food is permitted until the bowels have acted, and magnesium sulphate (4 drachms) should be repeated after 3 hours if necessary.

(2) *Carbon tetrachloride.*—Adult dosage 2 to 3 ml. This drug is of value in thread-worm and ascaris infestation, as well as in ankylostomiasis. The drug is given in a dosage of 3 ml., either in gelatine capsules or in milk or in magnesium sulphate solution. It is administered in the early morning on an empty stomach, and food is withheld until the bowels have been well opened—if necessary with magnesium sulphate. If available it is advantageous to combine this treatment with oil of chenopodium. As a routine, 1.5 ml. of carbon tetrachloride and 0.5 ml. of oil of chenopodium are administered in a mixture containing  $\frac{1}{2}$  oz. of magnesium sulphate, and the same dose is repeated in 1 hour's time. If necessary, a saline purge is given 3 hours later. Carbon tetrachloride when administered in poisonous doses causes a central lobular necrosis of the liver, with fatty degeneration. Clinical evidence of poisoning include vomiting, hepatic pain and tenderness, jaundice, hæmaturia, and temporary anuria. Fatalities have been reported, and it is inadvisable to employ this drug to (1) alcoholics; or (2) patients suffering from calcium deficiency, cirrhosis of the liver, or renal disease. A preliminary course of high protein dietary might lessen the tendency to or prevent hepatic necrosis developing in such cases.

(3) *Oil of chenopodium.*—Adult dose 1 to 2 ml. This drug is effective against ascaris, as well as ankylostomiasis. Its therapeutic action is dependent on the ascaridol content, which is by no means always constant. It is best given in gelatine capsules, or it may be taken in an emulsion or in water mixed with other anthelmintics, such as tetrachlorethylene or carbon tetrachloride. If used alone, the drug may be administered in divided doses, i.e.,  $\frac{1}{2}$  ml. half-hourly for 2 hours, or in a single dose of 2 ml. followed by a saline purge. Narcosis and other ill effects have followed its

administration, and cumulative effects have been noted. Treatment should not be repeated under 10 days. In case of poisoning, digitalis and epinephrine have been found useful, but there is no chemical antidote.

The effectiveness of treatment is determined by the disappearance of symptoms, and of ova from the faeces as revealed by later microscopic examinations.

Treatment of anaemia depends on: (1) eradication of the ankylostome infection; (2) a well-balanced diet containing meat, proteins, fruit, vegetable, lipoids and vitamins, and as regards the latter a whole-wheat bread is most desirable if obtainable; (3) iron in large dosage; (4) treatment of intercurrent infections, such as malaria. Ground-itch may be treated with an ointment containing zinc oxide and salicylic acid. If there is secondary coccal infection, antiseptic dressings are indicated.

## ASCARIASIS

**Definition.**—An intestinal infection of man with the round worm *Ascaris lumbricoides* (Linnaeus, 1758).

**Ætiology.**—Adults ♂ 17 to 25 cm. × 3 mm.; ♀ 20 to 40 cm. × 5 mm. The eggs are yellow, elliptical, possess a thick outer shell and measure 50 to 70 × 40 to 50 $\mu$ . Ova passed in human faeces develop in night soil, and the fertilised eggs, swallowed by man in contaminated water or food, pass into the intestines where the larvæ penetrate the bowel wall and migrate to the lungs, sometimes producing ascaris pneumonia; thence, via the trachea and œsophagus, they reach the intestine (Stewart). Ova appear in the faeces in 2 to 2½ months.

**Symptoms.**—During larval migration urticaria, ascaris pneumonia and, more rarely, ascaris nephritis may occur. Pulmonary complications appear early in the first week and are generally transient in nature. Adult worms may produce symptoms by toxic, reflex or mechanical means. Sensitised individuals occasionally develop rashes such as urticaria and œdema of the face, and in children, gnashing of the teeth, enuresis and convulsions may occur (ascaris dysentery), while masses of coiled-up worms sometimes produce acute intestinal obstruction. Perforation of the intestine leads to peritonitis or localised abscess from which worms may be discharged. Wandering worms may produce appendicitis or obstruct the pancreatic or bile ducts causing jaundice, or reach the liver producing liver abscess or cholecystitis. They have been known to enter the larynx and cause œdema of the glottis or even to appear in the antrum of Highmore.

**Treatment.**—Oil of chenopodium (1.5 ml.), carbon tetrachloride and tetrachlorethylene (3 ml.) are specific remedies; in combination given as in ankylostomiasis they are particularly efficacious (see Ankylostomiasis). Santonin (gr. 3 to 5) is the stock remedy; it may be given on consecutive or alternate days on three occasions combined with preliminary starvation and followed by castor oil; in children, where the dosage is proportionately lowered, it may be combined with scammony or castor oil. Hexylresorcinol in 1 g. doses is also recommended and should be followed by a saline purgative. Worms sometimes take 48 hours to be ejected, and the only index to cure is the permanent disappearance of ova.

## TRICHURIASIS

**Definition.**—An infection of the human intestine with the whip-worm *Trichuris trichiura* (Linnaeus, 1771), formerly known as *Trichocephalus dispar*.

**Ætiology.**—Adults, ♂ 40 to 45 mm.; ♀ 45 to 50 mm. Ova are brown, barrel-shaped with terminal knobs and measure 50 to 54 × 23 $\mu$ . Man is infected by swallowing the fertilised eggs in food and water; on reaching the cæcum the larvæ are

liberated and attach themselves to the mucosa. Occasionally they invade the appendix, colon and terminal ileum.

**Symptoms.**—Clinical features are generally entirely absent, but reflex symptoms are described in children and occasionally urticaria and eosinophilia are induced. Rarely verminous appendicitis and peritonitis may result, and possibly caecal lesions may open up the way for other infections.

**Treatment.**—Thymol and oil of chenopodium may be effective, but worms are often difficult to eradicate.

## ENTEROBIASIS

**Definition.**—Infection by the thread or pin-worm *Enterobius vermicularis* (Linnaeus, 1758), formerly known as *Oxyuris vermicularis*. Adults ♂ 3 to 5 mm.; ♀ 10 mm. × 0.6 mm. The ova measure  $50 \times 20 \mu$ , and are thin-shelled, colourless, plano-convex and contain coiled embryos; they are rarely found in the faeces, being mainly liberated in the perianal region from migrating gravid female worms at night, after the patient has gone to bed. The maximum length of the life cycle is 30 days, long-standing enterobiasis resulting from autoinfection via the infected fingers of the patient.

**Symptoms.**—The worms inhabit the colon, and when the patient is warm in bed at night may produce great discomfort and itching by migrating out through the anus. Eczema and pruritus ani may result causing sleeplessness and neurasthenia. Sexual disorders, vesical irritability, frequent micturition, prolapsus ani and mucoid secretion may be observed, also in young girls vaginal discharge. Catarrhal appendicitis sometimes occurs, and worms may wander into the stomach.

**Diagnosis.**—Eggs are best demonstrated by swabs made from the perianal skin or by a moistened camel's hair brush applied to the anal folds and perianal skin. Less than 1 per cent. of proved cases have demonstrable ova in the faeces. Inspection of the anal region at night immediately when itching commences may reveal the gravid female worms outside the anal canal before they have had time to retreat to the rectum.

**Treatment.**—The basis of successful treatment is the prevention of auto-infection. This is best done by the most scrupulous care of the hands and nails which may become contaminated (1) by scratching in the anal region, especially during sleep, (2) when completing the anal toilet with sanitary paper or (3) from infected clothes. The nails should be kept short, and the hands well washed and scrubbed with carbolic soap immediately on waking, after defaecation and every time there has been possible contact with infected material or clothing. Bathing drawers or pyjamas should be worn at night and sterilised each day, and infected children should occupy separate beds. Enemas of 4 to 8 fl. oz. of hypertonic saline solution should be injected immediately the anal irritation commences, for at this time the worms are accessible and can be washed out from the rectum (Macarthur). After local bowel treatment each night yellow mercuric oxide ointment should be applied to the perianal region. The process should be repeated each night whenever anal irritability recurs. If reinfection be prevented this measure alone will generally result in cure.

Gentian violet appears to exert a specific lethal effect on the adult worms. Wright advocates special keratin-coated tablets of this drug, the adult dose being gr. 1 thrice daily before meals for 8 days; this course is repeated after a clear interval of 7 days. Toxic features include anorexia, nausea, abdominal cramp and vomiting.

The disease often involves several members of the same family or several people living in the same house: it is advisable that they should be treated simultaneously to prevent reinfection.

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## D. DISEASES DUE TO INJURIOUS ARTHROPODS

## TICK BITES

Apart from relapsing fever, tularæmia, Russian spring-summer encephalitis and certain typhus-like fevers the bites of several species of ticks, including *Dermacentor andersoni*, *D. venustus*, *Hæmophysalis punctata*, *Ixodes ricinus* and *I. holocyclus*, may give rise to paralysis in man. Cases have been recorded from Australia, South Africa and the United States. The incubation period varies from several hours to 6 days; the bites, which are generally situated on the nape of the neck, are painful and œdematous, and the disease, which is afebrile, may be fatal, especially in children. The paralysis is of lower motor neurone type resembling that seen in infantile paralysis, and develops first in the legs and later in the arms and neck. In removing ticks the parasite should not be forcibly extracted until paraffin or carbolised oil has been applied, as this causes withdrawal of the head and so prevents it being broken.

## MITES

Apart from scabies, camel itch and copra itch, all of which are caused by different species of mites, the scrub-typhus group of fevers are transmitted by larval mites. The harvest mites of temperate climate cause considerable itching and skin erythema, which comes on 12 hours after exposure and increases for 36 hours, sometimes persisting for several days. Mite bites may be prevented by anti-mite fluids, such as dibutyl or dimethyl phthalate applied to the socks and clothing; they are treated by washing the legs with benzine, green soap or salt solution, while the itchiness may be combated, as in flea-bite, by the use of 1 in 10 carbolic lotion or an ointment composed of acid. carbol. (gr. 10), menthol (gr. 5), zinc oxide (gr. 60) and adip. præp. (1 oz.) (Roxburgh) may be used. Larval mites of the family *Trombididae* are known to cause skin eruptions in various parts of the tropics. One, in the West Indies, produces red mite dermatitis (bête rouge), the little crimson spot in the middle of the itchy papule being diagnostic: another, in Mexico, has a predilection for the skin of the eyelids, prepuce and axilla. Owing to the fact that many adult mites have never been identified, species names are not generally available for the larvæ. Scrub-itch commonly results from the bites of trombiculid larval mites, such as *T. minor* in Australia and New Guinea (*vide* Tsutsugamushi Disease, p. 288).

## TONGUE WORMS

The adults, which are degenerated, segmented arachnids superficially resembling tape-worms, live in the lungs or nostrils of certain carnivora or ophidia, and deposit their eggs on vegetation; when these are eaten the larvæ encyst in the viscera of the intermediate host. Several species have been reported in man, including *Linguatula serrata*, which occurs in parts of Europe and Brazil, the larvæ encysting harmlessly in the human liver, and *Porocephalus armillatus*, which encysts in the mesentery, liver and lungs. This infection is not uncommon in the Belgian Congo. Pulmonary symptoms have been reported, and sometimes the larval forms wander free in the

peritoneal cavity. If the cysts have become calcified they may be detected by radiographic examination; otherwise the disease is only recognised at necropsy. No treatment is known for either linguatulosis or porocephalasis.

## INSECT BITES

Apart from specific disease transmission, bites from mosquitoes, biting flies, midges, lice, fleas, bugs, bees, ants, wasps and hornets may cause considerable inconvenience to man and occasionally result in local sepsis or septicæmia which may end fatally. Mosquito bites occasionally give rise to streptococcal septicæmia, and those of horse-flies to anthrax.

Locally, insect venom may have hæmolytic, neurotoxic or irritant effects producing limited inflammation or dermal whealing of anaphylactoid origin dependent on previous sensitisation, as Boycott has proved for midge bites. The stings of bees, wasps and hornets are invariably painful, and in certain situations like the tongue and fauces may lead to respiratory obstruction, or in the larynx to death from œdema of the glottis. Anaphylaxis may follow bee or wasp stings in a sensitised individual. Such patients have been known to develop profound vasomotor collapse, become comatose and die in 20 minutes. In a case of wasp sting seen by the writer, the patient, who gave a history of having been stung on the scalp 6 years previously, was again stung on the third right finger; a wheal about 2 cm. in diameter rapidly appeared with surrounding erythema, and within 5 minutes the patient developed headache, lacrimation and injection of the conjunctivæ. Giddiness, nausea, severe vomiting, rapid low tension pulse with vasomotor collapse, generalised urticaria, especially involving the arms and neck, and respiratory distress followed; 3 hours later the general condition was greatly improved, but next day there was a large, puffy, painless swelling involving the subcutaneous tissues of the whole hand. The early and late local effects closely resembled those observed in the immediate and delayed intradermal reactions for hypersensitiveness to helminthic protein.

**Treatment.**—Mosquito, midge and fly bites may to a great extent be prevented by the use of dimethylphthalate. They should be treated by the immediate application of iodine, the subsequent itching being relieved by a 1 in 20 watery solution of carbolic or a 1 per cent. alcoholic solution of menthol. In bee and wasp stings, the sting should be carefully lifted or scraped out, as pressure expels the contents of the poison sac. Ammonia, alkaline soap or methylene-blue may be applied locally for the acid bee stings, and vinegar for the alkaline wasp stings. Adrenaline (min. 10 of 1 in 1000 solution) should be immediately injected subcutaneously whenever anaphylactic symptoms develop. Sepsis is treated along the usual lines.

## MYIASIS

**Definition.**—An invasion of the tissues by larvæ of dipterous insects.

**Ætiology.**—Many flies deposit their eggs or larvæ in decomposing discharges, and in the tropics wounds should always be protected as well as natural orifices discharging pus or fetid material. Larvæ of special flies may develop in the nasal cavities, the ear, vagina, urethra, skin or in the intestine, and the fly *Wohlfartia magnifica* may deposit its eggs in the conjunctival sac with serious consequences. Two chief varieties are distinguishable—the dermal and the intestinal.

**SCREW-WORM FLIES.**—Two species of flies of the genus *Cochliomyia* infect man in tropical and subtropical America. The adults measure 9 to 10 mm. in length and are distinguished from the ordinary green-bottle (*Lucilia*) by the black linear

dorsal marks on the thorax. *C. americana* lays its eggs in large numbers in open wounds or discharging orifices; the eggs hatch out rapidly and the larvæ generally take about 4 to 10 days for development; when fully grown they superficially resemble a screw and are about two-thirds of an inch in length. They bore into healthy as well as necrotic tissue, causing great destruction locally and produce foul-smelling, suppurating lesions. Nasal infection causes much pain and swelling and is often associated with a sensation of crawling; occasionally larvæ crawl out or are expelled by sneezing. They may invade the accessory sinuses, bore their way through the bones and penetrate the skull, producing purulent meningitis. The vagina and ear may also be attacked, and the middle ear destroyed. The mortality rate for nasal and aural myiasis is approximately 8 per cent. The larvæ of *Cochliomyia macellaria* are often found associated in the same wound with *C. americana* as a secondary or later infection, being apparently attracted there by the foul-smelling, purulent discharge; its larvæ invade necrotic rather than healthy tissue, and for this reason are of less importance medically.

**Treatment.**—This consists essentially in covering all wounds and discharging orifices and avoiding sleeping during the day except under nets or in screened houses. Larvæ can be removed from wounds by local application of antiseptic lotions or chloroform water. In nasal myiasis larvæ may be anæsthetised by the local application of chloroform, ether or benzol on a pledget of cotton wool or by the use of an atomiser. Irrigation with 15 per cent. chloroform in liquid paraffin is also effective. If the larvæ are not removed by blowing the nose or sneezing they must be removed by forceps. The accessory sinuses may need to be opened up surgically in some instances.

**THE MOSQUITO WORM (Ver macaque, beef worm) (*Dermatobia hominis*).**—This fly, common in Central America and adjacent parts of South America, measures 14 to 16 mm. in length, has a yellow head with brown eyes, a greyish thorax and dark metallic-blue abdomen. The eggs somehow become glued to the under-surface of mosquitoes (particularly of the genus *Janthinosoma*), biting flies and even ticks, and in this fashion the larvæ are conveyed to the human skin where they invade the tissues via the puncture wound. A boil or warble results, containing a central opening through which the maggot breathes, discharges black excreta and later escapes to the ground where it develops into a chrysalis and finally a fly. Cattle are also affected. Hadwen and Bruce have described a remarkable anaphylactic condition in oxen and sheep infected with larvæ of warble flies (*Hypoderma bovis*, *H. lineatum* and *Cestrus ovis*) characterised by dyspnoea, salivation, lacrimation, incontinent sphincters, vasomotor collapse, cyanosis and even death. This may be experimentally induced by injections of larval protein extracts or may result from natural trauma during life. Similar clinical features have not yet been recognised in man, though they probably occur.

**Treatment.**—Natives kill the larvæ with tobacco juice. The opening should be enlarged with a bistoury and the maggot removed with forceps; the cavity soon heals if treated antiseptically.

**VER DU CAYOR OR TUMBU DISEASE.**—This disease, common in Central and West Africa, is due to the larvæ of the Tumbu fly, *Cordylobia anthropophaga*, which is 8.5 to 11.5 mm. long, yellowish in colour, with black abdominal spots. The eggs are laid on the ground or clothing, and the emerging larvæ bore their way into the tissues by means of mouth-hooks. The first symptom is a pricking sensation, followed by the appearance of a boil with a central opening or warble which commonly affects the forearms, scrotum, buttocks, thighs and scalp of children and often becomes inflamed. The larva takes about a fortnight to mature and then escapes via the central hole through which its faeces were previously excreted. Sometimes the cavity suppurates. Blacklock and Gordon demonstrated an acquired local skin immunity against *cordylobia* larvæ in guinea-pigs subjected to previous infection.

**Treatment.**—The aperture is enlarged if necessary, the maggot squeezed out and the cavity treated antiseptically. The application of paraffin or chloroform facilitates extraction.

**THE CONGO FLOOR MAGGOT.**—The adult fly, *Auchmeromyia luteola*, is found throughout tropical Africa; it deposits its eggs on the floors of huts and outhouses, and when the larvæ have hatched out they suck the blood of people sleeping on the ground without causing pain. The larvæ crawl actively, are 15 mm. long and consist of eleven segments. The adult is orange-yellow in colour, with longitudinal dorsal stripes on the thorax, and measures 10 to 12 mm. in length. Prophylaxis consists in sleeping on raised beds and the eradication of larvæ from the earth floors of infected huts.

**INTESTINAL MYIASIS.**—Fly larvæ are common in human fæces; generally they are deposited after defæcation, but sometimes they originate from the intestine, the eggs being swallowed by man in food. Many species have been described, the genera *Sarcophaga*, *Fannia*, *Apiocæta* and *Anthomyia* furnishing the majority of examples. *Fannia canicularis* accounts for most cases in Europe. Gastro-intestinal symptoms may be mild or severe and include malaise, vomiting, diarrhœa and severe griping. General toxic features may include fever, rigors, headache, thirst and vertigo; even convulsions have been described. The bile ducts may also be implicated.

**Treatment.**—Castor oil is generally sufficient, but thymol, filix mas, santonin and turpentine have also been recommended. If larvæ are vomited an emetic should be given.

## SPIDERS

Though spiders (Araneæ) generally possess poison glands and inject venom into their prey, only a few species, mostly of the genus *Latrodectus*, are dangerous to man. Experimentally such venoms may slow the pulse and respiration, and produce tetanoid-like spasms and bronchial contraction in guinea-pigs. These red-marked spiders include *L. mactans* in America (known as the black widow), *L. hasseltii* in Australia and New Guinea, *L. geometricus*, *L. concinnus* and *L. indistinctus* in South Africa (knoppie spider) and *L. tredecimguttatus* in Eastern Europe are amongst the most dangerous species. The female often weaves its web and lays its eggs on the underside of privies; if disturbed it is liable to bite man on the genitals, buttocks or thighs during the act of defæcation. The bite itself may or may not be felt as a local pricking sensation; local swelling, œdema and numbness may follow. Within a few minutes to an hour agonising severe cramping pains often set in, involving the muscles of the abdomen, legs, back and thorax. Intestinal colic due to muscular spasm may follow and in some instances paralytic ileus may supervene. Fever, sweating, respiratory embarrassment, paræsthesia and sometimes priapism follow. The reflexes are hyperactive and there is increased pressure of the cerebrospinal fluid. In Peru the "pruning spider", *Glyptocranum gasteracanthoides*, causes local gangrene, hæmaturia and neurotoxic symptoms. Kobert noted oxyhæmoglobin and methæmoglobin in the urine of persons bitten by the "cross spider", *Epeira diadema*, and Sachs found in its venom a powerful hæmolysin. Probably many other spider venoms, like zootoxins generally, exert agglutinative, hæmolytic and neurotoxic effects. The tarantulas, on the other hand, give rise only to minor symptoms, though any spider with an effective biting mechanism may produce secondary bacterial infection.

**Treatment.**—If seen early, treatment consists in immediate ligature if practicable, incision and suction, or washing out the wound with permanganate solution. Specific antivenene, if available, is effective. Morphine may be necessary to relieve pain, and injections of calcium gluconate (10 ml. of a 10 per cent. solution) for laryngeal and muscular spasm. Intravenous saline and dextrose solution, and injections of nikethamide (Coramine) and pituitary (posterior lobe) extract assist circulatory failure.

## CENTIPEDES

The Scolopendridæ possess poison glands which discharge at the apices of a pair of specialised claws taking the place of the first pair of legs. The small centipede gives rise only to local manifestations associated perhaps with an erysipelas-like eruption, but the tropical species, *Scolopendra gigantea*, may cause around the punctures local necrosis and lymphangitis; headache, vomiting, fever, coma and, in children, even death may follow. Treatment is similar to that of spider bites. Strong ammonia applied locally is useful.

## SCORPIONS

Scorpions possess paired poison glands in the post-anal segment of the spined tail; this is thrust forward into its prey which is held in position by the formidable pedipalps. Scorpions in the tropics not infrequently kill children, and occasionally adults, and several species of the genus *Buthus* and *Centruroides*, as well as *Euscorpius italicus*, *Tityus bahiensis* and *Centruroides exilicauda*, etc., are much feared. The bite is most painful, and toxic symptoms may include fever, sweating, drowsiness, dyspnoea, vomiting, diarrhoea, muscular cramps, trismus, stiffness of the neck, muscular paresis, respiratory failure and coma. The reflexes are hyperactive and strabismus and convulsions may occur. Hæmorrhage from the gastro-intestinal tract or lungs is reported. Secondary bacterial infection is not uncommon. Local treatment may be instituted as for spider bite, and the immediate application of strong ammonia or a local injection of Novocaine and adrenaline relieves the pain. The intravenous injection of specific antivenene, prepared by inoculating scorpion venom into horses, has greatly lowered the mortality rate amongst children in Upper Egypt and South America.

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## E. DISEASES DUE TO SNAKES AND POISONOUS FISHES

## SNAKES

Ophidiiasis or snake poisoning results from the inoculation of venom by snakes of the families colubridæ or viperidæ; non-poisonous species occasionally cause death through septic infection following their bites.

**Ætiology.**—Snakes are carnivorous, and Alcock and Rogers showed that even non-poisonous species may have poisonous saliva. The venom is simply a specialised secretion of the parotid (poison gland) utilised in killing and digesting prey, while the fangs are modified maxillary teeth anteriorly grooved in the colubridæ, and completely canalised in the viperidæ. The biting mechanism is vastly superior in the vipers since the fangs are longer, and capable of considerable forward rotation, whereas in the colubridæ they are generally shorter and less mobile. In biting, the snake strikes with great speed, opens the jaws, rotates forward the fangs, snaps the jaws together and ejects its venom from the poison gland via the duct and fang into the tissues in one almost instantaneous movement. The vipers withdraw immediately after biting. The colubridæ often hang on to the bitten part and may need to be forcibly evulsed: to inject venom effectively they must have the lower jaw fixed, and though their venoms are more poisonous the yield is, as a rule, considerably

less than that of the vipers. The toxic action of venoms is mainly dependent on (a) proteolytic enzymes, (b) phosphatidases and (c) neurotoxins. The proteolytic enzymes, so well represented in viperine venoms, digest the tissues and damage the vascular endothelium (hæmorrhagin), leading to the escape of blood and the liberation of histamine which causes extensive local œdema and gives rise to symptoms of cardio-vascular failure (Kellaway). The coagulant properties of venoms are due either to a direct coagulation of the fibrin by the venom or to the conversion of prothrombin into thrombin (Eagles). The phosphatidases cause hæmolysis and also directly affect the heart and circulation; the acceleration of venom hæmolysis by lecithin is attributed to the transformation of lecithin into lysolecithin, which is itself actively hæmolytic. The neurotoxin formed in colubrine venoms has a strong peripheral effect, paralysing the sensory, proprioceptive and motor nerve endings. Paresis of the musculature is due to the curare-like action on the motor endings and a further direct action on the muscle itself (Kellaway).

**Pathology.**—In colubrine bites there is a congestive mode of death from peripheral respiratory failure, associated with fluid blood, a dilated right heart and congestion and œdema around the fang puncture. In fatal viperine bites there is hæmorrhage, thrombosis and digestion of tissue locally, associated with a spreading gelatinous œdema resembling "red currant jelly", which sometimes involves the subcutaneous tissue of the whole limb; multiple hæmorrhages are found in the viscera, serous membranes, etc. Ante-mortem clotting is present in small animals, but not in man where the blood is fluid unless, as rarely happens, the fangs enter a vein: death results from cardiac failure, peripheral circulatory failure, secondary hæmorrhage or septic infection and local gangrene.

**Symptoms.**—The clinical picture depends on the quantity and quality of the venom injected. Symptoms appear generally within 10 minutes to 2 hours after the bite, nausea, faintness and vomiting being characteristic early manifestations. Cardio-vascular shock follows both colubrine and viperine bites; paretic features predominate in the former, and general hæmorrhagic manifestations in the latter. In colubrine bites the fang marks are not always visible, and pain and local swelling are minimal; these features, however, are marked in the case of viper bites, which show in addition much hæmorrhagic oozing. Histamine shock probably accounts for the cold extremities, blanched, white skin, low blood pressure, vomiting, rapid thready pulse and extreme prostration. Psychological shock is sometimes an added factor, and may produce a somewhat similar picture in terrified natives bitten by non-poisonous snakes. In the earlier stages in colubrine bites the muscular weakness, ataxic gait and blurred speech may produce a picture simulating alcoholism, and diplopia, ptosis and blunting of sensation are not infrequently added; later there is inability to swallow, the tongue appears swollen, saliva dribbles from the mouth, the breathing, which was at first stimulated, becomes shallow and slow, and in fatal cases cyanosis, coma and convulsions of asphyxial origin ensue; the respirations may become costal in type and death occurs from peripheral respiratory failure. Hæmorrhagic extravasations (viperidæ) may lead to cutaneous petechiæ, epistaxis, hæmoptysis, hæmatemesis, hæmaturia and melæna. In the early stages the gums may ooze blood and the urine contain red corpuscles.

**Complications.**—Blunting of the cough reflex and paresis of the muscles of deglutition may be followed by insufflation pneumonia. After krait bites an acute ascending spinal paralysis has been recorded. With viperine poisoning, local supuration and gangrene sometimes necessitate amputation.

**Course.**—Death may occur within 20 minutes or many days later from complications.

**Diagnosis.**—Generally this is not difficult, but cases may need to be differentiated from alcoholism and the bites of non-venomous snakes and scorpions. The grooved or canalised anterior fangs in the upper jaw make identification of a poisonous snake easy.

**Prognosis.**—This depends on the amount of venom injected, the efficacy of local treatment and the availability of specific antivenene. Even with really deadly snakes, factors such as clothing, inefficient biting or a poor venom yield may prevent a lethal dose being injected, and this fact accounts for many extravagant claims regarding the value of weird cures. Most first-aid measures are useless since the ligature is applied ineffectively or too late, and once a lethal dose of venom has been absorbed into the circulation, antivenene given intravenously is the only measure that will save life.

**Treatment.**—**PROPHYLACTIC.**—Snakes bite man more often by accident than design, and in snake country a little knowledge and common sense regarding the natural habits of the ophidia, the use of torches or lanterns in walking along roads at night and the wearing of strong boots and leggings would greatly lessen the incidence of snake bite. Every second case is bitten below the knee.

**CURATIVE.**—Only two methods of treatment are of recognised value after a lethal dose of venom has been injected into the tissues: (1) Immediate ligature which delays absorption of venom, followed by such local measures as incision, excision, suction or the injection of chemicals, the object of which is to remove or destroy inoculated venom before a lethal dose can be absorbed; (2) the intravenous injection of specific antivenene. By temporarily prolonging life, effective ligature may enable antivenene to be given in otherwise fatal cases.

**Local measures.**—The most important local measure is the immediate application of a tourniquet, as every minute's delay increases the chances of the absorption of a lethal dose of venom into the general circulation. Pressure must be applied over a single bone proximal to the heart, i.e. over the femur in foot and leg bites, and over the humerus in bites on the hand and forearm; in finger and toe bites a boot lace may also be tied at the base of the implicated digit. Complete stasis of the circulation has to be attained as judged by blanching of the nails and failure of incisions to bleed. Thick rubber tubing ( $\frac{3}{8}$ -in.) is an ideal tourniquet, but in the field, strips of clothing, loosely knotted and twisted with a stick, are effective; every 20 minutes the tourniquet should be loosened for 30 seconds to flush the limb with blood. The skin should be washed with permanganate or antiseptic (if available), and if the tourniquet has been applied shortly after the bite and antivenene be not immediately available, it may be worth while making incisions over the fang punctures and then applying mechanical suction, preferably with a breast pump or a Bier's suction glass, with the object of extracting the venom from the tissues. Where ligature is inapplicable as in body bites, excision of the bitten area and washing with permanganate solution, followed by mechanical suction, is the best local treatment.

**Antivenene.**—Whatever the local treatment may have been, specific antivenene must be given intravenously as soon as possible. Specific polyvalent antivenenes are now available for the common deadly snakes of India, Africa, South America and the United States, while monovalent antivenenes are available in certain other countries. Polyvalent antivenenes are mixtures of specific antivenenes and generally are only life-saving when the venom of the particular species of snake which has bitten the patient has been utilised in their manufacture. Some antivenenes are now being put up in concentrated form in a dried state. Antivenene must always be given intravenously and the dosage varies inversely with body weight—children receiving much larger doses than adults. No patient is too ill to receive it, and even those with most severe paralysis may recover: after its injection patients must be kept under careful medical observation as paralysis may reappear and further antivenene injections be necessary to save life. Infiltration of the tissues with antivenene in the vicinity of the bite may be useful (Fitz Simmons).

**General measures.**—Patients must be kept warm and at rest. Black coffee and sal volatile may be given early, and injections of cortin, adrenaline or pituitary (posterior lobe) extract and of reconstituted plasma, followed by isotonic dextrose (5 per cent.), administered for circulatory shock. Nikethamide (Coramine) has value

as a respiratory and circulatory stimulant. Artificial respiration may prolong life, so permitting the administration of antivenene. It is important in cases with pharyngeal paresis to swab out the throat and keep the head low when the patient vomits; food should be withheld, and, if necessary, fluid given through a stomach-tube.

## POISONOUS FISHES

In tropical waters casualties from poisonous fish are not infrequent. The effects of jelly-fish stings vary with different species; many are harmless, others produce local features such as urticaria, œdema, marked itching, burning and erythema, sometimes followed by vesicular dermatitis or actual sloughing and ulceration. Systemic symptoms may follow rapidly and include lacrimation, coryza, muscular pains, constriction of the chest, dyspnœa and cardio-vascular shock. Deaths have been reported.

Fish of the genus *Muraena* bite with their powerful, grooved teeth down which poison from the venom sac enters the tissues; many harmful species are known, and their venom may have a depressant action on both the cardiac and nervous systems.

In other fish, such as the sting-rays, there are barbs in the dorsal fin or elsewhere connected with poison glands and these may produce not only severe inflammation locally, but neurotoxic features. Tetanus organisms may simultaneously be inoculated. Certain species of *Trachinus*, such as *T. draco* found in the Mediterranean, and of *Scorpena*, such as *S. scropha* inhabiting tropical waters, are particularly dangerous, causing excruciating pain and local irritation, œdema, paralysis of the part, collapse, dyspnœa, delirium and even death within 24 hours. Septic infection may follow. Local treatment as for snake bite should be adopted. Infiltration of the tissues with procaine hydrochloride (Novocaine) (2 per cent.) is often advisable for relief of pain, and morphine also may prove necessary.

N. HAMILTON FAIRLEY.



## SECTION IV

# DISEASES DUE TO CHEMICAL AND PHYSICAL AGENTS

## PLANT POISONS

There are more than 200 varieties of British plants which are poisonous to human beings. They may either be eaten unintentionally or in mistake for others known to be edible, and even plants grown for their food value may sometimes be dangerous. They are rarely the instruments of murder and suicide.

Some of the more poisonous belong to the Solanaceæ, including deadly nightshade (*Atropa belladonna*), henbane (*Hyoscyamus niger*), thornapple (*Datura stramonium*), woody nightshade (*Solanum dulcamara*) and black nightshade (*Solanum nigrum*). Berries of deadly nightshade may be mistaken for cherries, its leaves taken as dried herbs and even consumption of the meat of rabbits which have fed on the leaves has been known to cause poisoning. Suicidal attempts have been made with the seeds of henbane and thornapple. The Solanaceous plants owe their toxic effects to the alkaloids hyoscyamus and hyoscyamine, but the plants of the genus *Solanum* contain, in addition, the solanine alkaloids which are protoplasmic poisons and hæmolytic agents. These alkaloids are present in the leaves of the tomato (*Solanum lycopersicum*) and potato (*Solanum tuberosum*) and even in the tuber of the potato when methods of cultivation or storage are faulty. In epidemics of potato poisoning headache, nausea and vomiting are early symptoms, and in severe cases nephritis, hæmoglobinuria, neurological disorders or cardiac arrest may occur.

Umbelliferous plants have been responsible for many deaths because of the similarity of their roots to parsnips and their leaves to parsley. They contain the coniine alkaloids which cause paralysis of motor nerve terminations and stimulation followed by depression of the central nervous system. Water dropwort (*Eranthis fistulosa*) is the most notorious, but horsebane (*Eranthis phellandrium crocata*), cowbane (*Cicuta virosa*), common hemlock (*Conium maculatum*), wild celery (*Apium graveolens*), wild parsley (*Carum petroselinum*) and fool's parsley (*Æthusa cynapium*) are also dangerous.

The most poisonous of the Ranunculaceæ is monkshood (*Aconitum napellus*) which is often mistaken for horseradish. Its action is due to the highly toxic alkaloid aconitine, which gives rise to prickling of the skin and pharynx, respiratory paralysis and ventricular fibrillation. Anemone (*Anemone nemorosa*), clematis (*Clematis vitalba*) and marsh marigold (*Caltha palustris*) are poisonous during certain seasons and the fetid helleborine (*Helleborus fœtidus*) throughout the year. The fresh sap of the marsh marigold and of the water-buttercup (*Ranunculus aquatilis*) contains anemonin, which causes vomiting, blistering and dermatitis, and the root of the Christmas rose (*Helleborus niger*) is the source of helleborein, a glycoside which has an action similar to that of digitalis but is not absorbed from the gut and results only in diarrhœa. The stems and leaves of celandine (*Ranunculus ficaria*) are also poisonous.

Senecio of the Compositæ family is the largest genus of flowering plants and in South Africa is responsible for a fatal disease of animals and humans. *Senecio ilicifolius* and *S. burchelli* grow as weeds in the wheat fields and when the wheat is milled in old-fashioned mills where winnowing is inefficient their seeds are ground with the wheat grain into meal. Hæmorrhage occurs in various organs, particularly the liver, and the symptoms produced are nausea, vomiting, severe abdominal pain, hæmatemesis, ascites and jaundice. Although Senecio disease has not been described in Great Britain the toxic alkaloids have been extracted from Ragwort (*Senecio jacobea*) and other British species. Tansy (*Tanacetum vulgare*), also one of the Compositæ, was once used as an emmenagogue, ecbolic and anthelmintic, and half an ounce of

the oily extract, which contains thujon has been known to cause convulsions and coma, with death in 2 to 4 hours.

Poisonous plants of the Lily family include one of the autumn crocuses (*Colchicum autumnale*), wild hyacinth (*Scilla nonscripta*) and jonquil (*Narcissus jonquilla*). *Colchicum autumnale* may cause vomiting, diarrhoea, ascending paralysis and death due to the alkaloids colchicine and colchicine.

Hemp, white bryony, spurge, foxglove, horse-chestnut twigs and the stems and seeds of convolvulus and cuckoopint are all poisonous, and not only has death resulted from eating yew but also goats having eaten the plant have caused children drinking their milk to have gastro-enteritis. Poisonous berries not already mentioned include those of honeysuckle, guelder rose, mountain ash, dwarf elder, blackbryony, yew, budcherry, sea buckthorn, snowberry, privet, berberis, mezereon, spurge laurel, common laurel and the fetid iris of the south, and at Christmas the berries of mistletoe, holly and a species of Jerusalem cherry (*Solanum pseudocapsicum*) are especially important. The seeds of laburnum, juniper and daphne and the kernels of almond are also dangerous.

#### POISONOUS FUNGI

These include the ergot of rye and certain mushrooms which are sometimes eaten in mistake for the edible varieties.

**ERGOTISM.**—The fungus *Claviceps purpurea* grows as a parasite on rye, and in its mature form it protrudes as a spur, grey or purplish black in colour, between the leaves or glumes of the rye head. Because it is ground with the rye grain into flour, epidemics of poisoning are more common in countries such as France and Russia where rye bread is a staple article of food. Ergot contains at least ten alkaloids including ergotoxine, ergotamine, ergometrine and a number of bases including histamine and tyramine. They are present in varying proportions, which accounts for the complexity of the clinical picture of poisoning.

**Symptoms.**—The onset of the illness is usually gradual over a period of weeks or months, although in some cases it is rapid with premonitory symptoms for only 2 or 3 days. These include nausea, vomiting, diarrhoea, headache, vertigo and lassitude. Paræsthesiæ described as tingling, pricking, itching or numbness are characteristic. In the *gangrenous type* of ergotism there are severe pains, paræsthesiæ and swelling of the extremities followed by gangrene of the fingers and toes. In the *spasmodic type* painful muscular contractions seize the limbs, and the fingers and toes are powerfully flexed and adducted. The posture may resemble tetany, with which the condition is sometimes confused. The patient may be thrown to the ground when the spasms are generalised and they may assume a convulsive or *epileptoid form*. Absent knee- and ankle-jerks, ataxia, impairment of sensibility and loss of pupillary reaction to light are found in the *tabetic type*. Lower motor neurone lesions, cervical sympathetic paralysis, loss of upper limb reflexes and hypæsthesiæ in the cervical and dorsal regions have also been described. There is often a toxic psychosis causing either excitement or hypomania with hallucinations and delusions, or anxiety, melancholia and stupor. Uterine hæmorrhage or abortion may complicate pregnancy.

**Prognosis.**—In acute poisoning the outlook is good, although old and debilitated patients may die from cardio-vascular collapse or following severe and prolonged spasms. Permanent sequelæ include loss of fingers and toes from gangrene, hemiplegia, dementia and visual impairment due to cataract formation.

**Treatment.**—Atropine is sometimes an effective antidote. Sedatives may be required when there are mental symptoms.

#### POISONOUS MUSHROOMS

*Amanita phalloides* and *Amanita muscaria* are the most important poisonous mushrooms.

(a) *Amanita phalloides*.—This contains the deadly substance, phallin or amanita toxin. The susceptibility of children is greater than that of adults. The ingestion even of part of a plant may result in poisoning and the mortality rate is high. After a prodromal period of 4 to 24 hours, acute abdominal pain, vomiting and diarrhoea occur. The vomit and stools may contain blood and mucus. Anuria may occur. Short periods of remission may follow, but usually within a day or two jaundice, cyanosis and coldness of the extremities develop. In fatal cases coma supervenes. When poisoning is less severe, the symptoms abate in about a week and the patient is well within 4 weeks.

(b) *Amanita muscaria*.—This contains muscarine. After a small dose the patient becomes mildly excited, and the fungus is used by Siberian peasants to induce drunkenness. After larger doses the first symptoms appear within 2 to 6 hours. They are salivation, sweating, retching, vomiting and diarrhoea. Giddiness, confusion and hallucinations rapidly follow, and the pupils become contracted and fail to react to light or on accommodation. Amaurosis and diplopia may occur. Although the symptoms are violent the mortality rate is low. In all cases of mild poisoning the prognosis is good.

## EFFECTS OF TOBACCO

Tobacco is obtained from the dried and cured leaves of *Nicotiana tabacum* L. It derives its botanical name from the island of Tobago and from the name of the French diplomat Nicot, who introduced it into Europe at the end of the sixteenth century. In the three forms smoking, chewing and snuffing, tobacco is now indulged in by many millions of people throughout the world.

**Ætiology.**—Tobacco smoke contains nicotine, collidine, lutidine and other pyridine bases, furfural, acrolein, methyl alcohol and various volatile oils. Carbon monoxide and hydrocyanic acid are present in concentrations too low to be significant. There is no evidence that the lead and arsenic contained in insecticidal sprays used on tobacco plants contribute to the ill effects of tobacco smoking.

**Symptoms.**—Certain ill effects occur from handling the tobacco plant and its products in factories.

*Acute nicotine poisoning*, usually mild, may follow heavy smoking by a novice. It may occur also in a new worker who handles the leaves in curing tobacco. One fatal case took place in a workman employed in steeping tobacco in water. Gardeners and vine growers have been affected after using insecticidal sprays containing nicotine. The features of poisoning are pallor, faintness, sweating, nausea, vomiting, diarrhoea, bradycardia and hypotension.

In moderation tobacco smoking gives rise to a feeling of ease and relaxation, and some habitués claim to work better while smoking, although in the majority there is a lessening of efficiency. Some of the effects are neither pleasurable nor harmless, and the more important of these are described below.

**Cardio-vascular.**—Elevation of the blood pressure is commonly observed, and in certain patients excessive smoking may cause sinus tachycardia, premature contractions, paroxysmal tachycardia and rarely paroxysmal auricular fibrillation. Lowering or inversion of the T waves of the electrocardiogram has been demonstrated in a proportion of smokers who are normal subjects, and when coronary artery disease is present, attacks of angina pectoris may be precipitated. Most patients with thrombo-angiitis obliterans are heavy smokers and less than 10 per cent. are non-smokers, but the ætiological connection is far from clear. Since smoking causes peripheral vasoconstriction and lowering of skin temperature, it should also be avoided by those with Raynaud's phenomenon.

**Respiratory.**—In cigarette cutters employed in factories the local irritation of

tobacco dust may cause asthma. The chronic laryngitis and pharyngitis of heavy smokers which causes smoker's cough is probably due to inhaled irritating pyridine bases. Bronchitis is commoner in smokers than in non-smokers. It has also been shown that there are more heavy smokers and fewer non-smokers among patients with lung cancer than among patients with other diseases, and the incidence of both bronchitis and lung cancer increases significantly with the amount smoked.

*Gastro-intestinal.*—Squamous carcinoma of the lip may occur from the chronic irritation by tobacco and heat of pipe smoking, especially in the case of clay pipes. Some heavy smokers partially lose the sense of taste. The relationship of smoking to peptic ulceration is indefinite. In general it causes loss of appetite and lessening of gastric motility, factors which increase the symptoms of gastric ulceration and delay healing. The effect in duodenal ulceration is not so uniform, the pain sometimes being relieved by smoking. It is clear that smoking decreases the effectiveness of treatment and increases the tendency of peptic ulcer to relapse. Systematic experimental studies have shown that smoking increases the motor activity of the colon, hence the mild laxative effect experienced by many habitual smokers.

*Skin.*—In factories, tobacco dust affects especially beginners, causing irritation of the eyelids and conjunctiva with lacrimation. The dust or juice from the leaves may cause dermatitis on the back of the hands and face. The genitalia may become affected where the dust is conveyed by unwashed hands.

*Nervous system.*—In heavy smokers, in those who chew tobacco and in those exposed to tobacco dust in factories, tobacco amblyopia is a rare complication. The hazard is greater in pipe smokers than in cigarette smokers and especially affects those who use *shag* and other strong tobaccos. The patients are between 35 and 55 years of age and complain of blurring of vision, especially in bright daylight. The condition is bilateral, though often worse in one eye. There is a scotoma in the first instance for red between the blind spot and the fixation point, which extends to involve the fixation point, leaving peripheral vision intact. This is followed at first by temporal pallor of the optic disk and later by optic atrophy. The condition is primarily retinal and results from degeneration of ganglion cells, especially in the macular area.

*Prognosis and Treatment.*—Tobacco smoking is contraindicated in tobacco amblyopia, thrombo-angiitis obliterans and gastric ulcer. As indicated by the incidence of amputations, thrombo-angiitis obliterans is less severe and more amenable to therapy in those patients who give up smoking early and completely. Treatment of tobacco amblyopia consists in total abstention from tobacco. Insistence on this always leads to improvement and may save the patient's sight. In duodenal ulcer and in angina of effort it is unfair to demand abstention from smoking unless there is clear evidence in the patient concerned that this brings on the attacks.

Prevention of acute nicotine poisoning in tobacco curing factories is achieved by providing rubber gloves for all workers who must handle the tobacco leaves. Where a factory worker, gardener or horticulturalist gets the juice of tobacco leaves or a solution of nicotine on the skin, the use of hot water must be avoided, otherwise absorption will be facilitated. Prevention of asthma in the manufacture of cigarettes turns upon mechanisation, which must include enclosure of machines in such a way as to avoid contamination of the working environment with tobacco dust.

The tobacco habit is difficult to break. The abstinence symptoms are mainly craving and restlessness; none of the profound constitutional symptoms found on withdrawal from addiction to narcotics is seen. The patient must have the courage and determination to abstain completely and it is better that he should not try to decrease the amount of tobacco gradually. On occasions treatment may include a mouthwash containing 1 per cent. of copper sulphate in order to render the taste of tobacco smoke extremely unpleasant at least for an hour or so.

DONALD HUNTER.

## EPIDEMIC DROPSY

**Synonym.**—Argemone Poisoning.

**Definition.**—A condition characterised by œdema, vascular changes and cardiac insufficiency, resulting from the ingestion of the seeds of the Mexican poppy (*Argemone mexicana*) or their products.

**Ætiology.**—Epidemic dropsy is most commonly seen in India, especially in Bengal, Bihar, Orissa and the Central and United Provinces. It has been recorded in Mauritius, Fiji and South Africa.

The toxic agent, which has not yet been identified, is contained in the seeds of the Mexican poppy which sometimes grows as a weed amongst the mustard or wheat crops. The seed is very similar to the mustard seed, and may be mixed with the latter accidentally or deliberately as an adulterant in the manufacture of mustard oil, which is widely used for cooking in many parts of India.

The incidence of epidemic dropsy in India depends to some extent on the issue of the first season's oil; there is some evidence that the toxicity of the oil may be reduced during storage. It is highest during the rains or soon after, *i.e.*, in July and August, and lowest in April.

Breast-fed infants and children under 4 years of age are not often affected, presumably because they do not have access to the oil. All other age groups may be affected. The racial distribution of the condition depends on dietetic habits. Wherever mustard oil is eaten and there is a possibility of contamination, epidemic dropsy may appear. The appearance of the syndrome is independent of the presence of rice in the diet. It appeared in South Africa in individuals after eating flour made from badly sieved wheat. It is probable that malnutrition and deficiencies may be conditioning factors, especially in those, such as rice eaters, who live on a high carbohydrate diet.

**Pathology.**—There is a generalised acute vasodilatation, affecting the capillaries and small vessels, especially of the skin, heart muscle and uveal tract. Irregular formation of new blood vessels takes place, particularly in the subcutaneous tissues. In some cases hæmangiomas (so-called "sarcoids") develop and may become small pedunculated tumours which bleed readily. Hæmorrhage may also occur from mucous membranes. There may be some secondary normocytic orthochromic anæmia.

Vascular dilatation in the iris and ciliary body commonly leads to raised intra-ocular pressure. Glaucoma and blindness from optic atrophy may result.

Vascular engorgement of the skin, liver and other organs is seen at necropsy. The heart muscle is often intensely congested and œdematous. Where cardiac insufficiency is evident the characteristic engorged and enlarged liver is present.

**Symptoms and Signs.**—The clinical picture varies widely. Many cases are mild, and except in "epidemics" may be overlooked. Some outbreaks are notable for the severity, others for the mildness of the syndrome.

The onset is insidious in most cases. There is usually a history of a few days of loss of appetite, nausea and diarrhœa, followed by the appearance of œdema. The severe case may, however, begin suddenly and end fatally in a few days.

Œdema is present in all cases. Other signs vary in intensity from one case to another and from one outbreak to another.

The œdema appears rapidly. It is soft and easily pitted and mostly confined to the legs. It becomes worse if the patient is allowed to walk about. Occasionally, there may be general anasarca, with effusions into the pleural and pericardial cavities. Terminal lung œdema may occur.

The patient is chiefly concerned with the severe dyspnœa which is constant and worsened by exertion. The blood pressure is low, especially the diastolic, and the pulse is fast and thready. In severe cases the heart is dilated, the apex beat displaced to the left and the basal dullness extended to the right. Apical systolic murmurs

are common. The electrocardiogram may show evidence of myocardial damage, with sinus tachycardia and extrasystoles. Acute heart failure may develop with fibrillating muscle and irregular pulse, and enlarging tender liver. Fatal heart insufficiency may develop steadily or appear suddenly.

Peripheral vascular changes are present in most cases. Dilated vessels give the skin an irregular bluish mottled appearance, which may be present from the onset in severe cases, or develop after the œdema in moderate cases. Subcutaneous telangiectases or hæmangiomas become visible in some patients. The latter may develop into small tumours or "sarcoids" up to half an inch across and raised above the surrounding skin or sometimes sessile. Sarcoids bleed freely if injured; they gradually reduce during convalescence. Hyperæsthesia, tingling of the skin and tenderness of the calf muscles are prominent signs in some cases. The knee jerks may be absent. General effects vary. There may be mild fever. Nausea is the rule and there is often vomiting. Watery diarrhœa is common.

Glaucoma is one of the most serious complications. In some outbreaks up to 10 per cent. of those affected may exhibit raised intraocular tension, with or without local pain and associated with dimness of vision and contracted visual fields.

**Course and Prognosis.**—In the average case the signs, especially those related to the cardio-vascular system, subside upon rest in bed and are exacerbated on exertion. In some cases the cardiac signs are progressively severe and fail entirely to respond to treatment, the patient dying from cardiac failure in a few days.

The death-rate is usually about 5 per cent. but varies from outbreak to outbreak, reaching as high as 50 per cent.

Prognosis in the individual case should be guarded. It depends chiefly on the cardiac state. It is bad where there is decompensation. Serious cardiac failure may develop at any stage.

**Diagnosis.**—Diagnosis is easy in a recognised outbreak but may be difficult in isolated cases. A knowledge of the patient's diet is essential.

Acute œdema appearing in several members of a family or of a community known to use mustard oil is highly suggestive. Wet beri-beri, and famine œdema may cause confusion. Information about the diet, or lack of it, is important in differentiating epidemic dropsy from these conditions, which usually develop more slowly. In the former there may be prominent associated nervous signs and a vigorous response with diuresis to thiamin therapy. Both may occur concurrently with epidemic dropsy.

**Treatment.**—Rest in bed is essential. Mustard oil or other possible sources of the toxic agent should be excluded from the diet.

In diarrhœic cases an initial saline purge may be given. The cardiac insufficiency may or may not respond to digitalis. A combination of ammonium chloride and mersalyl may help.

Dietary deficiencies should be adjusted. Vitamins A, B, C and P may be required, and can be supplied most easily in the form of vegetable extracts, cod-liver oil and fruit juices. Epidemic dropsy, unlike beri-beri, does not respond to vitamin B<sub>1</sub>. The salt intake should be limited in the acute stages.

Bleeding from hæmangiomas can be controlled by pressure. Glaucoma requires operative treatment. It does not usually respond to eserine. Convalescence is slow.

BRIAN MÆGRAITH.

## LATHYRISM

**Definition.**—A disease of limited geographical distribution, characterised by spastic spinal paralysis, and caused by poisoning with peas of a vetch of the genus *Lathyrus*.

**Ætiology.**—The disease, formerly met with in Italy, has been reported from India, especially North Behar and the United Provinces, Algiers, France, Persia, etc.

Three species of *Lathyrus* may be associated with poisoning in man: (1) *Lathyrus sativus*, known in India as Khesari dal; (2) *Lathyrus cicera*, the dwarf chick-pea found in France, Italy and Algeria; and (3) *Lathyrus clymenum*, found in Spain, North Africa and the Levant. It is solely confined to countries where different kinds of chick-pea are used for food, but the causative principle is unknown. Young people are specially liable, and men are more affected than women. It occurs as an epidemic amongst the poorest classes in times of great scarcity, when bread is made from a mixture of pea and wheat flour. It may also be eaten as porridge, or the peas may be boiled with oil and then consumed. Formerly it was attributed to the grain of *Lathyrus sativus* (Khesari dal), but in India, Howard, Anderson and Simonsen failed to demonstrate any poisonous principle. They succeeded in isolating two toxic alkaloid-like bases, vicine and divicine from *Vicia sativa* (akta), an allied vetch, the seeds of which were a common contaminant of Khesari dal and produced symptoms of lathyrism when fed to ducks.

**Pathology.**—A chronic sclerosis is found in the spinal cord involving the posterior and lateral columns. Possibly a toxic spasm of the arteries of the cord, followed by thrombosis, is the basis of the condition.

**Symptoms.**—The onset may be insidious with backache, burning pains and weakness of the legs, or it may be sudden, as when after a hard day's work in the rain the patient wakes up with stiff, weak and trembling legs, which feel heavy to lift. These symptoms increase rapidly, and in 10 days walking may be impossible without the aid of a stick. Both legs are usually affected simultaneously, first the calves, then the thighs. Gradually a peculiar gait develops, the patient laboriously progressing by means of a two-handed staff; "the leg bearing the weight of the body is bent at the knee and trembles, while the advancing limb dragged wearily forward and strongly abducted, is planted unsteadily directly in front of its fellow, the toes reaching the ground first". When lying on the back, spasm of the adductors ceases and the thighs can be separated. There is little or no atrophy or loss of muscular tone, the knee-jerks are increased and ankle clonus is marked. Sensation is normal. Incontinence of urine and feces and possibly loss of sexual power follow involvement of the lumbar segment, but the upper extremities are rarely implicated.

**Diagnosis.**—The occurrence of multiple cases simultaneously and the history of eating chick-peas as food confirm the diagnosis.

**Prognosis.**—This depends on the stage at which the case is diagnosed; if early, great improvement follows treatment, but in later cases when the cord has become permanently damaged spasticity persists.

**Treatment.**—Varieties of chick-pea must be avoided as human food, and their abolition stamps out the disease. Avoidance of damp and wet ameliorate the symptoms. A generous diet adequate in vitamins should be given. Massage and electricity are indicated.

## ACKEE POISONING

**Synonym.**—Vomiting sickness of Jamaica.

**Definition.**—A frequently fatal disease, especially affecting children in the West Indies, characterised by vomiting and nervous symptoms due to eating the unripe ackee fruit.

**Ætiology.**—Ackee fruit grows on the tree *Blighia sapida* (Sapindacæ) in the West Indies and West Coast of Africa. The mature fruit is harmless, but when eaten in an immature state before the fruit opens, it proves a deadly poison, especially if soup be made from it or other ingredients like rice be boiled in ackee water. The poison is contained in the arilli of the unripe fruit.

**Pathology.**—Intense fatty changes are found constantly in the liver and to a

lesser degree in the kidneys, heart and cortical brain-cells. Hyperæmia of the meninges and other organs occurs, also hæmorrhages in the viscera.

**Symptoms.**—The patient, who is generally a healthy child, suddenly commences vomiting some 2 hours after a meal containing unripe ackee fruit and complains of nausea and abdominal discomfort. After 3 or 4 hours of sickness a calm interval ensues, followed by nervous symptoms, including cerebral vomiting, twitching of muscles, convulsions and coma.

**Prognosis.**—Once nervous symptoms supervene the condition is invariably fatal, the average duration being 12 to 14 hours.

**Treatment.**—Prevention consists in discarding the immature unopen fruit and in not utilising the water in which ackee fruit is boiled as soup. Alcohol precipitates the poison, and the immediate administration of rum or ether and ammonia as advocated by Scott has reduced the mortality in school children from 90 to 27 per cent.

N. HAMILTON FAIRLEY.

## ACUTE MORPHINE POISONING

Under this heading can be included poisoning due to opium, diamorphine (Heroin) and Dilaudid, for the picture in each case is similar. (*For Chronic Morphinism, see p. 1640.*)

**Ætiology.**—Poisoning occurs by accident or suicide, after ingestion or injection, though cases have followed rectal administration or absorption through wounds. The fatal dose is variable; of morphine, probably gr. 2 to 3 is needed, and of opium gr. 10 to 30, though less in some cases. Tolerance is easily established, but conversely children are unusually susceptible. The fatal period is from 6 to 12 hours, regardless of the dose.

**Pathology.**—Death is from respiratory failure, and necropsy reveals cyanosis of the head and extremities and dark blood. There may be a smell of opium in the stomach, and demonstrable quantities of the drug in the urine and organs.

**Symptoms.**—In 10 to 30 minutes if the drug was taken by mouth, or less if by injection, a transient phase of euphoria and exhalation may be seen, then nausea and vomiting, later dizziness, heaviness in the head and sleepiness, soon resulting in coma. The patient in coma shows slow stertorous respiration at 2 to 4 per minute, with cyanosis of the face, slow pulse, general flaccidity and loss of reflexes, perhaps an extensor plantar response and pin-point pupils. Sweating is considerable and the skin is warm in spite of a low temperature. Oliguria, pruritus and skin rashes are sometimes seen. The pupils dilate in the ultimate stage of respiratory failure.

**Diagnosis.**—Coma, stertor and constricted pupils are a suspicious triad. Pontine hæmorrhage finally shows a rising temperature.

**Treatment.**—Warmth, oxygen and artificial respiration are needed; then a stomach wash, first with water, preserving the stomach contents, then with potassium permanganate solution, gr. 5 to 10 to the pint with charcoal suspension. Gastric lavage is used, and repeated, even if the drug has been injected. Nalorphine (Lethidrone) is an antagonist to drugs with a morphine-like action and it has proved an effective antidote to morphine, pethidine (Demerol) and methadone (Physeptone). It can be given intravenously, intramuscularly and subcutaneously in repeated doses of 10 to 40 mg. Its action is specific for the morphine derivatives and similar compounds, and it should not be used in coma due to other depressants.

Apart from acute poisoning, an individual idiosyncrasy is sometimes seen, in particular in the very young and the very old, and in allergic persons. Such patients often vomit and they may show tremor, and even delirium and convulsions. It is dangerous to use morphine in cases of head injury, raised intracranial pressure, myxœdema and bronchial asthma.



## COCAINE POISONING

Cocaine is obtained from the leaf of *Erythroxylum coca*; it is expensive and its habitués tend, therefore, to be wealthy psychopaths.

**Ætiology.**—The drug is most commonly met as a white powder, known to the underworld as *snow*, and taken as snuff; it can be injected or taken by mouth. A tolerance may be established, though not as high a one as in morphinism. Its chief delight is the speed with which it relieves fatigue; it temporarily enhances mental and physical vigour, being a true cortical stimulant.

**Symptoms.**—The patient suffers digestive disturbances and remarkable anorexia, dispenses with food and becomes emaciated. He complains of salivation and of formication or else a sensation of sand grains under his skin. There may be convulsions, hallucinations, delirium or even mania. He is usually unpleasant to others, his behaviour alternating between exaltation and dejection, with a lowered moral tone and a proclivity to sexual excesses. He may have dilated pupils and sparkling eyes, tremor, nasal inflammation, ulceration or even perforation of the septum, or otherwise the tell-tale scars on the forearms of old sites of injection. He takes the drug for its stimulant effects and not to ward off withdrawal symptoms, which are slight.

**Treatment.**—Though the habit is not so compelling as morphinism, and withdrawal symptoms are less, the discipline of an institution is needed. The drug is abruptly stopped, and sometimes hyoscine by mouth is given as a temporary substitute.

## ATROPINE POISONING

Atropine occurs in such solanaceous plants as *Atropa belladonna* (deadly nightshade) and *Datura stramonium* (thornapple) together with hyoscine and hyoscyamine, the toxic actions of which are similar.

**Ætiology.**—Children are susceptible and apt misguidedly to eat the berries or seeds of these plants. Intoxication has occurred in using the drugs therapeutically, even in ophthalmology, but homicidal and suicidal cases have been few. Individual idiosyncrasy, revealed as a local reaction to atropine eye-drops, or as a general erythema and pyrexia, is not uncommon. The fatal dose is uncertain, but quantities of the order of gr.  $\frac{1}{4}$  to 2 of pure atropine or 14 belladonna berries have been quoted.

**Symptoms.**—These appear quickly: there is a dry burning mouth, intense thirst and difficulty with talking and swallowing; the skin is dry and flushed, vision is blurred and photophobia present. The temperature rises and a state of excitement follows, suggesting acute mania or alcoholism, with obstreperous behaviour, disorientation and hallucinosis. This picture may persist for some hours, or may in more severe intoxication give place to a stage of depression, when the victim is quiet and lapses into coma, dying from respiratory failure. Fatalities are rare.

When examined in the earlier stages, the patient has dilated fixed pupils, a red dry skin, tachycardia, pyrexia and rapid respirations, perhaps a generalised erythematous rash; tremors and convulsions have been noted. Such signs may persist several days into convalescence, when there is mental confusion and loss of memory for recent events.

**Treatment.**—Use a locally acting emetic, and wash out the stomach with warm water and potassium permanganate gr. 5 to 10 to the pint. In the stage of excitement, morphine is to be avoided. Chloral hydrate, paraldehyde, or the rapidly acting barbiturates should be given. In the later depressive stage respiratory stimulants and oxygen may be needed. An injection of pilocarpine gr.  $\frac{1}{10}$  to  $\frac{1}{2}$  gives some relief to the dry mouth and ocular disturbances. Children should be especially watched at the height of the fever.

## ALCOHOLISM

Alcoholism is dealt with in this section mainly from the point of view of the physical effects. The subject may be conveniently divided into (1) acute alcoholism; (2) alcoholic coma; (3) dipsomania and (4) chronic alcoholism. The section of Psychological Medicine (p. 1637) should also be consulted.

## 1. ACUTE ALCOHOLISM

**Synonyms.**—Acute Alcoholic Poisoning; Drunkenness.

**Definition.**—A person is said to suffer from acute alcoholism when as a result of alcohol he is unable to do with safety to himself or others that which he attempts.

**Ætiology.**—The effect of alcohol varies in different individuals, and depends not only on the amount taken but also on the physical state and mental stability of the patient.

**Pathology.**—Repeated sublethal doses cause no pathological changes in experimental animals. However, alcohol enhances the effects of other poisons and accelerates such degenerative processes as atheroma. Clinical observations on healthy human adults support these findings. It is a matter of common experience that post-alcoholic intestinal symptoms, malaise and headache, are more apt to occur when some other poison is taken at the same time. Examples are tobacco and the harsh acids of badly prepared wines. In alcoholic intoxication, the blood and urine alcohol reach a level between 0.1 and 0.3 per cent. The basal metabolism is raised, and there is great water loss from over-breathing, sweating, diuresis and sometimes vomiting. Alcohol depresses nervous activity. Reaction time is prolonged and perception dulled. The special senses become less acute, weakness of accommodation and of ocular synergia occur with blurred vision and diplopia. The normal social inhibitions become dulled so that the animal tendencies escape repression, with consequent non-social or even anti-social behaviour. Indeed this lessening of inhibition is the end aimed at in taking alcohol, and allows a certain freedom and exhilaration in over-repressed persons. This escape from inhibition should not be regarded as an increase in general efficiency. In unstable persons, pathological mental tendencies may become uncovered, with resulting epileptic attacks either in the form of fits, or as "epileptic equivalents" such as *mania a potu* or automatism (see p. 1637).

**Symptoms.**—The clinical picture of drunkenness is well known. After sleeping the patient awakens with headache and the usual symptoms of a mild gastro-intestinal upset. As has been inferred before, there is little after-effect in the healthy person who drinks sensibly. People who have drunk unwisely or have taken too much tobacco will feel ill all the next day. They show the clinical picture of a mild melancholia with gloomy thoughts, poor volition and excessive irritability. Strong sensory stimuli are poorly tolerated. Mental concentration is poor, and there is marked lessening of general efficiency.

**Diagnosis.**—It is often impossible for an exact diagnosis to be made until the patient has been kept under observation, and this precaution should be taken where there is any doubt. No exact percentage of alcohol in the blood and urine can be fixed as the precise limit between sobriety and drunkenness for medico-legal purposes.

**Prognosis.**—Recovery usually takes place within 24 hours and can be hastened by appropriate treatment.

**Treatment.**—If the drunken person is seen before going to sleep, he should be given an emetic of warm sodium bicarbonate solution (gr. 60 to a pint) and subsequently encouraged to take a drink of water. The aim of this treatment is to remove any of the poison that remains in the stomach, to soothe the mucosa and to combat the dehydration. If the patient needs treatment and refuses it, apomorphine gr.  $\frac{1}{10}$  or gr.  $\frac{1}{15}$  hypodermically will induce vomiting within a few seconds and leave the

patient amenable to subsequent treatment. He should then be put in a warm bed and allowed to sleep as long as possible. On waking a Seidlitz powder should be given and the patient encouraged to take plenty of fluid. This is usually acceptable in the form of tea. If tolerated, dextrose in some form should be given. When anorexia is marked, food should not be forced. If a great deal of alcohol has been taken, gr. 2 of calomel can be given half an hour before the Seidlitz powder. If the patient has to get on with his work, gr. 10 of calcium aspirin will improve his general feelings and combat the headache. Large doses of ordinary aspirin often irritate the stomach and should be avoided, as most of the symptoms of the next day are due to the gastro-intestinal upset. To give bitter alcoholic drinks as part of treatment is contrary to all medical principles and has no real therapeutic effect.

## 2. ALCOHOLIC COMA

**Synonyms.**—Acute Alcoholic Poisoning; Wet Brain.

**Ætiology.**—Individual susceptibility varies so much and case histories are so falsified by prejudice and folklore that there are no reliable figures of what constitutes a dangerous dose. Alcohol is much more dangerous in states of debility, whether such debility be the result of disease, exhaustion or hunger. Naturally beverages of high alcoholic content are more poisonous than those of low.

**Pathology.**—At post-mortem alcohol is present in all the body fluids. There is mucous catarrh of the stomach and evidence of right heart failure. The nervous system shows a moderate excess of cerebrospinal fluid and the superficial parts of the cortex are oedematous.

**Symptoms.**—These come on quickly. The euphoric exhilarated period is short, the patient becomes sleepy and soon passes into coma with stertor. Vomiting or even convulsions may occur during the early drowsy period, but neither of these symptoms is constant. In the coma, the patient lies in any position in which he is put, and is commonly found lying on his back. He is pale, collapsed and sweats profusely. In the early and middle stages he can be roused sufficiently to make a few disjointed remarks, and this has some diagnostic value. In these stages the pupils are dilated, the pulse full, the temperature subnormal and the respirations deep. In the later stage the coma becomes dangerously deep, the pupils contract, the pulse weakens and the respirations are shallow. At all stages the limbs are flaccid, with diminished reflexes. In the early stages the plantar reflex is flexor, while in the later stages it cannot be elicited. Examination of the blood and urine show an alcohol content of 0.3 to 0.6 per cent.

**Diagnosis.**—It is of paramount importance to exclude cerebral trauma before making a final diagnosis of alcoholic coma. Sometimes the history of trauma is deliberately withheld by the person who has called the doctor. When there is a history of unconsciousness followed by a lucid interval and subsequent coma, this is good presumptive evidence of ruptured middle meningeal artery. The absence of such a history does not exclude this accident, as often the patient has taken alcohol, which implements the original concussion and does not allow the intermediate return of consciousness. Alcohol can precipitate other comas, notably diabetic coma, uræmic coma and epileptic coma. The urine must be examined in all cases, and when there is any doubt a lumbar puncture should be done. A careful general examination will reveal evidence of such conditions as renal disease or arterial degeneration, and may show scars on the tongue or elsewhere suggestive of epilepsy. Cerebral hæmorrhage or thrombosis must not be forgotten. Reference should be made to p. 1441 and elsewhere.

**Prognosis.**—With adequate treatment that is not too long delayed, this is good provided that the patient is otherwise healthy. The prognosis is unfavourable in those with cardio-vascular disease, or when the acute attack occurs in the course of chronic alcoholism. Miosis is an unfavourable sign.

**Treatment.**—Treatment is necessary to combat shock and dehydration. Warm the patient, raise the limbs and give fluids. The stomach should be washed out with 1 quart of a warm aqueous solution of sodium bicarbonate (gr. 60 to a pint), and a rectal drip of warm water should be started immediately. If there be evidence of heart failure with gross venous congestion, venesection should be done provided that the measures to combat shock and dehydration have been applied.

### 3. DIPSOMANIA

**Definition.**—An intermittent compulsion to get drunk.

**Pathology.**—This is a compulsion neurosis.

**Symptoms.**—The periodicity varies in different individuals and in the same individual under differing stresses. Commonly it is about once a month. An irresistible desire to take large quantities of alcohol seizes the patient. Usually he begins drinking after work one day, takes a large amount, comes home with a bottle of spirits, and after drinking this becomes stuporose and has to be put to bed. The bouts tend to become more frequent. Usually no alcohol is taken between the attacks.

**Prognosis.**—A good deal of amelioration can be expected in expert hands; otherwise the outlook is not good.

**Treatment.**—The patient must be referred to a competent psychiatrist.

### 4. CHRONIC ALCOHOLISM

**Definition.**—A patient is said to be a chronic alcoholic when he cannot carry on his ordinary life without alcohol.

**Pathology.**—This is primarily a mental disorder. The psycho-pathology is dealt with in the section on Psychological Medicine (p. 1637). Physically alcohol enhances degenerative tendencies, such as atheroma, and implements the toxicity of poisons; these effects are well seen in experimental animals. Gastro-intestinal catarrh occurs and results in deficient absorption of essential food elements. This is made worse because the patient prefers drinking to eating. In advanced cases achlorhydria is found. Bronchial catarrh and conjunctivitis are common, probably as a result of vitamin A deficiency. Deficiency of vitamin B results in parenchymatous degeneration of nerves, and wasting of brain cells with chromatolysis. Ultimately the brain may be so wasted that the post-mortem appearance simulates that of G.P.I. Pachymeningitis hæmorrhagica is sometimes observed. The well-known susceptibility to pulmonary tuberculosis may be related to dietary deficiency. In the cardio-vascular system atheroma and related degenerations are accelerated. However, it is a commonplace of pathology how little cardio-vascular change there may be in an alcoholic subject. Gout is made much worse by alcohol, and osteo-arthritis is common in alcoholics. The majority of persons with cirrhosis of the liver are heavy drinkers. No doubt some factor in addition to the alcohol is necessary to produce this condition, for it may be absent even in the worst chronic alcoholic. Alcohol is dangerous in diabetes, for it interferes with treatment and increases the tendency to complications.

**Symptoms.**—Typically the chronic alcoholic is a plethoric person with a plum-coloured complexion. The colour is most marked on the cheeks and nose. Its blue component is due to dilated small veins. After exposure to cold, the colour may darken to a deep mauve. The lips tremble, and there is a fairly coarse tremor of the hands. This tremor may affect the handwriting. The patient is fidgety, often wiping his mouth with his hand, fiddling with his tie, pulling at his ear or playing with his watch chain. He is restless in his chair, and often has tics involving the whole trunk or the head. He is often swift but superficial with his replies, and though his manner is calculated to be disarming he is inclined to be irascible. He readily responds to the mood of the examiner. His eyes have an appearance that is variously described as

glassy or watery. The conjunctivæ are red. His appetite is poor, and he has a preference for spicy and pungent foods. He rarely takes any breakfast, and does not feel himself until he has had a drink. On rising he clears his throat of much viscid mucus, which he usually refers to as "my catarrh". Often the hawking induces an attack of vomiting. Cases with much gastric catarrh vomit either on rising or at a fixed time afterwards. He is usually proud of the freedom of his bowels, but when careful inquiry is made it is found that he has diarrhœa. Night-rising once or twice is common. The majority of cases have attacks of paræsthesia in the limbs from time to time, and on examination the reflexes are found sluggish and the calves tender. In the presence of arterial degeneration a cerebral vascular accident may occur at any time, but more frequently the final illness is uræmia.

**Neurological complications.**—Some degree of peripheral neuritis is common (see p. 1589). *Korsakoff's psychosis* may be present (see p. 1638). Sometimes in alcoholic neuritis the pupil is very sluggish to light. In such cases, if the neurological signs overshadow the mental, the condition is often referred to as *alcoholic pseudo-tabes*; if, on the other hand, the mental signs predominate over the physical, it may be called *alcoholic pseudo-paresis*. These terms are self-explanatory. *Acute hallucinosis* or the more serious *delirium tremens* are acute psychoses and are dealt with in the section of Psychological Medicine (see p. 1638).

**Prognosis.**—(a) **GENERAL.**—As regards cure this is often bad. In many cases, however, suitable management leads to a good all-round improvement. Intercurrent diseases, especially those of the respiratory system, are poorly tolerated. Pneumonia and tuberculosis have a much worse prognosis in these patients than in normal people. Anæsthetics are taken badly, and there is more likelihood of post-anæsthetic complications.

(b) **NEUROLOGICAL.**—This has been greatly altered for the better since the true nature of these complications has been understood, namely, that they are due to deficiency of vitamin B<sub>1</sub>. Provided that no permanent damage has been done, cure can now be obtained of both the neuritis and the Korsakoff syndrome.

**Treatment.**—(a) **OF THE CHRONIC ALCOHOLISM.**—This is difficult, and usually disappointing in the hands of the general physician. The underlying causes are mental and these need the attention of experts. Should it be necessary to treat the patient in his own home without a psychiatrist the friends should be spoken to earnestly, and everyone in contact with the patient must be above suspicion, because absolute withdrawal of alcohol is essential. Since the patient has been used to this nerve depressor, he may experience severe withdrawal symptoms and some simple sedative such as paraldehyde min. 120 should be available. Where paraldehyde is not tolerated, soluble barbitone (Medinal) gr. 7½ is suitable. The patient's appetite will be poor, and may be encouraged by a simple stomachic before meals. After meals he should be given a sedative alkaline mixture, such as bism. carb. gr. 15, sodii bicarb. gr. 15, tr. bellad. min. 10, tr. card. co. min. 120, aq. menth. pip. ad min. 240. He should be handled sympathetically, and any outstanding domestic difficulties and worries resolved. Graduated doses of strychnine are employed in many cases. Such treatment acts by suggestion. Better results will be obtained in these patients if at the beginning they are put to bed for a few weeks, and if the gastro-intestinal illness is treated intelligently. For psychological effect, the patient may be put on a rigid diet with all the quantities carefully prescribed and supervised. The form of the diet will depend on the circumstances, but it should be bland, well balanced and rich in vitamins.

(b) **NEUROLOGICAL.**—Rest the affected parts, including the mind, and give large doses of vitamin B<sub>1</sub> (aneurine hydrochloride, thiamine hydrochloride). For the first 2 weeks, 10 mg. should be given intramuscularly every alternate day, and thereafter, twice weekly. In addition, 30 g. of brewer's yeast should be given by mouth twice daily. After recovery the patient should continue to take vitamin B<sub>1</sub> indefinitely.

## METHYL ALCOHOL POISONING

Methyl alcohol or methanol is a clear colourless, volatile, inflammable liquid with a burning taste and an odour somewhat resembling that of ethyl alcohol.

**Ætiology.**—It is used in anti-freeze for motor-car radiators, as a denaturant of ethyl alcohol, as a solvent for paints, varnishes, shellacs and paint removers, and in dry cleaning. It is employed also in the manufacture of formaldehyde, synthetic indigo, explosives, felt hats, shoes and linoleum. Outbreaks of poisoning can be expected when alcoholic drinks contaminated with methanol are illegally distributed, and it should be remembered that certain patients with chronic alcoholism are addicted also to methyl alcohol. Poisoning in industry, by inhalation of the vapour or its absorption through the skin, may occur when methyl alcohol is used as a solvent, especially in spray painting. This was at one time common in the U.S.A., but it has almost disappeared since that country adopted denatured ethyl alcohol as a safe substitute.

**Pathology.**—Acidosis is a feature of all severe cases and the plasma-bicarbonate level is often below 20 meq./l. In the body methyl alcohol is partly oxidised to formaldehyde and formic acid, and it has been suggested that these toxic substances inhibit certain oxidative processes in the cells, possibly by combining with iron in the respiratory oxidase. Carbon dioxide is not formed and organic acids accumulate, which accounts for the extreme acidosis. It has been observed that drinking ethyl alcohol can prevent or delay the toxic effects of methanol. The ethyl alcohol competes successfully with it for the available alcohol dehydrogenase in the liver, and the oxidation of methyl alcohol cannot proceed until all the ethyl alcohol has been metabolised.

**Symptoms.**—There is usually a latent period of about 24 hours before the onset of symptoms; these include headache, dizziness, anorexia, nausea, weakness and visual disturbances. The trouble with the eyes begins usually with pain in the eyeballs and tenderness on pressure, slight photophobia and then indistinct vision with dancing spots, snowstorm effects or flashes before the eyes. If loss of vision progresses there is concentric constriction of the fields both for form and for colour. Severe headache is rapidly followed by blindness, delirium, stupor, acute mania with retrograde amnesia, coma, convulsions and death in respiratory failure. In industrial cases there is often irritation of the skin, and, when the concentration of methyl alcohol inhaled is very high, the worker may suffer a degree of poisoning equal to that when it is taken by mouth.

**Physical signs.**—The patient is apprehensive and the skin cool and cyanosed, with profuse perspiration. The pupils are dilated and react sluggishly, and ophthalmoscopy sometimes shows hyperæmia of the optic disk and retinal œdema.

**Treatment.**—In severe cases an immediate intravenous infusion containing sodium bicarbonate can be life-saving. Sixty to 70 g. may be required in the first instance, but the exact amount should be decided on the results of serial estimation of the alkali reserve or the pH of the urine, because over-treatment leads to tetany, hypokalaemia and sodium retention. Small amounts of ethyl alcohol can be given 4-hourly.

## CARBON MONOXIDE POISONING

Carbon monoxide, or carbonic oxide (CO), is a very poisonous gas. If present in the air breathed in an amount equal to 0.2 per cent. it is capable of destroying life; while an atmosphere containing 0.05 per cent. of carbon monoxide gives rise to definite symptoms of poisoning.

**Ætiology and Pathology.**—When carbon is burnt in a limited supply of oxygen, carbon monoxide is produced in varying amount. *Domestic poisoning:* Charcoal

fires and braziers as well as coke furnaces give rise to considerable amounts of CO. Certain types of water heaters and slow combustion stoves are common sources of production of the gas, which may give rise to poisoning if the ventilating flues are inadequate. The exhaust fumes from motor-cars and petrol-burning engines contain approximately 6 per cent. of carbon monoxide. Diesel engines are widely used in motor-buses, lorries and tractors. When a diesel engine is run on a high fuel-air ratio, carbon monoxide is produced in amounts comparable to those from a petrol engine burning a rich mixture. The commonest source of carbon monoxide poisoning is from coal gas which is used for illuminating or heating purposes. Coal gas contains normally from 4 to 10 per cent. carbon monoxide, and it often approximates to the latter figure. It is a common cause of death either from accidental leakage from pipes or from purposive exposure due to turned-on taps. Carbon monoxide occurs in the smoke and fumes from fires with inadequate chimney ventilation. It is important to remember that the products of combustion of gas stoves and gas fires contain an appreciable amount of carbon monoxide and the flues from these must be adequate completely to carry away the products of combustion. *Industrial poisoning*: This occurs from the fumes from blast furnaces, in iron smelting, and in blasting operations in mines. In coal mines the explosions from coal dust, or inflammable gases, lead to the production of carbon monoxide (after-damp). *Water gas* is prepared by passing steam over red-hot coke, and contains upwards of 30 per cent. CO. It is used for heating purposes, and is sometimes added to coal gas before its distribution. It is very poisonous and, owing to its slight smell, is very dangerous unless mixed with odorous gases. *Producer gas* is prepared by passing a mixture of steam and air over red-hot coke in retorts. It is used for heating the coal retorts for the preparation of coal gas. Producer gas is a mixture of carbon monoxide, hydrogen and nitrogen, and is similar in composition and properties to water gas, and may contain as much as 30 per cent. of carbon monoxide. Industrial dangers also arise from leakages in the plant and from the process of charging the producer-gas retorts.

*Action of carbon monoxide.*—Carbon monoxide has 220 times the affinity for hæmoglobin that oxygen has. If respired, it will, therefore, more or less completely displace the oxygen from its combination with the hæmoglobin of the red cells. This prevents oxygen being carried in requisite amount by the red cells to the tissues of the body, which thus become deprived of the oxygen necessary for their vital functions. The extent to which the hæmoglobin is saturated with carbon monoxide depends upon the percentage of the latter in the air breathed. When the hæmoglobin becomes one-third saturated with carbon monoxide, definite symptoms of poisoning occur, and when the saturation exceeds 50 per cent. there is grave danger of a fatal issue. It is important to note that carbon monoxide is a tissue poison. It does not act simply as an oxygen depriver to the tissues, but undoubtedly has in addition a narcotic action upon them. This is best illustrated by considering the serious symptoms of narcosis (muscular paralysis and loss of consciousness) which occur in a person in whom 50 per cent. saturation of the hæmoglobin with carbon monoxide exists. These symptoms far exceed in gravity those of a person possessing only 50 per cent. of hæmoglobin as the result of anæmia from disease or hæmorrhage. Carbon monoxide acts as a tissue poison especially to the nervous system, but there is evidence to show that it acts on all the tissues of the body, notably the cardiac muscle, and may cause degenerative changes in them.

*Post-mortem appearances.*—The external appearances are characteristic, the cheeks and lips and post-mortem stains appearing cherry-pink in colour. On opening the body, the blood, muscles and internal organs have a characteristic cherry-pink colour. The lungs may show areas of consolidation due to broncho-pneumonia. Small hæmorrhages may be visible, and œdema is common. The brain shows congestion and œdema, and small punctiform hæmorrhages may be found in the cortex and basal ganglia. The heart muscle may show cloudy swelling with punctiform hæmor-

rhages beneath the pericardium. In some cases of carbon monoxide poisoning putrefaction is much delayed.

**Symptoms.**—Carbon monoxide is odourless and any smell of an atmosphere containing it is due to the presence of other gases or vapours having a characteristic odour. It may be respired freely without any irritation to the air passages. Premonitory symptoms are giddiness, ataxic gait, a swimming sensation, headache or a sensation of heaviness or constriction in the head, noises in the ears and a feeling of oppression in the chest. Sometimes nausea and vomiting occur. The onset is, however, often sudden, and this is likely to be so when the percentage of carbon monoxide is relatively high. In these cases, the first symptoms may be sudden collapse, with loss of consciousness, and this is associated with complete loss of power in the limbs. In sub-acute cases the symptoms may resemble those of acute alcoholic poisoning.

The blood pressure rises at first, and the pulse is full and may not be increased in rate. Muscular weakness and drowsiness quickly supervene in severe cases, and the patient falls unconscious. In the condition of coma the blood pressure falls and the pulse becomes rapid and small. The conjunctivæ become hyperæmic and the eyes have a staring appearance, the pupils being partially dilated and inactive to light. The complexion has a cherry-red appearance. Froth may be present on the lips. The breathing is stertorous. The temperature is usually subnormal in the early stages of coma, but is sometimes raised in the later stages. There is relaxation of the sphincters in severe cases. Broncho-pneumonia may develop if the coma is prolonged for more than a few hours. Occasionally prolonged asphyxia permanently damages the brain and the patient survives with paralysis, sensory loss, Parkinsonism or loss of memory. Such sequelæ are due, not to retention of carbon monoxide but to degeneration of nerve cells. The determining factor in their production is the length of time that the tissues have been subjected to oxygen lack. Old people or patients suffering from cardio-vascular disease do not stand asphyxia as well as do robust persons.

Repeated daily exposure to small amounts of carbon monoxide occurs sometimes in garage mechanics, blast-furnace workers and cooks. They suffer no impairment of health, and they may develop true acclimatisation as indicated by compensatory polycythæmia—that is to say, an increase in the red-cell count and hæmoglobin figure. Carbon monoxide is not a cumulative poison. In pure air, and with a sufficient volume of breathing, small amounts of this gas are readily ventilated out of the blood. There is therefore no such condition as chronic carbon monoxide poisoning.

**Diagnosis.**—A simple test can be employed to prove the presence of carbon monoxide in the blood. A greatly diluted solution of the suspected sample is compared with that of normal blood similarly diluted. The latter is yellow, whereas blood containing even very small traces of carboxy-hæmoglobin is pink. When the proportion of carbon monoxide in the blood is more than 40 per cent. of saturation, spectroscopic examination affords a confirmatory test.

**Treatment.**—**PROPHYLACTIC.**—The fact that his safety-lamp continues to burn is no proof to the miner of the safety of air in which afterdamp may be present. He therefore carries a canary in a cage, for a bird shows signs of poisoning in a fraction of the time necessary in the case of a man. Hence, by watching the canary, timely warning may be obtained of the presence of enough carbon monoxide to endanger the life of the miner and his rescuer. A more convenient method for determining the concentration of carbon monoxide in the air is a portable direct-reading instrument sensitive to 10 p.p.m. of the gas. This employs a catalyst to promote oxidation of the gas, and the corresponding rise of temperature is indicated on a sensitive thermocouple. Carbon-monoxide recorders which operate continuously are installed in up-to-date vehicular tunnels.

In industry the structure of buildings must be regulated in such a way as to obviate unnecessary risk. Preventive measures must be strictly applied and a com-



petent person should be made responsible for inspecting the plant concerned at stated short intervals. He should see that there is no leakage and must keep a signed and dated record of such inspection. No person should be allowed to work single-handed in a place where exposure is to be anticipated, and a safe form of breathing apparatus must be worn. Activated charcoal does not effectively protect against carbon monoxide. Respirators must contain a mixture of 50 per cent. manganese dioxide, 30 per cent. copper oxide, 15 per cent. cobaltic oxide and 5 per cent. silver oxide, known by the name *hopcalite*. This catalyses the oxidation of the carbon monoxide by the oxygen of the air. Iron and steel works must have first-aid men constantly on duty, trained to work as rescue squads and taught how to keep all apparatus in good order.

**CURATIVE.**—Warmth is essential in treatment. The patient should be wrapped in dry blankets and provided with hot-water bottles. Rest is absolutely necessary. The first and immediate consideration is the restoration of breathing, and the second the promotion of warmth and circulation. Work done in many countries since 1950 has shown that the Schafer method of artificial respiration gives inadequate ventilation in many subjects. It is now agreed that the arm-lift, back-pressure method of Holger Nielsen gives a higher uptake of oxygen than does the Schafer method and is easy to teach, accurate in performance and can be readily carried out over long periods. It has therefore been adopted by the International Red Cross and by all three of the Armed Services of Great Britain. All workers responsible for rescue work must understand that in resuscitation of persons who have ceased to breathe it is vitally important to apply artificial respiration *promptly*. Rescue men generally work in teams of three, each man working for 20 minutes and the team continuing for as long as 4 hours or until *rigor mortis* has obviously begun. The delay incident to the removal to a hospital may be fatal, and is justifiable only when there is no one at hand to give artificial respiration. If complications exist or arise which require hospital treatment, artificial respiration should be maintained in transit and after the arrival at the hospital until spontaneous respiration begins. For resuscitation of subjects exposed to carbon monoxide the use of a mixture of 95 per cent. oxygen and 5 per cent. carbon dioxide is of great value. It has been shown that the blood of men gassed with carbon monoxide up to 35 per cent. and to a 50 per cent. hæmoglobin saturation can be brought down to 15 per cent. saturation in 30 minutes when the oxygen-carbon-dioxide mixture is inhaled. The same men, gassed to comparable saturations, are relieved very slowly when oxygen alone is inhaled.

## POISONING BY BARBITURATES

Acute barbiturate poisoning is rarely accidental and comes second to carbon monoxide as a cause of death by suicide. The barbiturates can be divided into four groups depending on their rapidity of action. The long-acting derivatives include barbitone (Veronal), phenobarbitone (Gardenal, Luminal) and methyl phenobarbitone (Phemitone); barbiturates with intermediate action are allobarbitone (Dial), butobarbitone (Soneryl) and amylobarbitone (Amytal); and those with short action are cyclobarbitone (Phanodorm), pentobarbitone (Nembutal) and quinalbarbitone (Seconal). The ultra-short acting compounds used as anaesthetics are the soluble sodium salts of thiopentone (Pentothal), hexobarbitone (Evipan) and thialbarbitone (Kemithal). Sodium salts of the other derivatives are also obtainable for parenteral use. By far the most frequently encountered barbiturate in suicidal attempts is phenobarbitone.

**Symptoms.**—The history from witnesses is often unreliable and circumstantial evidence confusing. Thus unconsciousness may be attributed to injury due to a fall in the early stages of intoxication, or a patient in deep coma due to a barbiturate may be found in circumstances which suggest carbon monoxide poisoning. Diplopia, nystagmus, dysarthria and ataxia are constant in mild intoxication. In severe intoxication there is deep coma with subnormal temperature, raised pulse-rate, low blood

pressure, a variable but usually raised respiration rate with shallow and sometimes irregular breathing, small fixed pupils, absent reflexes, diminished deep reflexes and absent or flexor plantar responses. The pupils are normal in mild cases, constricted in severe intoxication and dilated and fixed when death is imminent; barbiturate poisoning is but an exaggerated form of surgical anaesthesia in which pupillary size and reaction can be related to depth of coma. The skin is usually cold and dry; cyanosis when present is peripheral in shock, or central in asphyxia. Fever is a sign of pneumonia; hyperpyrexia is of grave prognostic significance. Uncommon features include bullous skin lesions resembling burns, methaemoglobinæmia, hippus, strabismus, muscular rigidity and extensor plantar responses. Generalised convulsions or a state of mania rather than coma are unusual. Excitement and aggressive behaviour may occur during recovery from coma, especially in epileptics.

**Diagnosis.**—Other causes of prolonged coma, including head injury, cerebral vascular lesions, diabetes, hypoglycæmia and uræmia can usually be excluded without difficulty. In aspirin poisoning there is hyperpnea with ketone bodies in the urine; alcohol is made apparent by its distinctive smell; and cocaine produces wide dilatation of the pupils. Coma due to morphine, however, may be indistinguishable from barbiturate poisoning. Laboratory aids to diagnosis include qualitative and quantitative estimations of barbiturates in the blood by ultra-violet spectrophotometry. Qualitative analysis is possible also by means of paper chromatography. For specimens with a relatively high concentration of barbiturate such as stomach content and urine, the estimation depends upon extraction and melting point determination or microcrystalline appearance.

**Treatment.**—The early and effective treatment of anoxia and shock are of vital importance. Depth of coma may be increased by anoxia, and the establishment of a free airway may be followed by dramatic improvement. Where secretions have accumulated below the level of the glottis intermittent bronchoscopic suction is probably preferable to prolonged endotracheal intubation. Oxygen can be supplied by naso-pharyngeal catheter at a rate of 7 litres per minute. When shock is marked, warmth is essential and the foot of the bed should be raised. Turning the patient frequently to either side and the administration of penicillin will delay the onset of broncho-pneumonia; fluid loss should be replaced by means of intravenous therapy. Feeding by mouth should not be resumed too early because of the danger of the inhalation of vomit. Gastric aspiration and lavage are effective in removing unabsorbed barbiturates if performed within 4 hours of ingestion and colonic lavage may also be employed, but cerebrospinal fluid drainage is both useless and dangerous. Analeptics are of doubtful value in poisoning by the long-acting derivatives, and if given in convulsive doses may increase the depth of coma. They may hasten the return of consciousness in poisoning due to the barbiturates with short action, and in milder cases dramatic awakening may occur. Picrotoxin is the most effective analeptic and is best given intravenously in 6 mg. doses every 30 minutes. Large doses at more frequent intervals are sometimes tolerated but cumulation usually occurs if the intervals are less than 20 minutes.

**Prognosis.**—The duration and depth of coma, the age of the patient and his general condition are factors which influence the immediate prognosis. Patients with Parkinsonism are particularly susceptible to the barbiturates, and alcohol is known to potentiate their effect. The prognosis is better in poisoning due to butobarbitone or allied compounds provided treatment is not delayed; paradoxically death may occur with smaller doses than are usually fatal in poisoning due to phenobarbitone or barbitone. Consciousness is retained when the level of phenobarbitone in the blood is below 5 mg. per 100 ml., it may be retained when the level of barbitone in the blood is between 7 and 10 mg. per 100 ml., but death may occur when the level of butobarbitone is between 2 and 3 mg. per 100 ml. Where an underlying personality defect exists further suicidal attempts are not uncommon, but when the attempt is attributable

to painful or prolonged organic disease, treatment or alleviation of the cause will lessen the chance of recurrence. Peripheral neuritis, mental impairment and pulmonary fibrosis are rare sequelæ of acute barbiturate poisoning.

Idiosyncrasy to barbiturates is rare, but death has been recorded in one instance after taking gr. 2½ of phenobarbitone spread over 6 hours, and in another after a dose of gr. ½ had been taken three times a day for 2 days. A generalised maculopapular rash becoming vesicular, with œdema of the face, limbs and often of the glottis may occur and may be accompanied by fever, severe toxæmia and delirium or coma. There may also be hæmorrhage, jaundice, renal failure and bronchopneumonia.

## CORROSIVE POISONS

The most commonly encountered members of this group include the strong alkalis, potassium hydroxide, sodium hydroxide and ammonia, and the strong acids, sulphuric, hydrochloric, hydrofluoric, nitric and acetic. They may be taken accidentally or for suicidal purposes but are rarely used with homicidal intent. The more volatile corrosives, hydrochloric acid, nitric acid and in particular hydrofluoric acid and ammonia cause injury not only to the upper alimentary tract but also, following inhalation, to the lungs and upper respiratory tract. Oxalic acid, phenol and hydrocyanic acid need to be considered separately because their corrosive action is of secondary importance compared to their systemic effects after absorption.

**Symptoms.**—Severe pain in the mouth, throat and abdomen occurs immediately after ingestion, with violent retching and vomiting of dark brown material containing altered blood and fragments of mucous membrane. Thirst cannot be relieved because of severe dysphagia, and any attempt to drink results in further vomiting. In poisoning due to the volatile corrosives, intense irritation of the eyes, throat and lungs with cough, dyspnoea and cyanosis are prominent symptoms. Death may occur within 24 hours from shock and dehydration, or more rapidly from asphyxia due to acute œdema of the larynx. When delayed for 2 or more weeks it may be attributable to exhaustion and secondary infection or to stricture of the œsophagus.

**Oxalic acid.**—This is used in the home as a cleaning agent and may be taken accidentally because the crystals resemble Epsom salts. It has a powerful toxic effect on the central nervous system and heart, which has been attributed to combination of the acid with calcium in the body. The early symptoms of pain and dysphagia are followed by increasing prostration, with a small irregular pulse and slow sighing respiration. Paræsthesiæ and convulsions usually follow and death in coma often occurs within 1 hour of ingestion.

**Phenol** is used as an antiseptic. It may be absorbed through the skin or mucous membranes when it causes burning and numbness followed by anæsthesia. It has a strong depressant action on the central nervous system and large doses cause death within a few minutes. After small doses there is nausea, giddiness and faintness; consciousness is gradually lost. The clinical picture of deep coma with cyanosis, cold perspiration, contraction of the pupils and slow irregular breathing may be wrongly attributed to morphine poisoning. The urine becomes dark green on exposure, owing to the presence of hydroquinone and pyrocatechin.

**Hydrocyanic acid** and the soluble cyanides act as general protoplasmic poisons interfering with the internal respiration of tissue cells. Symptoms occur at once; after small doses there may be headache, vertigo, weakness, dyspnoea and convulsions, but after large doses loss of consciousness is sudden, with convulsions followed by death in a few minutes. The characteristic smell of bitter almonds is diagnostic.

**Treatment.**—The shock and pain following ingestion of one of the *strong acids* or *alkalis* necessitate the use of morphine in repeated doses, warmth and the parenteral replacement of fluid loss. Gastric lavage is contraindicated because of the risk of perforation, but the appropriate neutralising antidote should be introduced into the

stomach as soon as possible. In the case of acids calcined magnesia, lime water or soapy water may be used; carbonates and bicarbonates are best avoided because the liberation of carbon dioxide may cause distension of the stomach and perforation. Alkalis can be neutralised with vinegar, dilute acetic acid or the juices of lemon or orange. In both cases olive oil or white of egg may be used to protect the stomach wall.

In *oxalic acid poisoning* there is less danger of perforation and the stomach should be washed out with warm water as soon as possible. Alkaline solutions should not be used because the soluble oxalates produced are very toxic. Calcium lactate, 10 to 30 g., can be left in the stomach to form the insoluble and inert calcium salt. Calcium lactate or gluconate should also be given parenterally.

In *phenol poisoning* gastric lavage should be performed with warm water until the characteristic smell disappears from the returned fluid. Alternatively a 10 per cent. solution of alcohol can be used. A solution of magnesium sulphate, white of egg or milk can be left in the stomach after the washing is completed. Atropine sulphate subcutaneously may be of some value, and when breathing is embarrassed artificial respiration is indicated.

*Poisoning by cyanides* is usually fatal, but on rare occasions immediate lavage of the stomach with water and artificial respiration may prevent death. While these procedures are being carried out glass capsules of amyl nitrite should be broken into a handkerchief and the vapour inhaled. A dose of 0.5 g. of sodium nitrite is given intravenously, 3 to 4 minutes being taken for the injection. Following, but not together with, the sodium nitrite injection, sodium thiosulphate should be given by slow intravenous injection. The dose is 25 g. in a total volume of 50 ml. administered over a 10-minute period.

## LEAD POISONING

### I. ACUTE LEAD POISONING

This is rare. It usually results from swallowing a large dose of a soluble lead compound, such as lead acetate, which is also known as sugar of lead, from its sweetish taste. It has occasionally occurred when white lead has been mistaken for chalk and when lead chromate has been used in error to colour cakes or confectionery. Innumerable babies have died in the convulsions of lead encephalopathy from the use by the mother of lead nipple shields or ointments containing lead salts in the treatment of cracked nipples. In 1950 the Ministry of Health sent notices to all doctors and hospitals in the National Health Service warning them against these deadly practices.

**Pathology.**—There are the usual signs of acute gastro-enteritis, and the stomach may be covered with a whitish grey deposit. The wall of the stomach and duodenum is sometimes thickened and softened, and erosions may occur from the local action of the lead compound.

**Symptoms.**—An astringent metallic taste is at once experienced, followed by a feeling of constriction in the *œsophagus*. A burning sensation and pain are felt in the epigastrium, and vomiting occurs. The vomit contains opaque whitish material, due to the precipitated albuminate of lead and lead chloride, formed by the action of the lead salt on the gastric contents. Blood may also be present. Severe colicky pain occurs in the abdomen, with rigidity of the abdominal muscles. Pressure on the abdomen gives relief, and the patient may bend forwards for this purpose, or lie on his abdomen. The tongue is coated, and constipation usually occurs, but occasionally there is diarrhœa. The stools are dark coloured, owing to the formation of lead sulphide. Prostration and collapse occur if the abdominal symptoms are severe. There may be numbness or *paræsthesia* of the limbs, cramps in the legs and partial suppression of urine. A blue line on the gums does not usually occur during the acute symptoms following a single dose of the poison.

The subacute form of poisoning follows the taking of repeated doses of a soluble lead compound. It may occur from repeated medicinal doses of lead acetate given to control diarrhœa. Abdominal colic is pronounced, and constipation severe. The other symptoms of acute lead poisoning occur, but are less intense in character. A blue line usually appears in the gums. If the teeth are frequently cleaned it is less likely to be formed. If the symptoms are of long duration lead palsy may result.

**Diagnosis.**—The diagnosis of acute or subacute lead poisoning can be confirmed by analysis of the vomit and fæces for lead during life, and after death by finding lead in the gastro-intestinal tract, liver, spleen and kidneys. Acute and subacute lead poisoning are rarely fatal.

**Treatment.**—If the patient is seen within 3 hours of swallowing the poison the stomach should be washed out with water. Intravenous injections of calcium versenate (calcium di-sodium E.D.T.A.) must be given at once (see p. 371). The abdominal pain may be relieved by hot applications, repeated drinks of milk and large doses of calcium lactate, 5 g. (gr. 75) three times a day. In severe colic by the slow intravenous injection of 15 ml. of a 20 per cent. solution of calcium gluconate, or of 10 ml. of a 5 per cent. solution of calcium chloride, it is possible to relieve the pain by the time the injection is over. If necessary this treatment may be repeated in 2 hours. Should it not be available a hypodermic injection of gr.  $\frac{1}{8}$  atropine sulphate and gr.  $\frac{1}{4}$  morphine sulphate may be given. For some weeks saline aperients and a high calcium diet should be given. The diet should contain 3 pints of milk daily, including milk puddings, junket and ice cream, together with butter, cheese and eggs.

## 2. CHRONIC LEAD POISONING

**Synonyms.**—Plumbism; Saturnism.

**Ætiology.**—Apart from a few cases arising from accidental causes, chronic lead poisoning is of occupational origin. Lead is now encountered in more than 200 industries. In Great Britain there are more than 1,500 workers in the lead industries and 150,000 painters. It has been known clinically for more than a hundred years that absorption of lead through the respiratory tract is very much more important than by the gastro-intestinal tract, and this view has since been amply confirmed by experiments on cats. In the prevention of dust and fume great success has been secured from the application of the Factories Acts. Idiosyncrasy is a factor in the development of lead poisoning, certain persons being more susceptible than others. Alcoholism also seems to be a predisposing cause. The sources from which lead is derived in chronic poisoning are very numerous, and they may be divided into three groups.

1. **Occupational risks.**—Men are exposed to danger in the smelting and tinning of metals, in vitreous enamelling, pottery glazing, shipbuilding, coach painting, plumbing and soldering, house painting, and in the manufacture of white lead, red lead, litharge, rubber, glass, cement, varnish, coloured pigments, linoleum and electric accumulators. Lead smelters are exposed to the fume and dust of furnaces and flues. Lead burners and chemical plumbers use oxy-acetylene, oxy-hydrogen, or oxy-coal gas blowpipes in their work. The very high temperature of such flames constitutes a much greater risk than that faced by the domestic plumber who uses a spirit blow-lamp. Painters are exposed when they rub down interior surfaces which have been painted with lead paint. The use of a blowlamp for burning off old paint is not without risk. A painter nowadays is very rarely exposed in mixing paint from the dry material, because it comes to him already mixed in oil. There is some risk to compositors who handle type metal, and to gasfitters who use red and white lead. It frequently happens that changes in methods or the appearance of new industries provide new causes of lead poisoning. Thus in ship-breaking, especially when warships are scrapped, the volatilisation of lead from the paint and red lead stopping on

the plating occurs in the heat of the oxy-acetylene blowpipe flames used for cutting purposes. In 1923 the great increase in the use of wireless receiving apparatus and motor-cars led temporarily to a greater number of cases of lead poisoning in electric accumulator factories. Sometimes the converse is true, and lead poisoning is found to show a remarkable diminution in a given industry. Thus, the substitution of machine methods for hand labour has abolished the disease among file cutters. The fall in the incidence of poisoning in coach painting is due to the enormous development of spray painting of motor-cars with leadless cellulose lacquers.

2. *Accidental causes.*—Drinking water, especially if it is soft, or contains traces of acid derived from peat or dead leaves, may dissolve lead from lead pipes or cisterns and so give rise to poisoning. Beer or cider drawn from casks through lead pipes may become heavily contaminated. Aerated waters delivered from syphons with pewter or lead valves may give rise to poisoning. The lead glaze on earthenware vessels may be dissolved by vinegar, lemon juice, cider or home-made wine. At one time the cooking of food in vessels tinned with a mixture of lead and tin gave rise to lead poisoning, especially if vegetable acids were present. The tinning of saucepans and food tins is carried out nowadays with pure tin. Tinned foods sometimes contain lead from solution of the solder used in the tinning process. The lead foil used for wrapping sweets or food may contaminate them. Cosmetics, hair-dyes and snuff weighted with litharge all have given rise to cases. Children with perverted appetites may chew the paint off their cots or toys. In Queensland, Australia, where the hot, dry climate causes flaking of painted surfaces, so that lead carbonate comes away as a white powder, children have been poisoned owing to nail-biting, thumb-sucking and the habit of licking the raindrops off the painted balconies, railings, fences and roofs of wooden houses.

3. *Abortifacient uses of lead.*—Lead attacks the chorion epithelium, causing abortion in pregnant women. A like effect has been observed in animals in the proximity of lead works. Lead oleate plaster, known as diachylon, has been used in certain districts by pregnant women in order to cause miscarriage, the substance being swallowed in small portions rolled up in the form of a pill. To do this is very dangerous, for if miscarriage comes about, death occurs later from lead poisoning. In consequence the sale of lead oleate has been restricted by placing it in Part I of the Poisons Schedule.

*Pathology.*—In chronic poisoning lead is stored in the skeleton, and under certain circumstances is released to attack (i) muscle, causing abdominal colic and lead palsy; (ii) the reticulated red cell, causing punctate basophilia (stippling) and anaemia; (iii) the chorion epithelium, causing abortion and (iv) the brain, causing encephalopathy.

In 1925 Fairhall studied the physico-chemical behaviour of lead in the animal body. It is probably transported in the blood plasma as the insoluble tertiary phosphate in the highly dispersed or colloidal form. At different stages of intoxication its distribution within the body varies somewhat. When absorption is slow it migrates to the skeleton, where about 95 per cent. is held without harm during the chronic stage of plumbism. If, however, large quantities of lead are being absorbed or are being liberated from the bones, lead is distributed throughout the tissues and the percentage in the bones is reduced. Under these conditions acute symptoms of poisoning occur. It has been shown that the total amount of lead stored in the skeleton in lead workers varies from 0.2 to 0.8 g. This deposition of lead suggests a mechanism similar to that involved in the deposition of calcium phosphate. Repeated observations by Aub and Fairhall showed that conditions which favour storage of calcium in the body also favour storage of lead. When conditions are unfavourable for the retention of calcium the excretion of stored lead increases.

In studies of lead excretion it is to be noted that normal persons with no tional exposure to lead may excrete lead in the faeces and urine. This happens t

lead is frequently present in the soil, and hence in vegetation and animal food. In normal persons the concentrations of lead may be 0.03 mg. per 100 g. of blood, 0.027 mg. per litre of urine and 0.28 mg. per 24 hours' sample of faeces. In toxicological analysis no satisfactory figures can be obtained unless specimens of stool and urine are collected for at least 3 days. A man working in a dusty lead industry, in addition to inhaling lead, may swallow repeated small amounts and pass lead unabsorbed in the faeces. The only proof of absorption, therefore, is to find lead in the urine. If specimens be taken some weeks after removal from exposure, the output may reach about 1 mg. for each 24 hours in the faeces and about 0.3 mg. in the urine. Under effective treatment the faecal excretion may rise to about 2 mg. in each 24 hours. It should be emphasised that the presence of lead in the excreta is not necessarily proof that a lead worker is suffering from lead poisoning. Many such workers are insusceptible and have never suffered from any of the toxic episodes.

Lead palsy begins in the muscles, and fatigue determines the site of paralysis. The chemical explanation offered is that in regions of muscular activity the excess lactic acid which diffuses from the fatigued muscle cells combines with the lead phosphate in the blood to form lead lactate. As this soluble lactate comes into contact with inorganic phosphate at the surface of the muscle cells the lead is re-precipitated as insoluble phosphate, causing alterations in the surface permeability.

Studies of the blood in lead poisoning show that the stippled red cell arises from the reticulocyte. Blood films can be prepared showing all stages between stippled fragments and typical reticulum. The presence of punctate basophilia in the blood is not, of course, a specific sign of lead poisoning. It is seen in pernicious anaemia, in leukaemia, in the anaemias of carcinomatosis and in pneumonia in infants. Its occurrence in these various conditions is relatively rare and slight as compared with the frequency and intensity of its appearance during plumbism. For this reason the demonstration of stippling of the red cells in the blood has come to be considered as almost definite evidence of absorption of lead. It is not an absolute indication of the severity of lead poisoning, but it often runs parallel to the state of health. If on examination of the films its presence is detected in a sufficiently large number of fields of the microscope, further exposure to lead in the patient concerned should be prevented immediately. Punctate counts are of value in the prophylaxis of plumbism among lead workers and are essential in the adequate hygienic control of lead processes. Lane (1931) demonstrated the value of dark ground illumination in counting the stippled cells and showed that large granules, because they denote excessive absorption or mobilisation of lead, have greater significance than small ones.

The intensity of stippling is invariably higher in the bone marrow than in the peripheral blood and it has been postulated that the action of lead is primarily upon the nucleated red cell precursors in the bone marrow. The work of Rimington (1938) points to inhibition of haemoglobin synthesis as the chief mechanism whereby anaemia develops in chronic lead poisoning. The synthesis appears to be inhibited at the point where iron should be incorporated into the porphyrin molecule. Lead may also act by interfering with the enzyme system concerned in the conversion of coproporphyrin III to protoporphyrin, as well as at a lower level in the pathway of haemoglobin synthesis, by partially preventing the synthesis of coproporphyrin III.

Except in cases of encephalopathy, which are now very rare, chronic lead poisoning is not a direct cause of death. In 1854 Garrod pointed out that gout was quite common among lead workers in Great Britain, but there is nothing to show that the occurrence of these two conditions in one patient was other than fortuitous. Beyond the blue line on the gums and that in the mucosa of the rectum near the anal margin, chronic lead poisoning produces no characteristic post-mortem changes.

**Clinical History.**—The past occupations of the patient should be inquired into, for latent lead poisoning is well known to occur. The present occupation is obviously of importance and the exact details of the work he does should be elicited from

the patient himself. Often a man's occupation does not at first sight suggest that he is exposed to compounds of lead. A man describing himself as a fitter may be exposed to dust or fume of lead; this fact is only elicited in answer to a leading question. The occupation of a cooper becomes dangerous when the barrels worked upon have contained compounds of lead. Vitreous enamellers working, for example, on baths, sift a powder containing lead silicate on to the bath which has been heated in a furnace. They sometimes use a compressed-air apparatus which forces the enamel through a sieve. In the electric accumulator trade pasters fill the spaces in accumulator plates with a paste containing litharge and red lead. Colour manufacturers grind colours into a fine powder under edge runners with the necessary production of much dust. Amongst other things they grind lead chromate and red lead. A slate mason may construct storage tanks by fixing together slabs of slate with materials containing oxides of lead. A bullion refiner may use a process in which he adds lead to refinable silver in a furnace and taps off molten litharge. A rubber compounder adds oxides of lead to crude rubber in preparation for vulcanisation. A girl describing herself as a perambulator maker may be employed painting the body work of perambulators and then rubbing down the surface with dry sand-paper. An embroidery worker sometimes stencils materials by dabbing on the pattern commercial white lead instead of chalk.

**Symptoms.**—The toxic episodes resulting from the absorption of lead are colic, palsy, anaemia and encephalopathy. The blue line on the gums is a sign of absorption and not of intoxication.

**Lead colic.**—This is the most common and dramatic of the acute manifestations of plumbism. It is ten times as common as lead palsy. An attack of colic is preceded by several days of constipation. The pain is of a tearing or griping nature and of variable intensity. It is situated around or below the umbilicus, and the patient often indicates where it is by spreading both hands widely over the abdomen. While suffering from colic the patient is cold, pale and often drenched with perspiration. He commonly bends over and may writhe about the bed in intense pain. Examination shows a scaphoid abdomen, held tense, but showing no rigidity. Vomiting frequently occurs at the onset of the pain.

**Lead palsy.**—This does not belong to the category of polyneuritis, either clinically or pathologically. It is in the first instance a muscle disease. Fatigue plays a most important part in determining the sites attacked. Where the muscle palsy is neglected the lead attacks the motor nerve fibres and ultimately the anterior horn cells of the spinal cord (see also p. 1593). Paralysis does not appear to be closely related to length of exposure. It may develop during the first months of work, or only after many years' exposure. The commonest form is the well-known wrist-drop which begins usually in the right hand and later becomes bilateral. The palsy first appears in the long extensors of the middle and ring fingers. It spreads to the other fingers, and then to the long extensors of the wrists. The supinator longus (*brachioradialis*), and usually the long abductor of the thumb escape. The brachial type of paralysis involves the deltoid, biceps and supinator longus, but it is very rare for this to occur without wrist-drop. A third form of lead palsy in which progressive atrophy occurs of the thenar and hypothenar eminences, together with the interossei, used to be common in the left hand of file-cutters. In view of the theory that fatigue plays an important part in determining the site of lead paralysis, this observation is of great interest, for in their work file-cutters not only used particularly the muscles mentioned but placed the greatest strain upon the left hand. The substitution of machine methods for hand labour has abolished lead poisoning amongst file makers. Lead palsy rarely occurs in the lower limbs, but when it does so it affects the extensors of the toes, giving rise to foot-drop.

**Anaemia.**—Secondary anaemia with basophil punctation (stippling) of the red cells is characteristic. It is usually mild, and it is rare to find less than 3 million red



cells per c.mm. Because of the loss of circulating red cells there is compensatory regeneration of erythrocytes, with a high reticulocyte count.

*Encephalopathy.*—Most of the ancient writers speak of the frequent occurrence of convulsions in lead poisoning, but fortunately with the improvement of industrial conditions the incidence of lead encephalopathy has progressively decreased until to-day cases are rarely seen. It is the most dramatic manifestation of lead poisoning, and is always of serious prognostic significance. In severe cases of plumbism the patient is dull, with poor memory and inability to concentrate. The onset of encephalopathy is nevertheless sudden, usually with epileptiform convulsions. It may be divided into three groups—convulsive, comatose and delirious. The lymphocyte count in the cerebrospinal fluid may reach 100 per c.mm.

*The lead line.*—The lead line consists of fine granules of pigment arranged in the form of a dark blue stippled line within the tissues of the gum about a millimetre from the border of the teeth. It is more marked round infected or dirty teeth, and is occasionally found on the mucosa of the cheek opposite such teeth. Despite the pigment lying within the tissues, careful cleansing of the mouth and teeth often causes it to disappear. Its clinical significance should be clearly recognised. It is an indication of absorption and not of intoxication. Its intensity and size provide a rough guide to the duration and severity of exposure to lead.

*Coproporphyrinuria.*—In chronic plumbism the urine contains large amounts of coproporphyrin III. This is probably newly formed as the result of the action of lead and is not a product of hæmoglobin breakdown. Although coproporphyrinuria is found in conditions other than lead poisoning, it is much more marked in plumbism than in other disorders and is often found before basophilic stippling is demonstrable.

*Chronic nephritis.*—In Queensland in 1933 Nye studied a series of 34 patients with nephritis who had suffered from lead palsy in childhood. Inquiry showed that they had all spent their childhood in wooden houses; 30 were nail-biters or thumb-suckers, all but 7 had albuminuria and 29 had well-established renal insufficiency. Some had renal dwarfism, hypertension, marked urea retention and low urinary concentration. The death-rate was correspondingly high. In adults it seems that ischæmic nephritis may occur after prolonged exposure to lead dust or fume but that it is unusual.

*Diagnosis.*—Opinions differ widely as to what is necessary for the diagnosis of lead poisoning. Constipation and slight stippling of red cells are insufficient; neither a blue line on the gums nor detection of lead in the urine can be taken as proof of poisoning, for the patient may be insusceptible. Where a worker is exposed to risk, a diagnosis of lead poisoning can be made before the occurrence of a toxic crisis. A falling hæmoglobin percentage, with or without a rising punctate basophile count, raises a suspicion that absorption is passing into poisoning. The suspicion becomes a certainty when these changes are marked or progressive. The urine should be collected for at least 3 days and examined for lead. There is a danger of wrongly attributing to lead poisoning any symptoms which may occur in persons exposed to lead. Acute appendicitis, chronic gastric or duodenal ulcer, and carcinoma of the stomach occur in lead workers as they do in others. They must be carefully differentiated from colic. Equally a lead worker can suffer from pernicious anæmia or secondary anæmia due to piles, melæna or hæmatemesis. It is important to remember that lead poisoning has to be severe before the red cell count drops below 3 million. In industrial cases the blue line is unlikely to give rise to confusion. A similar phenomenon is commonly seen in patients under treatment with bismuth preparations given intramuscularly. The differential diagnosis of lead palsy should give rise to no difficulty, especially as the changes are entirely motor. In a case of peripheral neuritis in which there are motor, sensory and pigmentary changes, the possibility of arsenic poisoning must be considered. Litigation hysteria is all too common

in the lead worker. The manifestations include hysterical spasm of the hand and arm, weakness of various movements, including the flexors of the wrists and fingers, *glove and stocking anæsthesia*, *complete hemi-anæsthesia* and hysterical aphonia. Such symptoms are rarely alleviated until legal proceedings are completed.

**Treatment.**—**PROPHYLACTIC.**—The treatment of chronic lead poisoning is essentially preventive. Food and drink containing organic acids should not be stored in earthenware vessels glazed with lead. Supplies of soft water for drinking purposes when delivered through lead pipes should be artificially hardened by the addition of calcium salts. Lead pipes used to convey beer or cider from the cellar to the bar engine in public houses must be lined with tin. Children's toys and cots must never be painted with lead paint. The law must restrict the sale of lead oleate and forbid the addition of litharge to snuff in order to make it heavy.

In industry less than 60 cases of lead poisoning were notified in 1950 as compared with more than 1250 in 1889. In Great Britain preventive measures are carried out with such success that the majority of cases of lead poisoning are mild. It is unusual to-day to meet with a case either of severe colic or of extensive palsy, and encephalopathy has been abolished. The most important single measure of prophylaxis is the prevention of dust and fume. In achieving this, great success has been secured from the application of the principle upon which Sir Thomas Legge always laid so much stress, namely, to apply methods entirely external to the workman—methods over which he himself can exercise no control. One such method is exhaust ventilation applied through hoods at the point of origin of dust or fume. Benches, tools, floors and walls must be spotless, often at the expense of the constant vigilance of several good foremen. No scrap lead nor dry white lead should be handles unless it has been thoroughly soaked with water from a hose. As far as possible *mechanical means*, such as cranes, rails, hoists, *covered conveyers* and *hoppers*, and automatic packing machinery must be substituted for hand carriage.

Fortunately about 50 per cent. of the white lead manufactured in Great Britain is never handled in the dry state. It is made by the *Euston process* in which lead acetate is treated with carbon dioxide, giving results much more quickly than was possible with the old Dutch stack process. The plant is completely enclosed so that the white lead is not seen from the time the pig lead enters the process until it appears as the finished product, namely ground white lead in linseed oil. Since a white-lead worker may handle in the course of a day at least as much white lead as a painter handles in a year, the value of this enclosed method will at once be realised. In the manufacture of litharge and red lead it is impracticable to use wet methods, and it is therefore necessary to use machinery designed to minimise dust. Since 1937 it has been illegal for a painter to rub down by dry methods any indoor structure previously treated with lead paint. Dust can be avoided by using a damp rubbing down process for lead painted surfaces. Waxed sandpaper which the workman dips repeatedly in a bucket of water has made this possible.

In addition to cleanliness in the workplaces, personal cleanliness is of the first importance. Cloak-rooms, washing-rooms, mess-rooms, baths, nail-brushes, towels and soap must be provided. The hands should always be washed before eating and the work-people urged to take a warm bath frequently. The bringing of food or drinks into the work-rooms should be forbidden, and so also should smoking at work. Medical examination of the workers exposed must be carried out periodically. At present there is no biological test by which to select workmen immune to the toxic effects of lead. Since they have been found unduly susceptible, it is necessary to forbid the employment of pregnant women and of all persons under 18 years of age in the potteries and other lead trades.

Any worker who develops one of the toxic effects of lead must be suspended from work without financial hardship for 3 months. At the end of this time only if it has been possible to modify the operation or condition of work, including his

were responsible for the trouble may he be allowed to return to his job. By patient insistence the works' doctor must teach the men their own responsibilities in the safety programme. The co-operation of the workmen will be forthcoming if the approach be the right one; the responsibility for procuring it lies with the doctor.

In the prevention of lead poisoning a diet of high calcium content plays its part. In lead works in Great Britain it has for many years been customary to provide the workmen free of cost with a glass of milk each morning. This is empirical treatment of considerable merit, anticipating as it did by many years the discovery that a high calcium intake assists the storage of lead in a harmless form in the bones. Workers should, in addition, take aperients regularly.

**CURATIVE.**—Treatment which aims at the cure or amelioration of lead poisoning should never be made the excuse for negligence in enforcing all the known measures for the prevention of exposure and absorption. Aub and his collaborators showed in 1925 that a high calcium intake causes lead excretion rapidly to diminish. It follows that a high calcium diet is useful in treatment. In mild cases of lead poisoning a diet containing 2 pints of milk a day or a daily dose of 10 g. of calcium lactate is all that is necessary to store lead in the bones so that it will not be free in the circulation to cause harm. In cases of lead poisoning showing toxic symptoms the diet should contain 3 pints of milk daily and include milk puddings, junket and ice cream, together with butter, cheese and eggs. Large quantities of calcium lactate, 5 g. (gr. 75) three times a day, should be given. In the presence of acute symptoms no attempt should be made to increase the elimination of lead; so much is already circulating that it is safer to encourage further storage.

**Methods used to increase the excretion of lead.**—The ideal method to increase the excretion of lead from the tissues is still being sought. In more than a hundred years many nations have contributed to this problem. In 1844 France gave us potassium iodide, then the United States of America gave us first the use of acid salts with a low calcium diet (1925) and then sodium citrate (1943), and finally Switzerland gave us the use of versene compounds (1948).

(i) *Potassium iodide.*—Potassium iodide was first used in the treatment of lead poisoning in 1844. The dose should be increased from gr. 5 three times a day to gr. 15 three times a day. Its physiological effectiveness appears to diminish progressively after the first few days of treatment. It has been known to precipitate an acute attack of lead poisoning in an apparently healthy subject as long as 16 years after exposure to lead has ceased.

(ii) *Ammonium chloride with a low calcium diet.*—A few weeks after the acute toxic episodes have passed, the elimination of lead may be accelerated by the use of a low calcium diet, together with ammonium chloride to facilitate the release of lead from the bones. All milk, milk products, green vegetables and eggs are omitted from the diet, which may, however, contain meat, liver, chicken, potato, peas, rice, tomato, banana, apple, lemon, tea, coffee, sugar, honey, salt and pepper. In those places where the water supply is hard, vegetables should be cooked in distilled water and all drinks made up with it. Ammonium chloride is administered cautiously in doses of 1 g. (gr. 15) given in a glass of water eight or ten times daily for 3 weeks at a time. The dose should be reduced if loss of appetite and headache appear, for these symptoms indicate the limit of tolerance to such treatment. Since it would doubtless require several years, it is useless to attempt the elimination of all the lead stored in the body. It is desirable to eliminate only the most readily mobilised lead. Thus, after 3 weeks' treatment by a low calcium diet and ammonium chloride, there should be a rest period of a week with normal diet and abundance of milk to correct the calcium deficiency. Treatment to accelerate elimination should then begin again. Neither ammonium chloride nor potassium iodide should be used in the presence of nephritis or of toxic symptoms. Should any toxic episode appear during the use of ammonium

chloride or potassium iodide, these drugs must be stopped and a high calcium diet at once used to favour the storage of lead.

(iii) *Sodium citrate*.—Because all previous methods used to eliminate lead from the body involved the risk of making the symptoms worse, attempts were made to render the mobilised lead harmless by converting it into a more complex chemical substance. Since in dilute solutions sodium citrate dissolves tertiary lead phosphate, and since the soluble complex of lead citrate so formed has an extremely low dissociation constant it was suggested that this might prove to be a safe and effective way to rid the body of lead. Favourable results from treatment by sodium citrate were reported but better methods have since been devised.

(iv) *Calcium di-sodium versenate*.—In 1948 it was shown that sodium ethylenediamine tetra-acetate (sodium E.D.T.A.; sodium versenate) is a powerful chelating agent having a strong affinity for calcium and heavy metals. This property has been utilised in the treatment of acute and chronic lead poisoning. When calcium di-sodium E.D.T.A. (calcium E.D.T.A.; calcium versenate) is administered parenterally the lead displaces the calcium and the resulting lead chelate is excreted by the kidney. Not only is the rate of excretion of the metal thus increased, but the circulating un-ionised chelate is much less toxic than would be a similar quantity of ionised metal. Four to eight daily intravenous injections of 3 g. of calcium E.D.T.A. in 600 ml. of 5 per cent. dextrose in distilled water are given over a 2-hour period. Striking increases in the urinary excretion of lead as high as 13 mg. per day occur, and the urinary coproporphyrin level falls. Excessive dosage must be avoided. Calcium E.D.T.A. may be lethal in animals. Patients treated with large doses of sodium E.D.T.A. have died from renal tubular necrosis.

*Treatment of colic*.—Treatment with a high calcium diet almost invariably brings relief within 2 days. The relief of lead colic by calcium therapy involves more than the ability of calcium to favour storage of lead. Since the pain is due to violent peristalsis behind a contracted tonic ring of intestine, the antispasmodic effect of calcium salts on involuntary muscle is beneficial. In severe cases it is possible, by the slow intravenous injection of 15 ml. of a 20 per cent. solution of calcium gluconate, or of 10 ml. of a 5 per cent. solution of calcium chloride, to relieve the pain by the time the injection is over. The patient feels hot and flushed and may vomit. If necessary, the injection may be repeated in 2 hours. Should such treatment not be available, a hypodermic injection of atropine sulphate gr.  $\frac{1}{80}$  may be given. *Enemata* of olive oil and mild aperients may be used.

*Treatment of palsy*.—During the development of lead palsy a high calcium diet should be used to favour the storage of lead. Massage and electrical treatment are also useful. In the early stages the hands, when affected by wrist-drop, should be supported on splints.

*Treatment of encephalopathy*.—Lead encephalopathy should be treated by lumbar puncture and a high calcium diet. Of 6 cases observed in the United States of America, 3 occurred before this treatment was in use and all died. The other 3 were given large quantities of milk and calcium lactate and promptly recovered. The control of encephalopathy by the use of calcium E.D.T.A. in children who had ingested lead paint from toys shows promising results (1954).

### 3 TETRA-ETHYL LEAD POISONING

*Ætiology*.—Tetra-ethyl lead is an organic, lipid-soluble compound readily absorbed through the skin and respiratory tract. It is a clear, heavy, oily liquid with a peculiar sweetish odour, and is somewhat volatile at ordinary temperatures. It is added to petrol in proportions up to 1 in 1260 as an antidetonant. Twelve per cent. of the annual consumption of refined lead is used in its manufacture. In 1923, when it was first manufactured in the United States of America, 149 cases of encephalo-

pathy occurred in men employed on three separate plants. Within 17 months 11 deaths were reported. Much excitement and alarm were caused and this led at first to the prohibition of the manufacture. In the War of 1939-1945 a new hazard arose in the process of cleaning storage tanks which had held ethyl petrol. In England some of these tanks were underground and were of 4000 tons capacity. Twenty-five cases of poisoning by tetra-ethyl lead occurred, 2 of them fatal. War conditions in countries of the Middle East and Far East made the cleaning of tanks difficult to supervise, and there were 200 cases of poisoning with 40 deaths.

**Symptoms.**—The early symptoms include insomnia, loss of weight, anorexia and morning nausea but there is no colic. Mental manifestations dominate the clinical picture, and in severe cases restlessness, bad dreams, hallucinations and delusions are common. Several symptom-complexes have been distinguished—the delicious, manic, confused and schizophrenic. Weakness, tremor, muscular pains and ease of fatigue are frequent complaints. The tremors affect the extremities, lips and tongue, and are coarse and jerky, and aggravated both by effort and by attempts at control. With severe exposure there may be the abrupt onset of acute maniacal symptoms with suicidal tendencies or the occurrence of a convulsion. Less severe cases begin with insomnia, sleep being difficult, broken and restless, sometimes with wild and terrifying dreams. By day, mental excitement may be marked, headache is usual and often severe, and vertigo is frequent. Blurred vision and diplopia owing to weakness of the extrinsic ocular muscles are occasional complaints. Evidences of meningeal irritation are absent; the cerebrospinal fluid may at times be under increased pressure, but it is not otherwise abnormal. Punctate basophilia is absent or slight. In the patients who recover, all symptoms disappear in from 6 to 10 weeks. Occasionally an anxiety state persists for a time.

**Treatment.**—(a) SYMPTOMATIC.—The sedative action of repeated doses of barbiturates together with adequate fluid intake are the essentials in treatment. Morphine is contra-indicated. Glucose, 5 per cent. in saline, may be given intravenously up to 3 litres a day, and if it is given as a drip, hexobarbitone may be added. In severe cases from 2 to 4 g. of magnesium sulphate in 2 per cent. aqueous solution should be given intravenously accompanied by doses of pentobarbitone sodium up to gr. 15 daily by mouth. Enemata of 6 oz. of a saturated solution of magnesium sulphate often have a sedative effect when they can be retained.

(b) PREVENTIVE.—By meticulous attention to detail, it is possible to manufacture tetra-ethyl lead and to blend it with petrol without risk to the workers. Both manufacture and blending are carried out in closed systems. Elaborate precautions are taken in transport, storage and handling of the fluid, and great care is exercised to avoid leakage or spilling. In blending and laboratory work impervious gloves and respirators are used. Strict regulations must be laid down for the cleaning of tanks which have contained leaded petrol. Those responsible should make it quite clear that such work is never to begin without reference to some authorised person. This makes it possible to do the work under supervision and to use trained workmen properly equipped with protective clothing. Although ethyl-petrol contains less than one part in a thousand of tetra-ethyl lead it should not be used for cleansing the skin nor for dry cleaning, and to prevent this it is coloured by a dye. While decarbonising engines which have burned leaded petrols, mechanics must wear dust masks. Routine medical examinations of workmen and technicians should be carried out wherever possible.

## ARSENICAL POISONING

Arsenic is the most important of the irritant poisons, and owing to the almost tasteless property of many of its compounds and preparations it is one of the commonest poisons used for homicidal purposes. At one time it had a reputation as a

cosmetic, and was added to face powders and skin lotions. It is practically never used now for such purposes.

**Occurrence.**—*White arsenic*, arsenious acid, or arsenious anhydride,  $As_2O_3$ , is the most important of the compounds of arsenic. It occurs in the form of a white powder, or in lumps like glass or porcelain *vitreous arsenic*. The powdered form resembles powdered sugar or flour, and when mixed with food is tasteless. It is slightly soluble in cold water, an ounce of cold water dissolving from gr.  $\frac{1}{2}$  to 1. In boiling water it is twelve times more soluble, from gr. 6 to 12 dissolving in an ounce. Alkaline solutions readily dissolve arsenic. If white arsenic is sold to the public the law requires that it should be mixed with soot or indigo to colour it. It is used in the composition of sheep dip, arsenical soap and rat poison.

*Metallic arsenic* is a black powder. It is very poisonous, and is used for killing flies. *Copper arsenite* (Scheele's green) is bright green in colour, and used to be employed for colouring wall-paper, toys, floorcloths and fabrics. Its use for such purposes has fortunately been abolished. *Arsenious sulphide*, or orpiment, is a yellow powder known as king's yellow. *Arsenic acid*, in the form of its potassium and sodium salts, which are white, crystalline and soluble in water, is used as a fly poison. *Sodium arsenite*, in the form of solutions of arsenic in caustic soda, or in sodium carbonate, is commonly used for the preparation of fly-papers, weed-killer, preservative for wood and arsenical sprays for fruit trees. Some of these preparations contain from 20 to 40 per cent. of arsenic in solution, and are intensely poisonous.

**Arsenic in food.**—Accidental contamination of food with arsenic, or its preparations, such as weed-killer, has occurred. Arsenical pigments have been used for colouring sweets and cakes, with fatal result. A serious outbreak occurred in 1900, owing to the contamination of commercial glucose by arsenic. Sulphuric acid prepared from pyrites and containing a considerable amount of arsenic had been used in the process of the conversion of starch into commercial glucose, so that the latter became impregnated with arsenic. The use of the glucose in the manufacture of beer led to the outbreak of arsenical beer poisoning which occurred in Manchester. A Royal Commission investigated the cause of this epidemic, and made safeguards against the further occurrence of such poisoning. Limits of the amount of arsenic permitted in food-stuffs were fixed at  $\frac{1}{100}$  gr. per gallon for liquids and per pound for solids.

*Arseniuretted hydrogen*, or *arsine*, is a poisonous gas occurring as a by-product in industry. *Dimethylarsine* is a poisonous gas produced by the action of moulds upon certain compounds of arsenic. Other *aliphatic arsines* and also *aromatic and heterocyclic arsines* have been handled in studies directed to chemical warfare. The *arsenobenzene* derivatives which are used in the treatment of syphilis and other diseases, may give rise to poisoning.

**Pathology.**—Arsenic compounds poison the enzyme system responsible for the oxidation of pyruvic acid in the intermediary metabolism of carbohydrates in tissue cells. It is known that the pyruvate oxidase system contains a component sensitive to very small concentrations of arsenite. In 1909 Ehrlich showed that arsenic compounds had a strong affinity for sulphydryl groups, and his work led to the observation that when such substances combined with tissue proteins the active sulphydryl group of the latter spontaneously disappeared. In 1943 Peters showed that when Lewisite reacted with keratin, approximately 75 per cent. of the bound arsenic was in combination with two thiol groups. He then found that simple 1, 2-dithiols are capable both of exerting an antidotal action against the poisoning of the pyruvate oxidase system by trivalent arsenic compounds and of reversing this poisoning when once established. This work was the origin of dimercaprol (B.A.L., British Anti-Lewisite).

**Varieties.**—The varieties of arsenical poisoning are—(1) acute, (2) chronic, (3) arseniuretted hydrogen poisoning, (4) poisoning by organic arsines and (5) poisoning by arsenobenzene derivatives (see p. 229).

## 1. ACUTE ARSENICAL POISONING

**Pathology.**—The stomach contents usually contain much mucus, which may be blood-stained. The signs of gastro-intestinal inflammation are present. The mucous membrane is swollen, red and congested, and petechiæ are usually well marked. The redness is most marked on the summits of the rugæ. When the arsenic has been taken in solid form, white or pigmented particles may be seen on the mucous membrane of the stomach. The duodenum is red and congested, and petechiæ may be present; there is usually marked yellow staining, due to altered bile. The small intestine may show similar signs to the duodenum, but these diminish on passing downwards. The liver, kidney and other organs may show cloudy swelling. In fatal cases the arsenic absorbed into the tissues has a preservative action, and tends to delay putrefaction.

**Symptoms.**—When the poison is taken by the mouth, if diluted well or mixed with food, no taste or pain in the mouth or throat is experienced. The symptoms begin within an hour if the stomach is empty; but may be delayed if the stomach is full, and if the poison is in the solid state there will be further delay. A burning pain occurs in the epigastric region, and nausea and vomiting usually follow. The vomit will contain any food present in the stomach, and there is often much mucus. Bile is usually present, and sometimes streaks of blood. As the poison is passed on to the intestine, abdominal pain, of a griping or colicky type, and usually diarrhœa occur. The stools are watery, and may contain flakes of mucus. The continued vomiting and diarrhœa cause exhaustion, faintness and collapse. Cramps in the legs may occur, but are not a constant symptom. In a severe case restlessness, stupor and coma develop, and death follows shortly. Death in an acute case may occur within 24 hours, or may be delayed for 3 days or more. When several repeated doses are taken, so that the symptoms are protracted over several days, some of the symptoms of chronic arsenical poisoning may develop.

**Fatal dose.**—Grains 2 of arsenic have caused death in an adult, and this is accepted as a possible fatal dose.

**Treatment.**—The stomach should be washed out by copious lavage. In severe cases injections of 3 mg. of dimercaprol (B.A.L.) per kilogram of body-weight (200 mg. for an average adult) should be given every 4 hours for the first 2 days, followed by less frequent injections for 10 days. This treatment may give rise to nausea, vomiting, salivation, lacrimation and feelings of burning and constriction in the throat and chest. Pain is relieved by the hypodermic injection of morphine. Demulcent drinks such as olive oil, liquid paraffin, kaolin or egg albumen should be given.

## 2. CHRONIC ARSENICAL POISONING

**Symptoms.**—The gastro-intestinal symptoms—nausea, abdominal pain, vomiting and diarrhœa—are not prominent, and may even be absent. General malaise, anorexia and anæmia are usually present. If taken medicinally, or otherwise, over a long period, arsenic produces a finely mottled general brownish pigmentation of the skin—*raindrop pigmentation*. It affects principally the covered parts. The mucous membranes are not involved. Thickening of the epidermis of the soles and palms, and irregular thickening of the nails are present in long-standing cases. Squamous carcinoma of the skin of the palms of the hands may follow. In some cases salivation is a marked feature, paroxysmal attacks of excessive secretion of saliva occurring. Erythema, herpes zoster, pigmentation of the skin or erythromelalgia, are commonly to be noted. Symptoms of multiple neuritis are likely to develop, and these affect both the upper and lower extremities.

Long-continued poisoning causes anæmia, peripheral neuritis, progressive wasting and weakness, death resulting from exhaustion and cardiac failure, ascites and general

œdema occurring towards the end. Where the salts of arsenic settle in the skin of the workman in industry multiple neuritis does not occur. There is pharyngitis, laryngitis with husky voice and conjunctivitis with redness and swelling of the eyelids. Hyperkeratosis with multiple papillomata and even multiple carcinomata of the skin may occur. Often there is perforation of the nasal septum which is symptomless unless carcinoma supervenes.

The urine, fæces, the distal portions of the hair and the nails contain arsenic, its detection serving to confirm the diagnosis during life. The tests for arsenic will be found in works on toxicology. It must be remembered that in cases of suspected arsenical poisoning the diagnosis can always be made with certainty by an analysis of the urine, vomit and fæces, and these should always be taken for examination, the tests being made by an expert toxicologist. It is important to remember that acute arsenical poisoning, where a large dose is taken, may (if the patient recovers from the acute attack) be followed by symptoms of chronic arsenical poisoning. Severe peripheral neuritis may follow acute poisoning from a single dose of arsenic.

**Treatment.**—This consists in the prevention of the further absorption of arsenic. Dimercaprol (B.A.L.) injections usually have little effect. In the prevention of arsenical poisoning in industry dust must be suppressed. Workrooms should be well ventilated, and in all processes in which arsenical dust is likely to arise tables should be provided with downward exhaust ventilation. The wearing of respirators favours sweating and consequent ulceration of the skin. Instead the workmen must wear air-line helmets as well as gloves and washable suits. The floors of workrooms should be of impermeable material, and they should be frequently flushed with water. Neither food nor drink should be taken to the workroom and smoking should be prohibited.

### 3. ARSENIURETTED HYDROGEN POISONING

**Ætiology.**—Arseniuretted hydrogen is a poisonous gas which is not manufactured in industry but is evolved as an accidental by-product in certain processes. The majority of cases have been due to the use of acids and metals contaminated with arsenic. The occupations concerned are the extraction of mineral ores, pickling and galvanising of metals, cleaning of acid tanks, the manufacture of hydrogen and its use in ballooning, and the making and charging of accumulators. Poisoning may arise from the action of water upon metallic arsenides. Cases have also occurred when ferrosilicon, a substance used for hardening steel, has come in contact with water, when a mixture of arseniuretted and phosphoretted hydrogen is evolved.

**Pathology.**—The gas is inhaled and acts at once by hæmolysing the red cells within the vessels. Hæmolytic jaundice and anæmia follow. Death may occur from anuria if the renal tubules become affected. Degenerative changes in the cells of the liver and kidneys, and numerous petechiæ on the mucous and serous membranes, are to be noted.

**Symptoms.**—Malaise, headache, dizziness, shivering and hæmoglobinuria occur within a few hours. Within 24 hours there is nausea, vomiting and jaundice, and by the third day anæmia in which the red cell count may fall below 1,000,000 per c.mm. Delirium, stupor and coma precede death.

**Diagnosis.**—Mild cases are often mistaken for food poisoning. The sudden onset of hæmoglobinuria and jaundice at once suggests inquiry into a man's occupation.

**Prognosis.**—Mild cases quickly recover. The mortality rate is 30 per cent.

**Treatment.**—Workshops should be adequately ventilated and processes known to be risky should be forbidden in confined spaces. Sometimes a breathing apparatus suitable for use in irrespirable atmospheres must be employed. Such an apparatus consists of an oro-nasal mask with tube connection to the outer atmosphere. The wearer draws fresh air through the tube by his inspiratory efforts and expels the expired air through a valve in the mask.



## 4. POISONING BY ORGANIC ARSINES

The organic derivatives of arsine can be divided into three groups as follows:

(a) *Aliphatic Arsines*

*Dimethylarsine*.—The use of Scheele's green (cupric arsenite) in the preparation of artificial flowers and wall-papers has now only historical interest, because aniline colours have almost entirely taken the place of arsenic in these processes. The mould *Penicillium brevicaulis* growing in the paste behind wall-papers in damp rooms liberated dimethylarsine. The same process may occur in damp houses where coke breeze containing arsenic forms a constituent of the plaster on the walls. The use of concrete blocks containing this substance and the deliberate addition of arsenious oxide to cements to increase their rates of hardening are clearly undesirable. The symptoms of poisoning are coryza, conjunctivitis, gastro-enteritis and tinglings in the extremities. Some cases are fatal. Treatment is preventive.

*Chlorovinyl dichlorarsine (Lewisite)* is a colourless liquid with a faint odour recalling that of geraniums. It is a very powerful war gas having vesicant, lacrimatory and lung irritant effects. It is neutralised by water and alkalis.

(b) *Aromatic Arsines*

*Phenyl dichlorarsine* is used as a solvent for other war gases. Its aggressive action as a lung irritant is provoked by finely divided, solid particles which on liberation into the air form highly lethal smokes.

(c) *Heterocyclic Arsines*

*Phenarsazine chloride (Adamsite)* is a yellow, crystalline solid almost insoluble in water. Used as a toxic smoke it is a powerful war gas having vesicant, lung irritant and sternutatory effects.

**Treatment.**—Where a research chemist, workman, soldier at practice or victim of war is splashed with one of the arsenical blistering compounds he should be kept warm and put to bed in uncontaminated clothing. Where the skin has been contaminated, an ointment containing 5 per cent. dimercaprol (B.A.L.) should be applied, using 500 mg. of dimercaprol daily until healing is complete. Should the vapour or smoke have caused the lung irritant effect the administration of oxygen and injections of atropine may be required.

## PHOSPHORUS POISONING

## 1. ACUTE PHOSPHORUS POISONING

Of the allotropes of phosphorus two are important, the yellow and the red. Yellow phosphorus is rapidly oxidised in the air and must be kept under water, whereas red phosphorus is stable and has no poisonous properties.

**Ætiology.**—Poisoning by yellow phosphorus has become much less common because matches containing this substance are no longer made. Yellow phosphorus is still available to the public in the form of rat poisons, such as *rodine*, which contain the phosphorus in an oily suspension, thus preventing oxidation, so that it will keep for a considerable time. Rat poisons containing phosphorus can readily be recognised by the characteristic odour of the element. As little as gr. 2 can be a lethal dose.

**Pathology.**—The appearances at necropsy vary according to the time of survival, which depends on the dose taken and the amount absorbed. When death occurs within 24 hours the œsophagus, stomach, duodenum and a variable length of the small intestine show inflammatory reddening and usually petechial hæmorrhages. The mucous membrane of the stomach may be luminous in the dark. A garlic-like odour may be noticed and in severe cases this may be detected in the organs generally. There is intense fatty degeneration in the heart, kidneys, skeletal muscles and liver,

which is greatly increased in size. When death is delayed beyond 10 days the liver is small because of acute red and yellow necrosis, the so-called acute yellow atrophy.

**Symptoms.**—The clinical picture is divided into two periods with an interval of remission of symptoms. Usually 2 to 8 hours elapse between taking the poison and the onset of symptoms of the first stage. At the time the poison is taken a definite taste is noticed, with a sense of warmth in the mouth and throat. Then follow nausea, vomiting, burning abdominal pain, thirst, headache, subnormal temperature and a feeble pulse. Later there may be purging, but this is not constant. The abdomen becomes distended, and the patient is restless and exhausted. The vomit, which may contain blood, is sometimes luminous when examined in the dark. Rarely, delirium and convulsions occur followed by death. More often after 24 hours the condition improves. The period of remission may last as long as 6 days.

The symptoms of the second stage are jaundice, epigastric pain, vomiting and diarrhoea, sometimes with the passage of blood. There may be bleeding, especially epistaxis and menorrhagia, with hypoprothrombinæmia. On examination there may be purpura of the skin, the abdomen is distended and the liver enlarged and tender. Fever may be present at first but is variable. The pulse is normal and later becomes rapid, feeble and irregular. The urine is scanty and contains bile and often albumin and blood. The serum albumin falls and the globulin rises. The thymol turbidity and cephalin flocculation tests may be positive.

**Prognosis.**—Death takes place in 2 to 12 days, with an average of about 6 days. The liver is probably always enlarged at first, and, should the patient die in a short time, this enlargement will be confirmed at necropsy. On the other hand, if the patient lives for a week to 10 days, the liver will be small and death will occur in hepatic coma.

**Treatment.**—If the patient is seen within the first 36 hours active measures should be taken to remove the poison from the stomach and intestines as rapidly as possible. Gastric lavage with large quantities of potassium permanganate solution, 1 in 500, should be performed and repeated a few hours later. Active purgation should be carried out, oily purgatives being avoided, and at the same time a high colon wash should be given. If the apparatus to perform gastric lavage is not to hand emetic doses of gr. 10 to 15 of copper sulphate may be used. Should potassium permanganate be unobtainable other oxidising agents, such as solution of hydrogen peroxide (1 to 3 per cent.), may be used. During the next few days oils and fats must be excluded from the diet. When jaundice has begun there is but little to be done, the treatment being symptomatic only.

## 2. CHRONIC PHOSPHORUS POISONING

**Synonym.**—Phossy Jaw.

**Definition.**—A chronic disease characterised by necrosis of the mandible or superior maxilla with secondary osteomyelitis. Involvement of the long bones sometimes led to multiple spontaneous fractures.

**Ætiology.**—Although yellow phosphorus is no longer used in the manufacture of matches, it is made on a large scale for military purposes. Compounds of phosphorus are necessary in brewing, in food processing and for use as fertilisers. In paper-making, printing and the manufacture of baking powders, cellulose, dyes and soaps, phosphorus compounds are used in one form or another. The metaphosphates are of importance in water-softening, in the manufacture of detergents and in the processing of fibre. Organic phosphorus compounds are used as plasticisers and insecticides.

Matches made with yellow phosphorus were first manufactured in 1832 and within 15 years phosphorus necrosis of the jaw was identified in match factories in almost every civilised country. The poisoning was slow to occur, the average time of

onset after the man was first exposed being 5 years. Less than 5 per cent. of those exposed acquired the disease. Some extremely susceptible patients were found, who succumbed to the effects of the poison within a few months.

**Symptoms.**—The first symptom was toothache usually in a carious tooth. A dull red spot on the buccal mucosa was the first sign of phosphorus necrosis of the jaw. At a later stage it was common to find a sinus, surrounded by dull red mucosa, leading to a cavity beneath. Sequestra up to 1 cm. in diameter were found. Later the pain increased in severity and swelling of the gum and jaw appeared. Suppuration occurred spontaneously or, more commonly, after dental extraction. If the worker returned to work too soon, and was again exposed to phosphorus, the inflammation spread rapidly. Chronic abscesses were then formed, and sequestra continued to separate over many years, sometimes involving the whole jaw. It was very painful, and was accompanied by a fetid discharge which made its victims almost unendurable to others.

**Prognosis.**—The disease was obstinate and chronic, the treatment was agonising and the final result was a distressing disfigurement. Sometimes extension of the suppuration to the orbit or meninges caused death, but more often this was brought about by septicæmia. The mortality rate was about 20 per cent.

**Treatment.**—**PROPHYLACTIC.**—Abolition came in 1906 when all the important countries of Europe agreed by the Berne Convention to forbid the manufacture and import of yellow phosphorus matches. Since 1855 the allotrope, red amorphous phosphorus has been used as the inflaming ingredient on the outside edges of boxes of safety matches. In the hundred years which have elapsed since that time, red phosphorus has never produced phossy jaw or, indeed, any other harmful effect on the worker. Since 1900 in all countries the harmless phosphorus sesquisulphide has been used in the inflaming composition forming the heads of strike-anywhere matches and no harm has ever come to the worker who handles it. Although the use of yellow phosphorus is prohibited in the manufacture of fireworks, it is still used in making smoke screens, incendiary bombs and hand-grenades, as a constituent of rat poison and in the manufacture of phosphor-bronze.

**CURATIVE.**—Successful supervision of the worker handling yellow phosphorus demands examination of the teeth and jaws at regular intervals. A dental clinic with radiographic equipment and the services of dental surgeons is essential. Employees must be carefully selected. Not only must they have good general health, but also their teeth must be normal both clinically and radiologically. Radiographic examination of both jaws should be made before work begins and it must be repeated annually. The radiographs must be searched in detail for areas of decalcification indicating caries of bone. This is of special importance between the third to fifth years of employment. Records must be kept of all those exposed to the hazard, and it should be known which workers have been excluded permanently or temporarily from exposure.

When a sequestrum is found and removed, rapid and complete recovery follows. The dreadful sequelæ of the neglected disease need never occur. Indeed, in Great Britain, during the War of 1939–1945, when the amount of yellow phosphorus manufactured for use in incendiary warfare exceeded all previous records, no case of phossy jaw developed.

### 3. POISONING BY TRI-ORTHO-CRESYL PHOSPHATE

**Ætiology.**—Poisoning with tri-ortho-cresyl phosphate (T.O.C.P.) first occurred among patients with pulmonary tuberculosis who were treated with phospho-creosote. The condition became well known because of an outbreak of polyneuritis, in 1930, in the United States of America among individuals who had partaken of a beverage known as *Jamaica ginger* or *jake*. Nobody knows why the drink was contaminated

by this chemical substance. In 1931 poisoning occurred in Holland in women who had taken apiol as an abortifacient. In many parts of the world people have been affected because they have eaten food accidentally contaminated. T.O.C.P. is manufactured for use as a plasticiser in the plastics industry. The first cases resulting from exposure in an industrial occupation occurred in 1944 and since then relatively few cases have been seen.

**Pathology.**—The poison inhibits the action of pseudo-cholinesterase—an enzyme present in the blood serum, the peripheral nerves and the white matter of the spinal cord, and distinct from the true cholinesterase which is present at the motor end-plates and in the red blood cells.

**Symptoms.**—The clinical picture develops by three stages. (1) In some cases there are transient gastro-intestinal symptoms, including nausea, vomiting, diarrhoea and abdominal pain. These often clear up, and a symptom-free interval follows, lasting from 5 to 21 days, the average being 10 days. (2) This interval is followed by soreness of the muscles below the knees and numbness of the toes and fingers, lasting for several days and followed by weakness of the toes and bilateral foot-drop. (3) After another interval of about 10 days, weakness of the fingers and wrist-drop follow. This paralysis is not usually so severe as that in the feet and legs. In the upper extremities paralysis does not extend above the elbows. The thigh muscles may be involved in advanced cases. Loss of sphincter control is unusual. In severely poisoned patients, in addition to the peripheral motor nerves, the anterior horn cells, the pyramidal tracts and the spino-cerebellar tracts may be involved. Extreme muscular wasting tends to dominate the clinical picture in the early stage. When muscular activity is partially restored, the spastic signs of the previously hidden upper-motor-neurone lesion become apparent. In such cases the end-result resembles amyotrophic lateral sclerosis.

**Prognosis.**—Improvement may be slow to the point of exasperation but it often exceeds expectations. Thus a patient paralysed in both lower limbs for 18 months was able at the end of that time to walk unaided.

**Treatment.**—**PROPHYLACTIC.**—To prevent absorption through the respiratory tract, all rooms where T.O.C.P. is handled should be provided with exhaust ventilation. Tanks should be enclosed and the vents fitted with ejectors, so that the vapours may be quickly transferred to the open air. Measures must be taken to prevent skin contact. Elbow-length gloves should be worn, and workers should change into special clothing during their working hours and take a bath at the end of the work period.

**CURATIVE.**—Splints may be needed to prevent overstretching of paralysed muscles. Massage, physiotherapy and appliances such as shoes with uplifting toe-springs may be necessary.

#### 4. POISONING BY ORGANIC PHOSPHORUS INSECTICIDES

**Ætiology.**—Since 1946, organic compounds of phosphorus have been used as insecticides for the control of insect pests, such as aphids and red spider. Preparations in common use contain tetra-ethyl-pyrophosphate (T.E.P.P.), hexaethyltetraphosphate (H.E.T.P.), diethyl-*para*-nitrophenylthiophosphate (*Parathion*, E.605 f., D.P.T.F., or *Bladan*), octamethyl pyrophosphoramide (*Schradan* or O.M.P.A.) and *bis*-mono-isopropyl aminofluorophosphine oxide (*Mipafax*). Preparations include liquid sprays, dusts and wettable powders which are diluted before being applied in greenhouses, orchards and fields.

**Pathology.**—Insecticides containing organic compounds of phosphorus are poisonous to man and animals. They are related in chemical structure and physiological action to di-isopropyl-fluorophosphonate (D.F.P.), which is a powerful cholinesterase inhibitor sometimes used in the treatment of myasthenia gravis, paralytic ileus and

glaucoma. The insecticidal properties of T.E.P.P., H.E.T.P. and Parathion are similar to those of nicotine. The effects of H.E.T.P. are almost certainly due to contamination of the manufactured product by T.E.P.P. Schradan and Mipafox are systemic insecticides, that is to say they have no direct insecticidal action nor do they inhibit cholinesterase *in vitro*. They are converted in the plant or animal tissues and are effective as insecticides only against pests which eat the plants. In a single dose they are less toxic than nicotine, but the effects of absorbing small amounts of these anti-cholinesterase substances are prolonged and result in increased susceptibility to absorption of further amounts of any cholinesterase inhibitor. All types of preparations penetrate rapidly through the skin, producing only slight irritation at the site of absorption. Exposure to as little as 0.3 g. daily has been estimated as dangerous to man. The lethal dose by mouth for man is approximately 100 mg. of T.E.P.P. or Parathion, and symptoms follow the administration of more than 10 mg. Absorption may also occur from inhalation and ingestion.

**Symptoms.**—The early symptoms of poisoning are mild and non-specific and may include headache, nausea, anorexia and unusual fatigue. These may be accompanied by pin-point constriction of the pupils. The symptoms are aggravated by smoking or taking food. From 2 to 8 hours later, nausea, abdominal cramps, vomiting, diarrhoea, muscular twitching, coma, convulsions and signs of pulmonary oedema may develop. Incontinence of urine and faeces is common. Death may result in as short a time as one hour after the onset of symptoms.

About 3 weeks after recovery from the acute phase of the illness, patients may develop paralysis of the limbs similar to that which follows poisoning by tri-ortho-cresyl phosphate. Therefore, all patients who have had acute poisoning by organic phosphorus compounds should be kept under close observation until the cholinesterase activity of the blood has returned to normal.

**Treatment.**—PROPHYLACTIC.—Strict precautions are necessary to protect workers engaged in handling these insecticides. Protection is more easily arranged and applied in factories than in field operations. In factories where an organic phosphorus insecticide is made, mixed with wetting agents, or incorporated in dusts or wettable powders, exhaust ventilation should secure that this substance is absent from the atmosphere. Protective clothing must include overalls, gloves, boots, cap and underwear, which are laundered each day and changed immediately if accidentally splashed. Ordinary clothing must be protected from possible contamination. Respirators should be available in factories for use in emergency; in field operations they must be worn during dusting operations and the diluting of wettable powders. It is necessary that the workers should wash thoroughly before eating or smoking, and a bath should be taken at the end of a day's work. These instructions, together with an account of the symptoms of poisoning, must appear on the labels of containers of organic phosphorus compounds. The attention of all workers exposed to risk should be directed repeatedly to the toxic properties of these compounds.

Regulations under the Agriculture (Poisonous Substances) Act, 1952, prohibit the use of organic phosphorus compounds unless the men working with them are wearing protective clothing. The number of hours during which workers can be employed are restricted to 10 hours in any one day and 60 hours during seven days. The employment of any worker under the age of 18 is prohibited. The regulations also contain requirements about the provision and maintenance of protective clothing, the provision of washing facilities for workers, the notification of sickness and absence, the training and supervision of workers, and the keeping of registers. Unhappily, no provision is made for the estimation of the blood-cholinesterase activity at frequent intervals of people at risk.

**CURATIVE.**—Atropine is an antidote to the muscarinic and central-nervous-system effects of this form of poisoning. It should be given in doses of 1 to 2 mg. ( $\frac{1}{16}$  to  $\frac{1}{8}$  gr.) at hourly intervals until the pupils are dilated. Oxygen, under slight pressure

to overcome bronchial spasm, should be administered at the first sign of pulmonary œdema. The fibrillary twitching of muscles appears to affect particularly the diaphragm, and artificial respiration may be necessary. Involvement of striated muscle is the result of the nicotine-like action of these compounds. No antidote to this effect is known and death may occur from neuromuscular paralysis, even though the muscarine-like effects and the signs of involvement of the central nervous system have been controlled by atropine.

## MERCURIAL POISONING

### 1. ACUTE MERCURIAL POISONING

This usually arises from the absorption of mercuric chloride, also known as corrosive sublimate ( $\text{HgCl}_2$ ), which is largely used in medicine as a disinfectant or antiseptic. Biniiodide of mercury has similar uses. Both are usually purchased in the form of tablets ready for solution in a required amount of water. Acute poisoning generally occurs from the taking of the poison by the mouth, but it may also arise from the use of mercuric compounds in solution as uterine or vaginal douches. Grains 5 of mercuric chloride is a fatal dose for an adult, unless the poison is removed by gastric lavage within an hour or two. Calomel (mercurous chloride), even if taken in large doses, does not give rise to the same degree of acute poisoning, owing to its insolubility. Cases are known in which over gr. 100 of calomel were taken with suicidal intent, and beyond some vomiting and diarrhœa, little harm resulted.

**Symptoms.**—If mercuric chloride is swallowed in tablet form there is risk of local corrosion and perforation of the stomach, with rapidly fatal result. When taken in solution, or in tablet form with water, or on a full stomach, an acrid metallic taste is experienced, followed by a sense of constriction in the throat. A hot burning sensation occurs in the mouth and œsophagus. Acute abdominal pain and vomiting take place. The vomit contains mucus and often blood. Diarrhœa and tenesmus occur. Collapse is associated with these early symptoms. The mouth and pharynx may show white swollen patches, which may be followed by sloughing. Unless the poison is quickly removed by gastric lavage dangerous sequelæ rapidly follow. The condition is always accompanied by a very severe stomatitis, which begins within a few hours. The breath is foul, the mucous membrane becomes ulcerated, the teeth may become loose and necrosis of portions of the jaw occurs.

Later effects of acute mercurial poisoning are: (1) suppression of urine due to the action of mercury on the renal epithelium causing cloudy swelling and even necrosis; and (2) ulcerative colitis, the result of extensive necrosis and sloughing of the mucosa of the colon. Suppression of urine is followed by a rapid rise in the blood urea, and after 4 or 5 days symptoms of uræmia such as vomiting, stupor, delirium, coma and convulsions appear. The ulcerative colitis begins about 24 hours after the intake of the poison, and is associated with profuse diarrhœa, and the passage of sloughs and shreds of necrotic mucous membrane and blood. The colitis may be caused by the absorption of mercury into the blood-stream apart from its direct local action on the colon. Death may occur from dehydration and exhaustion.

**Treatment.**—Immediately the patient is seen the stomach must be washed out with 4000 ml. of 5 per cent. sodium formaldehyde sulfoxylate. Without delay 300 mg. of a 10 per cent. solution of dimercaprol (B.A.L.) in benzyl benzoate and arachis oil must be injected intramuscularly. This treatment is followed within the first 12 hours by two or even three further injections each of 150 mg. of dimercaprol. Subsequently a daily injection of 150 mg. of dimercaprol is given for 2 or 3 days according to the general condition of the patient. Where there is shock with hæmo-

filled without suitable exhaust-ventilation for the removal of mercury vapour. Overalls, mess-rooms and washing facilities are provided. The mouth and pharynx are frequently rinsed with a mouth-wash, and the teeth cleaned with a soft toothbrush and a dentifrice. Periodical medical and dental examination can achieve a great deal, especially by emphasis on the proper hygiene of the mouth. Cavities in carious teeth are filled, sharp angles smoothed, and stumps and teeth irremediably decayed extracted. In the felt-hat trade the workshops must be well managed and spotlessly clean. Efficient exhaust-ventilation must be applied to remove the particles of fur and all vapours of mercury compounds at the source of origin. A workman affected by mercurial tremor must give up his work, and abstain from alcohol. Stomatitis should be treated by the use of the toothbrush, mouth washes and dental extractions when necessary. In cases of medicinal poisoning saline aperients should be given daily to promote the free elimination of mercury by the colon.

### 3. POISONING BY MERCURY FULMINATE

Mercury fulminate is handled in explosives factories where detonators and percussion caps are made. In those processes where the fine dust of this substance falls upon the skin, dermatitis follows. The susceptibility of some individuals is such that they cannot stand the dust for a day, whereas others only suffer in warm weather. As a rule, the cases of "fulminate itch", as they are called in the trade, are slight. The face, eyelids, neck and forearms are attacked by erythema, accompanied by itching, swelling and oedema. Papules break out on the inflamed areas, and may become vesicles, bullæ and pustules. A pustular folliculitis commonly develops on the hairy parts of the skin. If the fulminate lodges in a crack or abrasion of the skin it may act as a corrosive, causing small painful necrotic lesions on the hands which last about a fortnight. The operatives call them "powder holes". Recovery takes place in from 1 to 2 weeks and is accompanied by desquamation. Inflammation of the conjunctivæ and mucous membranes of the nose and larynx may occur.

In the manufacture of mercury fulminate meticulous attention should be paid to detail in all matters of cleanliness in the entire plant. Where fumes are given off as the result of small explosions they must be removed by means of mechanical ventilation. All persons employed should be provided with well-fitting overalls, caps, india-rubber gloves and, if necessary, respirators. Washing accommodation must be available close to the workroom, and a separate towel provided for each worker. The hands and arms are washed before meals and before leaving work in a 10 per cent. aqueous solution of sodium thiosulphate. A lanolin ointment is rubbed into the skin after washing. For the conjunctivitis a 2 per cent. solution of sodium thiosulphate as an eyewash has been beneficial.

### 4. POISONING BY ORGANIC MERCURY COMPOUNDS

Fungicidal dusts containing organic mercury compounds are used extensively in agriculture to prevent certain smut diseases of cereals. For some years mercurial derivatives of the phenyl and tolyl series have been manufactured without any mishap worse than an occasional burn on the skin. Poisoning by inhalation of methyl mercury compounds leads to involvement of the nervous system in a unique way, salivation, stomatitis and erethism being absent. There is severe generalised ataxia, dysarthria and a gross constriction of the fields of vision, memory and intelligence being unaffected. In severe cases the patient remains crippled, and unable to stand or to speak intelligibly. The condition has been reproduced experimentally in the rat and the monkey; here degenerative changes involved the spinal cord and peripheral nerves. In a patient who died 15 years after exposure had ceased necropsy showed

atrophy sharply localised to particular areas of the cerebellum and the occipital cortex. The spinal cord and peripheral nerves were unaffected.

In the manufacture of organic mercury compounds elaborate precautions must be taken to prevent contact with the skin or inhalation. The use of gloves and respirators is not enough. The whole process of manufacture, including the final packing of the dusts, must be carried out mechanically in closed apparatus. The farmer should be protected both by warnings that mercurial dressings are poisonous and by schemes whereby he can obtain from the merchant seed already dressed. The seed merchant must dress the seed in a completely closed apparatus. The ataxia and dysarthria of methyl mercury poisoning must be treated by re-educative movements, persuading the patient to walk on chalked lines. An expert in charge of a speech clinic with great patience and the use of a mirror should teach the workman to speak. With great perseverance in some cases he may be taught to use knife and fork, a pencil and even a typewriter.

## CHROMIUM POISONING

Chromium is a silver-white, hard, brittle metal. It is an essential component of the alloys known as stainless and rustless steels. The only commercial use of pure chromium metal is in the form of electroplate.

**Ætiology and Pathology.**—Both in the chromium plating of metals and in the anodising of aluminium, the solution used contains chromic acid. During electrolysis the evolution of hydrogen at the cathode forces into the atmosphere a reddish-brown mist which contains 60 per cent. of chromic acid. Together with dust from chromates or bichromates this mist is the principal source of exposure in industry.

**Symptoms.**—*Acute poisoning* is confined to an occasional case of chemical pneumonitis.

*Chronic poisoning* is common and affects the skin. Exposure may cause either diffuse dermatitis or localised ulceration, according to whether trauma is present or not. The dermatitis appears on the hands, face, arms and chest.

Chrome ulcers begin in abrasions of the skin, and are most commonly found at the root of the finger-nail, the knuckle of the hand or the dorsum of the foot. They are circular in shape, clear-cut, usually 1 cm. or less in diameter and look as if punched out, hence the name *chrome hole*. These ulcers have a strong tendency to heal but may penetrate even as deep as bone. Although painless, they itch intolerably at night. If neglected, an ulcer may lead to infection of the adjacent joint, causing loss of the finger. Malignant change does not occur. Ulcers on the eyelids or the edge of the nostrils may occur. Irritation of the conjunctiva may be severe. The mucosa of the nose is commonly affected with perforation of the nasal septum. The process begins with sneezing, rhinorrhœa and slight pain. Once the perforation is established, the only inconvenience is the formation of plugs of mucus in the nasal passages. At this site, again, malignant changes do not occur.

The statistical study of mortality data and hospital records suggests that the incidence of carcinoma of the lung is unusually high in men employed in the chromate-producing industry.

**Treatment.**—**PROPHYLACTIC.**—The preventive measures necessary in handling chromic acid, chromates and bichromates include the removal of dust and mist, cleanliness, regular medical supervision and the covering up of cuts and abrasions with suitable dressings. Freedom from risk in chromium plating and anodising depends on the correct design of the vats to include exhaust ventilation. It may often be necessary to provide rubber gloves, boots and an apron for a person working around the chromic acid tanks, but these are not always of great value. Fair-haired people are particularly prone to chrome dermatitis and their employment calls for



peculiar care. Weekly inspection of the nasal passages should be carried out by the factory nurse for all workers.

**CURATIVE.**—The exposed skin should be washed and carefully dried. Application of an ointment made up of equal parts of lanolin and soft paraffin is useful. Soft paraffin should be freely applied through the anterior nares to the nasal septum.

## MANGANESE POISONING

**Ætiology.**—Manganese is used in the manufacture of dry batteries and in the pottery, soap and colour industries. Cases of poisoning have followed upon the inhalation of excessive amounts of dust in the grinding, sieving and packing of manganese ores, and in the manufacture of manganese steel in which the metal is first fused in the electric furnace.

**Pathology.**—Susceptible individuals are few. There is a similarity between this form of poisoning and progressive lenticular degeneration, except that in manganese poisoning the condition remains stationary or improves when exposure to manganese dust ceases. Histological studies on necropsy material have shown degenerative lesions of the nerve cells, particularly in the globus pallidus, the lenticular nucleus and the caudate nucleus. The fact that histological lesions have been found in the liver makes still closer the connection between poisoning by manganese and progressive lenticular degeneration. The condition has been reproduced experimentally in monkeys by administering manganese chloride by intraperitoneal injection. The animals developed choreic movements, passed into a state of rigidity, and finally developed tremor resembling paralysis agitans. Gross morbid changes were found in the lenticular nucleus and liver. The experiments afford an explanation of the symptoms in most of the cases described. The extrapyramidal motor system is clearly picked out by the poison, hence the rigidity, difficult gait, retropulsion, propulsion, mask-like facies, sleepiness, tremor and uncontrollable laughter.

**Symptoms.**—The symptoms include languor and sleepiness, low monotonous voice, mask-like facies, involuntary movements varying in degree from a fine tremor of the hands to gross rhythmical movements of the arms, legs, trunk and head, cramps in the calves, retropulsion and propulsion, unsteady gait and occasionally uncontrollable laughter or crying. There is no disability except in the nervous system.

**Prognosis.**—Although men seriously poisoned are life-long cripples, the condition is not lethal.

**Treatment.**—Manganese poisoning can be prevented by wearing respirators wherever dusts or vapours are encountered. Personal hygiene is important, and the worker must wear protective clothing and gloves, since the occurrence of skin absorption is established. Local exhaust ventilation should be applied, both at the furnaces to remove fumes and at the packing and sieving apparatus to remove dust. These measures are attended with good results, for it has been found that when they were applied in one particular factory they removed all risk of poisoning encountered by the workers over a period of 6 years.

## BERYLLIUM POISONING

Beryllium is a very light, hard, shiny metal which forms important alloys. Beryllium-copper is hard, resistant to corrosion, non-rusting, non-sparking, non-magnetic, and it has great tensile strength. Metallic beryllium is employed in steel-making and in the construction of atomic piles.

**Ætiology.**—Occupations involving exposure to beryllium compounds include the extraction of the metal from the ore, the preparation of beryllium steel and the manufacture and cutting of beryllium-copper alloys. A hazard exists in preparing the

complex beryllium salts used as phosphors for coating the tubes of fluorescent strip lamps.

**Symptoms.**—Symptoms attributable to exposure to beryllium compounds can be divided into six groups, of which the first five constitute acute berylliosis and the sixth chronic berylliosis.

(i) *Conjunctivitis* is frequently associated with dermatitis of the face. On removal from contact the lesions readily heal.

(ii) *Tracheitis and bronchitis*.—Anorexia may be followed by tracheitis and bronchitis and there may be loss of weight.

(iii) *Dermatitis*.—A severe oedematous papulo-vesicular eruption may appear mainly on the exposed surfaces.

(iv) *Subcutaneous granulomata* occur when beryllium compounds are introduced beneath the skin. Such lesions may occur in persons who have cut themselves on broken fluorescent lamps. The granuloma may measure as much as 2.5 cm. in diameter.

(v) *Acute pulmonary disease*.—Cough with bloodstained sputum is accompanied by retrosternal pain, dyspnoea, cyanosis and loss of weight. Rapid respiration, anorexia and marked prostration follow. Usually there is no fever, but cyanosis and tachycardia are present, and râles are heard over both lungs. Resolution begins in the third week of the illness and is complete in from 5 weeks to 5 months. In severe cases death occurs within 2 weeks. At necropsy the lungs show alveoli filled with exudate composed of oedematous fluid and fibrin. In cases in which death has occurred after several weeks there are areas of organising pneumonia. Sometimes an attack of the acute illness is followed by the onset of chronic lung disease after 2 years.

(vi) *Chronic pulmonary disease*.—The first symptoms of chronic berylliosis may not appear for as long as 6 years after cessation of exposure. Less than 5 per cent. of all persons exposed to dusts of beryllium compounds have developed this disease. The onset is with vague ill-health followed by weakness, anorexia, cough, extreme dyspnoea and progressive loss of weight, which may be as much as 20 to 30 pounds in a month. Clubbing of the fingers develops in the later stages. Persistent tachycardia may be followed by congestive heart failure.

The earliest change in the radiograph is a diffuse finely granular appearance, homogeneously distributed throughout both lungs. Later a fine nodulation appears on a granular background and there is lobular emphysema, particularly at the apices and bases. At necropsy the lungs are emphysematous with scattered fine nodules and diffuse interstitial fibrosis. Granulomata are formed within the alveolar spaces, in the skin and subcutaneous tissues and sometimes in the hilar and axillary glands and in the liver.

**Prognosis.**—In chronic berylliosis approximately 33 per cent. of the patients die, and 33 per cent. are permanently disabled and remain in great pulmonary distress. The rest lose their symptoms, the lung changes resolving to some extent.

**Treatment.**—**PROPHYLACTIC.**—In the manufacture of fluorescent lamps, halophosphates, which contain no beryllium, must be used in place of the poisonous phosphors formerly used. Where beryllium and its compounds are handled every effort must be made by engineering methods to keep the atmosphere concentration at the lowest possible level. Protective clothing and adequate laundry services should be provided. Since subcutaneous granulomata have developed in persons who have cut themselves on broken lamps, caution must be exercised in the disposal and salvage of burnt-out fluorescent lamp tubes. Workers at risk should be seen at regular intervals by a doctor and questioned about suggestive symptoms. They should be weighed at monthly intervals, and have their chests radiographed at least once a year.

**SYMPTOMATIC.**—In severe cases oxygen should be used for the relief of dyspnoea.

**SURGICAL.**—Any granulomatous mass in the skin must be completely excised otherwise healing may be long delayed.

## CADIUM POISONING

Cadmium is resistant to corrosion and withstands wear. The metal and its alloys are therefore used in many manufacturing processes. The principal industrial hazards arise in the smelting of ores, the manufacture of alloys, the welding of cadmium-plated metal and the manufacture of alkaline accumulators.

Cadmium poisoning occurs from domestic causes—by ingestion—or from exposure in industry—by inhalation.

## 1. BY INGESTION

**Ætiology and Pathology.**—The careless use of cadmium-coated vessels as containers for food and drink may lead to acute poisoning.

**Symptoms.**—The symptoms appear suddenly within 15 minutes to 2 hours after ingestion, and everybody who has eaten the contaminated food is affected. Increased salivation, severe nausea and vomiting are the first symptoms. In severe cases there is collapse with signs of shock, and sometimes hæmatemesis. Later diarrhœa occurs, sometimes with tenesmus. Recovery usually takes place within 7 hours and is invariably complete within 24 hours.

**Treatment.**—**PROPHYLACTIC.**—Anti-rust treatment by cadmium plating of the trays of domestic refrigerators should be abandoned.

**SYMPTOMATIC.**—Beyond fluid replacement no treatment is required.

## 2. BY INHALATION

**Ætiology and Pathology.**—When cadmium is heated, copious brown fume of the oxide is evolved. This attacks the structures of the respiratory tract. In acute cadmium poisoning, necropsy shows hyperæmia of the bronchi, gastro-intestinal tract and kidneys, and in severe cases confluent broncho-pneumonia. Necropsy in cases of chronic cadmium poisoning shows chronic vesicular emphysema, toxic nephrosis and fatty degeneration of the liver.

**Symptoms.**—In *acute poisoning*, the symptoms include irritation of the eyes, headache, vertigo, nausea, dryness of the throat and cough with pain in the chest. Delayed effects may follow after an interval of a few hours, and these include shivering, sweating, nausea, epigastric pain and severe dyspnœa, which may be aggravated by the development of broncho-pneumonia. Chronic rhinitis with complete anosmia is frequently found. A *chronic disease* may occur in men exposed to small quantities of cadmium in the working atmosphere for long periods. The striking feature of this disease is severe pulmonary emphysema, giving rise to dyspnœa on exertion. Proteinuria, detected by testing the urine with 25 per cent. nitric or trichloroacetic acid occurs in a large proportion of cases. This protein is distinct from both albumin and Bence Jones protein and has a very low molecular weight. A golden-yellow ring develops on the teeth of workers after 2 or more years' exposure, and is an index of absorption of, but not of poisoning by cadmium.

**Treatment.**—**PROPHYLACTIC.**—In the smelting of cadmium ores, the welding of alloys and the firing of cadmium-plated metal, precautions should be taken to remove all fume by means of adequate exhaust ventilation. It has been suggested that all cadmium-coated metal should bear a warning label. While this measure is effective for large pieces, it is somewhat difficult to ensure that small objects so coated are labelled.

**SYMPTOMATIC.**—Symptomatic treatment is directed specifically against pneumonia when it occurs.

and toxic jaundice appear. The blood picture is that of anæmia with granular degeneration of the red cells (stippling), and sometimes the presence of nucleated red cells. In severe anæmia a blood transfusion may be considered.

### 3. DINITROBENZENE

Dinitrobenzene is used in the manufacture of dyes, and is itself an important explosive. It is a solid, and in consequence poisoning develops less rapidly and is less severe than in the case of mono-nitrobenzene. Poisoning occurs amongst men who either shovel or melt dinitrobenzene. In a mild case there is a sense of pressure in the head, which increases to a violent throbbing headache, giddiness and dyspnœa. In severe cases the face is deeply cyanosed; the lips, tongue and ears are deeply purple; and there are nausea, sometimes vomiting, abdominal pain, a staggering gait and extreme weakness. An attack rarely occurs during work; the man is usually overcome some hours after he has left the plant. Cyanosis occurs, and is accompanied by anæmia with marked stippling of the red cells. Methæmoglobin, porphyrins, hæmoglobin and even albumin have been found in the urine. The smoky colour of the urine may be noticed by the men themselves soon after their first contact with nitrobenzene or aniline. Only very rarely does toxic jaundice occur. It is well known in industry that cases of poisoning are more frequent in hot weather than during the colder seasons of the year. Lack of care and unclean habits are predisposing causes. Those who do not change their working clothes on returning home may sit before the fire and absorb the poison from the evaporation of crystals or from the material in solution on their clothing. Absorption from the alimentary canal is more rapid if the stomach is empty, and it is therefore desirable that men should take a meal before they work. Alcohol undoubtedly favours absorption, and several instances are on record in which poisoning has supervened after indulgence in ordinary amounts.

### 4. TRINITROTOLUENE

Trinitrotoluene is handled mainly in the filling of shells. The first symptoms of poisoning are drowsiness, headache, nausea, loss of appetite, epigastric pain, vomiting and giddiness. There is some cyanosis of the lips, followed by dyspnœa with marked drowsiness and staggering gait. Dermatitis in the form of a diffuse erythema sometimes occurs on the dorsal surfaces of the wrists, and on the face and neck. The symptoms come on gradually after several days' or weeks' work, or they appear on a hot day after a few hours' work and cause collapse. If cyanosis occurs in 1 in 10 of the workers, toxic jaundice probably affects 1 in 500. The greatest incidence of jaundice is in the third month of employment. Premonitory symptoms, such as drowsiness, giddiness, depression and dark urine are sometimes present, but the onset is often quite sudden. Sometimes a latent interval occurs between removal from exposure and the onset of jaundice. The prognosis is always uncertain, but grave symptoms of hepatic insufficiency sometimes appear rapidly. The mortality is 25 per cent. The morbid appearances are those of yellow and red necrosis of the liver, with great reduction in its size and weight. The necrosis of the liver cells is associated with infiltration and subsequent fibrosis resembling ordinary portal cirrhosis. Aplastic anæmia sometimes occurs among trinitrotoluene workers, but its incidence is very small. The latency of the blood changes is even longer than the latency of the jaundice, for it is found that anæmia can develop as long as 9 months after exposure to trinitrotoluene has ceased. The anæmia is usually, if not always, fatal. At necropsy fatty marrow is found throughout all bones. There is an excess of iron pigment in the liver, and multiple hæmorrhages are found in the tissues. The skin is the main channel of absorption. Experience in industry goes to show that when a poison is absorbed by this route the application of preventive measures is most difficult. The

principles involved are cleanliness of the air breathed, secured by effective ventilation or filtration through an effective respirator; cleanliness of the implements used and cleanliness of the person secured by protective clothing and by personal attention to the skin. Filling factories must have their own laundries and each worker must have two lockers, one for his own clothing and the other for his protective clothing. Workers and supervisors must be specially trained for the job. Periodical medical examination is essential.

### 5. DINITROPHENOL

Of all the dinitrophenols it is only the 2-4 or *alpha* isomer which has toxic properties. It is a pale-yellow crystalline powder, which is used as an explosive, in the dye industry, and for the preservation of timber. Absorption takes place through the respiratory tract, the alimentary canal and the skin. Heat aids absorption and alcohol increases the incidence of toxic manifestations. D.N.P. acts by stimulating the general metabolism. Workers show yellow staining of the face, legs and forearms, and especially of the palms and soles. Staining of those parts of the body which have not been in direct contact with the powder indicates a dangerous accumulation of the compound in the body. In a small proportion of workers a pink maculo-papular eruption appears on the exposed skin. Mild poisoning is characterised by lassitude, slight headache, night sweats and fatigue on the slightest exertion. Workmen may lose weight from the time that they first take up the work. Acute intoxication comes on suddenly, with a sensation of extreme weakness in the limbs and painful constriction in the chest, a burning thirst, abundant sweats, and an agitation and anxiety which are characteristic. Other signs are pallor, dyspnoea and scanty urine, which may be a deep orange colour owing to the presence of 2-amino-4-nitrophenol. In more severe cases death may take place within a few hours after a rise of temperature to 104° F. or over. The victim has severe sweating, intense thirst and sometimes colic and diarrhoea. The basal rate of metabolism is increased to 200 per cent. or more. The state of anxious terror and restlessness is followed by hyperpnoea, coma, convulsions and death. Necropsy reveals no characteristic lesion. When the dose is not fatal the symptoms rapidly decrease and many workers develop a tolerance to the poison. The workmen must be provided with a complete set of underclothing and overalls into which they change from their working clothes, a separate cubicle being provided for each man. Well-designed exhaust ventilation must be applied locally to take away the fumes in the melting of the compound and also in the filling of shells. Any dust that collects around the margin of the shell must be removed by a vacuum cleaner.

In 1933 dinitrophenol became widely used in the treatment of obesity, especially in the U.S.A. A dose of 3 mg. per kg. of body-weight will cause a rise in basal metabolic rate and loss of weight, unattended by tachycardia. Toxic symptoms were soon reported, including urticaria, exfoliative dermatitis, jaundice, peripheral neuritis, loss of power to discriminate between sweet and salt tastes, fullness in the ears, deafness, fall in blood pressure, albuminuria, neutropenia and fatal agranulocytosis. After dinitrophenol had been employed for 4 years, cataract was found to be a late complication of the use of the drug. It appears from 3 months to 18 months after the first dose is taken, the change is bilateral and the lens fibres alter so quickly that the cataract swiftly progresses to total blindness. This final disastrous effect of dinitrophenol brought to a close the unfortunate popularity of this drug.

### 6. DINITRO-ORTHO-CRESOL

The compound 4:6-dinitro-ortho-cresol is a yellow solid, manufactured on a large scale as a weed-killer, insecticide, ovicide and fungicide. It is applied in agriculture as an aqueous solution of the sodium salt, while for locust control it is used

as a dust or solution in oil. Its use in the treatment of obesity, although effective, has been given up because it is too dangerous.

D.N.O.C. may be considered to be about twice as toxic as dinitrophenol (D.N.P.). It is a cumulative poison in man and is eliminated slowly. Like D.N.P., its lethal effect is due to excessive stimulation of the general metabolism. At necropsy the changes noted are yellow pigmentation of all the tissues, dehydration, petechial hæmorrhages of the brain and lungs, and parenchymatous degeneration of liver and kidneys. A papular dermatitis is common in workers handling D.N.O.C., and nasal irritation and burns of the skin of the hands have been reported. The earliest symptom of poisoning is an exaggerated feeling of well-being, but this is difficult to assess. It is likely to be present when the concentration of D.N.O.C. in the blood is of the order of 20 micrograms per gram of blood. In severe cases unusual thirst, excessive sweating and fatigue are followed by weakness, high fever, tachycardia, anxiety and great hyperpnoea. The basal rate of metabolism may rise even as high as 400 per cent. There is loss of weight, perhaps 20 lb. in a few weeks. Severe liver damage has sometimes occurred but cataract has been recorded once only.

Measures adopted to reduce the incidence of D.N.O.C. poisoning include (1) periodical medical examination of the workers, (2) the introduction of locally applied exhaust ventilation in factories, (3) the use of masks, protective clothing and enclosed tractor-cabins by spray operators, and (4) the exclusion from further contact, for at least 6 weeks, of workers in whom the concentration of D.N.O.C. in the blood is 20 micrograms or more per gram. No antidote to D.N.O.C. is known. Early diagnosis is essential, and treatment on general lines will result in recovery, even in seriously poisoned patients. The patient must be kept cool by tepid sponging; fluids and electrolytes, which are lost in the profuse sweating that characterises the illness in its acute stages, must be replaced; barbiturates should be administered in doses adequate to allay the anxiety.

## 7. ANILINE

Aniline is a colourless, oily liquid which darkens on exposure to light or air. It is handled in the manufacture of dyes, in the dyeing and cloth-pressing industries, in the extraction of resin and in the rubber industry. Aniline poisoning arises usually from inhalation, but absorption through the skin and, less frequently, inhalation of dusts of aniline compounds may cause it. Care must be taken to change the clothes at once whenever they are splashed with aniline. Men must avoid entering chambers filled with its vapour. The symptoms of aniline poisoning are similar in all respects to those of nitrobenzene poisoning. The convenient term *anilism* may be used to cover the symptoms produced by most of the nitro- and amino-derivatives of benzene.

In *acute aniline poisoning* there is headache, weakness, difficulty in breathing, cyanosis, loss of power in the limbs and giddiness. In severe cases the cyanosis is more intense and prostration occurs with a cold moist skin, small pulse, air hunger and even death in coma. When recovery occurs it is often gradual and may be accompanied by increased frequency of micturition. In *chronic poisoning* the workers show slight cyanosis, secondary anæmia, and sometimes sleeplessness, headache, giddiness and abdominal discomfort. In hot weather practically all the men exposed to aniline and similar compounds in a dye works show cyanosis.

The manufacture of nitrobenzene, and the reduction of nitrobenzene and nitro-toluene to aniline and toluidine must take place in closed vessels. Even so, escape of small quantities of aniline into the atmosphere is very difficult to prevent unless ample ventilation is provided. Therefore, in addition to the technical regulations, there must be insistence on cleanliness of the workrooms, personal cleanliness on the part of the workers and provision of baths and changes of clothing. Contact with aniline and nitrobenzene, especially on the skin, and also the spilling and splashing

of these fluids must be carefully avoided. All workers must be instructed as to the symptoms of nitrobenzene and aniline poisoning, and the right steps to take if poisoned. Regular medical inspection of workmen is desirable.

Workers, and especially those newly employed, must be under supervision in order that assistance may be rendered them on the first signs of poisoning. Medical assistance should be within easy reach. Systematic instruction should be given in first-aid methods, and in the use of apparatus for oxygen and carbon dioxide inhalation. The possibility of skin absorption must always be borne in mind. A victim whose skin or clothing has been splashed with aniline may turn blue in the face and begin to stagger. Someone may take him out to the fresh air or administer oxygen, when what he needs most is to have his clothes stripped off and be given a bath. Workers entering stills and similar chambers should always be equipped with breathing apparatus and a supply of oxygen. Other aids, such as safety belts which are held by helpers, involve certain risks, especially as the rescuer is easily induced to spring to the assistance of his unfortunate mate without the necessary breathing equipment. The frequency of such accidents calls urgently for the use of breathing apparatus.

### 8. PHENYLENEDIAMINE

Phenylenediamine is used for two similar purposes; for dyeing hair black and as a dye for furs. It is well known that it may cause dermatitis and sometimes asthma in susceptible persons. Its systemic effects are much rarer and have received less attention. Hairdressers handling the dye have suffered from attacks of weakness and vomiting, with intense violet cyanosis of the lips and face. In unusually susceptible individuals toxic jaundice has occurred, followed by death from hepatic insufficiency after about 6 months. At necropsy the liver is small and shows the changes of sub-acute atrophy with regeneration nodules. Patch testing of the skin should be carried out on all applicants for the job of ladies' hairdresser; those showing a positive result must be rejected. Persons handling the dye should wear rubber gloves.

## POISONING BY HALOGENATED HYDROCARBONS

The entrance of chlorine or bromine into an aliphatic compound increases its toxicity. This is less commonly true of an aromatic compound. The various members of this group are useful as refrigerants, as degreasers of metals, fire-extinguishers, cleansers of textiles, solvents for rubber and thinners of cellulose lacquers. Their usefulness is enhanced because they are non-inflammable, non-combustible and non-explosive. They vary greatly in their toxic effects, trichlorethylene being relatively harmless and tetrachlorethane deadly.

### 1. METHYL CHLORIDE

Men working in chemical plants or employed upon making, installing or repairing refrigerators may be exposed to methyl chloride. Symptoms of poisoning include giddiness, weakness of extremities, nausea, vomiting, restlessness, followed by somnolence and then by dimness of vision, which may not clear up until 14 days after removal from exposure. Later there is some rise of temperature, pulse and respiratory rate, usually with oliguria and occasionally with suppression lasting up to 48 hours. Evidence of acute nephritis is found in about half the cases. Anæmia may be found, the red cells dropping as low as 3 million per c.mm., and the hæmoglobin as low as 50 per cent. The death-rate is as high as 35 per cent.

## 2. METHYL BROMIDE

Methyl bromide is a colourless, non-inflammable gas, but it comes on the market compressed into containers, in which it assumes the liquid condition. It is valuable as a methylating agent, a fire extinguisher, refrigerant, fumigant and insecticide. Methyl bromide is a deadly and insidious poison with a delayed action like phosgene and nitrogen dioxide. The latent interval varies from 4 to 48 hours, and then the patient is seized abruptly with nausea, vomiting, headache, vertigo, dimness of vision, diplopia, euphoria and delirium. In severe cases pulmonary œdema, oliguria, suppression of urine, convulsions and even acute mania may occur. The skin is pale, the temperature normal, sweating is profuse, trismus and even opisthotonus may be seen and the pupils are dilated. The skin may be affected in susceptible people; premonitory pruritus is characteristic and may be intense. Methyl bromide burns are superficial, rarely extending deeply enough to destroy the whole dermis. They are characterised by excessive vesication with reddening and swelling of the surrounding skin. Healing readily occurs and in most cases there is considerable desquamation. Mild cases usually recover, but where there is œdema of the lungs, convulsions, anuria or severe burns the outcome is often fatal. In cases showing mild systemic symptoms treatment by rest in bed for 2 days with 3 weeks' convalescence will usually be adequate. If there is cyanosis little can be done except to administer oxygen. The skin lesions should be treated with 2 per cent. tannic acid in triple dye solution or with propamide isethionate cream.

## 3. CARBON TETRACHLORIDE

Carbon tetrachloride is used in industry as a solvent for fats and rubber, for dry cleaning, for cleaning oil from machinery and under the name Pyrene as a fire extinguisher. Acute and sometimes fatal poisoning has occurred from the anæsthetic effects of carbon tetrachloride used as a dry shampoo for the hair. Men exposed to the vapour sprayed from Pyrene fire extinguishers in confined spaces have suffered from oliguria and jaundice. In animal experiments carbon tetrachloride has been shown to cause necrosis of the liver. In man it may give rise to acute nephritis, necrosis of the liver, œdema of the lungs or retrobulbar neuritis. The early stages of the illness are characterised by persistent headache, nausea, vomiting, diarrhoea and tenderness over the liver. Such symptoms are often followed by oliguria, suppression of urine and uræmia. Sometimes the clinical picture closely simulates that of the acute abdomen. The blood urea may rise to 300 mg. per 100 ml. and the patient, though practically moribund, may suddenly develop polyuria and recover even after almost complete anuria lasting 10 days. When the liver is attacked recovery may follow an attack of jaundice lasting as long as 2 months. In the treatment of cases rendered unconscious by acute poisoning, it is important that the patient should not be placed upon the floor of the room where the accident occurred, for the vapour is five times denser than air and therefore accumulates on the floor. Hepatic insufficiency should be treated by glucose drinks, together with large doses of calcium lactate up to 15 g. a day. Calcium gluconate may be given by intramuscular injection. Protein hydrolysates, methionine and vitamin supplements have also been used.

## 4. TETRACHLORETHANE

Tetrachlorethane is the most dangerous of all the chlorinated hydrocarbons, being nine times as toxic as carbon tetrachloride. It is a very good solvent for cellulose acetate, which, being non-inflammable, is used for purposes for which cellulose nitrate (celluloid) is not adapted. Cellulose acetate was the chief constituent of the dope used as a waterproof coating for the wings of aeroplanes in the War of 1914-1918,



and it is now used to make non-inflammable cinema film. The symptoms of poisoning are general malaise, loss of appetite, nausea, headache and constipation. After several days or even weeks, jaundice develops and vomiting is then likely to become more marked. In fatal cases necrosis of the liver is found in the form of acute red and yellow atrophy. In one case the liver weighed only 19 oz. The blood changes in mild poisoning consist of an increase of large mononuclear cells up to 40 per cent., with a slight elevation of the white count. Blood counts have been taken in order to detect early poisoning. Elaborate exhaust ventilation in factories and workshops fails to prevent toxic jaundice. It is therefore necessary to use a harmless substitute such as amyl acetate.

#### 5. TRICHLORETHYLENE

Trichlorethylene is employed extensively in dry cleaning and as a degreasing agent. It has assumed an important place in the list of fat and rubber solvents, displacing to some extent carbon tetrachloride. Trichlorethylene has a powerful narcotic effect. The workman affected is usually found unconscious on the floor, and if there has been prolonged exposure to a large dose the effects may be fatal. Chronic exposure has been held responsible for paralysis of the sensory fibres of the fifth nerve, and also for retrobulbar neuritis followed by optic atrophy. An indirect form of injury to the eye sometimes occurs when a foreign body lodges in the cornea and produces ulceration. The workman is not aware of the presence of the irritant substance, because the cornea has been rendered insensitive. Trichlorethylene is not so likely to attack the liver as tetrachlorethane. Toxic jaundice and albuminuria have been recorded only rarely. Dry-cleaning establishments employing trichlorethylene should be provided with efficient exhaust ventilation. When solutions containing trichlorethylene are applied to the interior of closed vats the men should work in pairs, relieving each other frequently. The man in the enclosed space should be provided with a lifebelt and also with an apparatus through which he can breathe air from outside.

#### 6. CHLORINATED NAPHTHALENES

When naphthalene is chlorinated a series of wax-like substances is produced. These are used as an insulating coat on wires or on metal bars to circumscribe the action of plating processes. They may produce acne, starting on the face and around the angles of the jaws and malar prominences, and spreading on to the sides of the face, neck, shoulders and forearms. The skin lesions in a typical case are comedones, papules, pustules and, in severe cases, small cysts. Since 1936 several cases of jaundice have occurred in workers handling chlorinated naphthalenes. In one fatal case necropsy showed acute red and yellow necrosis of the liver, which weighed 650 g., the normal being 1500 g. By attention to ventilation, protective clothing and medical supervision of workers, the chlorinated naphthalenes can be handled in industry with safety.

### DECOMPRESSION SICKNESS

**Synonyms.**—Caisson Disease; Compressed Air Illness; Divers' Paralysis; Aeroembolism of Aviators.

**Definitions.**—Decompression sickness is the name given to the symptoms which appear (i) when workers in compressed air are too rapidly decompressed; (ii) when deep-sea divers or men escaping from sunken submarines come too rapidly to the surface; and (iii) when airmen or air passengers ascend too rapidly to high altitude.

**Ætiology.**—Caisson disease is an industrial hazard encountered in those processes of subaquatic engineering in which compressed air is employed. The work

of excavating for the foundations of piers, river bridges, skyscrapers and certain tunnels is carried out in a subaqueous chamber called a caisson. This is essentially a tube of iron or concrete open below and provided with a cutting edge by which it sinks when weighted into mud, sand or moist earth. The working chamber at the bottom is kept clear of water by compressed air, and it is here that the men work. Pressure is produced and maintained by pumps and regulating apparatus.

It follows that caisson workers are submitted to a pressure of air which just exceeds the hydrostatic pressure of that depth of water in which they work. Workmen descend to the working place of the caisson by passing from the normal atmosphere through a series of chambers with airtight doors in which the air pressure is raised by rapid stages until the high pressure of the working place is reached. They leave through the same chambers, the air pressure being lowered for some space of time in each as they pass through. This process is termed "compression" and "decompression", or "locking in and out". Caissons are usually worked at a pressure of below 35 lb. and in 6- to 8-hour shifts, but they have been successfully worked at a pressure of 45 lb. with 2-hour shifts, and at 50 lb. with 1-hour shifts.

Divers are employed in the construction of harbours, docks, piers, breakwaters and bridges; in recovering sunken ships, cargo and treasure, in cleaning and repairing the hulls of ships and in fishing for pearls and sponges. The diving dress used consists of a copper helmet attached to a metal corselet, the latter being secured watertight to a rubber suit fitting closely every part of the body except the hands, which pass through elastic cuffs. The boots are heavily weighted. Compressed air is supplied by an air-pump on the surface through a flexible pipe and is carried through a tube at the back of the helmet. The exhaled air escapes through a spring valve at the side of the helmet whenever the inside pressure becomes slightly greater than that of the surrounding water. For every 33 ft. (5½ fathoms) in depth of water the pressure increases by 1 atmosphere or 15 lb. to a square inch. Thus the diver is compressed as he slowly descends by an increasing air pressure from his pump and is decompressed as he ascends much more slowly. Divers frequently work at 120 ft. (53 lb.), and the record depth has been 420 ft. (182 lb.), but to resist the pressure at such a depth an incompressible metal suit must be worn. The working shifts of divers are much shorter than those of caisson workers.

Decompression sickness of aviators differs from caisson disease only in its lesser severity. In flying, symptoms may develop at 32,000 ft. if the rate of climb is 200 ft. a minute or more. They may appear after a few minutes or only after 2 or 3 hours according to the particular susceptibility of the individual. Above 37,000 ft. any reasonable rate of climb is very likely to produce symptoms even in the most resistant individual.

**Pathology.**—The evidence is overwhelming that the liberation of gas bubbles in the tissues is the primary cause of the lesions in decompression sickness. The gas bubbles are a mixture of about 82 per cent. nitrogen, 16 per cent. carbon dioxide and 2 per cent. oxygen. Whereas most of the dissolved oxygen in the blood is consumed by the tissues the nitrogen is inert physiologically and is not utilised. Therefore it is customary to speak of the gas bubbles as nitrogen bubbles. Whether they occur after decompression from high-pressure atmospheres or altitude the nitrogen bubbles are chiefly intravascular and they are held responsible for nearly all the symptoms of decompression sickness. Extravascular nitrogen bubbles occur also in severe instances of decompression from high-pressure atmospheres, but they are restricted to certain lipoid-rich structures, notably the white matter of the spinal cord. It has been shown that nitrogen is much more soluble in fat and oils than in water, and that body fat at blood temperature holds five times as much nitrogen per unit mass as does the blood itself.

Changes in air pressure in various body cavities are responsible for certain phenomena. These include earache, sinus pain, toothache and abdominal pain and

distension from trapped gases in the intestinal tract. Nitrogen released in the tissues appears to act principally by causing pain in the unyielding tissues such as bone, tendon, fascia, periosteum and nerve sheath. Neural damage due to aereocembolism varies greatly, is non-specific, and unpredictable. That part of the nervous system which is least vascular, namely the four lower dorsal segments of the spinal cord, is the region most commonly affected. Hundreds of bubbles have been counted in the spinal cord and these are much more numerous in the white than in the grey matter. In every fatal case which has been adequately examined at necropsy patches of necrosis in the dorsal region of the spinal cord with the usual secondary degeneration have been found. Haemorrhage is a relatively unimportant finding. Massive escape of nitrogen bubbles may occur into the blood-stream and, in rapidly fatal cases, the heart has been found distended with gas after death. Nitrogen bubbles in the pulmonary artery and its branches may cause death through occlusion of the circulation and asphyxia. Collections of nitrogen may be found in the subcutaneous tissues and may cause subcutaneous emphysema with palpable crackling. Nitrogen embolism may cause necrosis of the tissues in any part of the body.

**Symptoms.**—The actual ascent and descent of caisson workers, divers and airmen is associated with no worse symptoms than discomfort in the ears from disparity of air pressure in the middle ear ("ear block"). Rupture of the tympanic membrane is rare and may be associated with infection of the middle ear—"aero-otitis media". If air under pressure is trapped in the nasal sinuses there may be pain ("sinus block"). Teeth showing subacute inflammation of the pulp may ache at high altitudes ("aerodontalgia").

The symptoms resulting from decompression will be severe in direct proportion to the length of exposure to an abnormal pressure and to the rapidity of return to atmospheric pressure. No symptoms occur after short exposures to compressed air such as 15 minutes at a pressure of 45 lb., or 2 minutes at a pressure of 75 lb., even though decompression be as rapid as possible, for these periods are too short to allow of nitrogen saturation of the tissues. It is for this reason that decompression sickness is less common in divers, who for the most part work for a short time only at high pressures, and so much more common in caisson workers who work for many hours at a stretch at a pressure of from 30 to 40 lb. Similarly, airmen usually remain above 30,000 ft. for too short a time to be affected.

In caisson workers the onset of symptoms is relatively rapid, in 60 per cent. during the first hour, in 35 per cent. during the second hour, in 3 per cent. during the third hour and in the remaining 2 per cent. after 12 hours. The commonest symptom is dull throbbing pain, gradual in onset, progressive and shifting in character, and frequently felt in the joints, or deeply in muscles and bones. Pains of this nature are referred to as "the bends", a term established by long usage and arising in the fact that the limb affected is held in a semi-flexed position from which it is found difficult to straighten it. The elbows, wrists, knees and hips are the areas most frequently affected, but the epigastric and lumbar regions may be involved too. Numbness may precede the onset of pain. Skin temperature may fall as the part involved becomes blanched in appearance. Erythema of the skin with pruritus ("the itch" or "prickles") occurs with regularity if the skin is chilled during decompression. A type of asphyxia known as "the chokes" or "the chokers" may occur, though it is less frequent than "the bends". Several hours of complete well-being following decompression may elapse before the appearance of the earliest symptom of "choles", namely, a sensation of substernal distress felt only during deep inspiration which frequently serves to elicit the cough reflex. This sensation of substernal distress may be only transient or it may progress to frank asphyxia. Normal breathing becomes shallow, rapid and then dyspnoic. The skin becomes cyanotic, or ashen grey, cold and clammy. The pulse, at first slow and pounding, becomes thready. Paroxysmal attacks of coughing or true "choles" may precede loss of consciousness.

The picture presented is one of "shock" and represents a transformation within a period usually of several hours from a state of health and vigour to one of incapacity without any apparent trauma being inflicted upon the individual. It is this condition which not only frequently supervenes in divers when the premonitory symptoms of "bends" are ignored and treatment delayed, but may also be responsible for circulatory collapse and deaths which occasionally occur following too rapid decompression in the low-pressure chamber.

Vertigo ("the staggers") is a common symptom. The staggering gait may be accompanied by nausea, vomiting, tinnitus and nystagmus. When paraplegia occurs it usually extends as high as the ninth dorsal segmental level, but may reach the cervical region and involve the arms. It comes on rapidly and involves motor, sensory and sphincter functions. It may be of any degree of severity from a slight and transient effect to a complete and permanent loss of the functions of the spinal cord. It occurs with increasing frequency and completeness in proportion to the degree of pressure and the length of exposure to its influence. Hemiplegia or monoplegia of cerebral origin are less commonly seen.

The complications of decompression sickness are limited to certain lesions of the lungs, bones and joints which occur in caisson workers. Spontaneous pneumothorax is a rare complication of too rapid decompression. Where bone complications occur, the symptoms of onset are insidious and are delayed from 6 months to a year or more following repeated attacks of caisson disease. Various infarcts, possibly due to nitrogen emboli in end arteries of nutrient vessels, lead to aseptic necrosis of areas of bone and sometimes of articular cartilage. The bones of the lower limbs are commonly affected and the joints include hip, knee and shoulder. Where the diaphysis of a bone is involved the lesion results in an encapsulated calcified area. The joint lesion may lead to persistent pain and ultimately to osteoarthritis with disablement.

**Treatment.**—**PROPHYLACTIC.**—The ideal age for compressed air workers and aviators is between 20 and 40 years, since during these years the cardio-vascular system is at its greatest efficiency and therefore best able to withstand the hardship involved. All persons with disease of the heart, lungs, kidneys and peripheral vessels should be rejected. Obese men are bad risks because fat deposits act as a gaseous reservoir predisposing to bubble formation. Acute infections of the respiratory passages must temporarily disqualify a man for employment because the infection may involve the Eustachian tubes and the ostia of the sinuses with the risk that air will be trapped in the middle ear or sinuses with consequent infection or rupture of the tympanum. The workman, airman or air passenger avoids the consequences of unequal pressure on either side of the tympanum by opening the Eustachian tubes with repeated acts of swallowing or yawning. Dental supervision and treatment must be carried out in an endeavour to prevent aerodontalgia.

Since the malady is due entirely to the escape of nitrogen bubbles into the tissues during a too rapid return to normal pressures, it follows that it can always be prevented by adopting suitable limitation of exposure. The malady never arises from compression below 18 lb. to the square inch, or roughly 40 ft. of water, and those who work at such a pressure may do so for long hours and return to a normal pressure rapidly, and without any risk. At higher pressures the working shifts must be shortened as the pressure gets higher. The shifts should be not longer than 6 to 8 hours at a pressure of 30 to 35 lb., or 3 atmospheres; 2 to 3 hours at a pressure of 45 lb. and 1 hour only at a pressure of 50 lb. At higher pressures than this, which are only encountered by divers, a few minutes' exposure is allowed only.

Decompression sickness never occurs if the return to the normal atmospheric pressure be sufficiently slow. In the case of caisson workers a series of air-locked chambers is provided in which the air pressure is lowered in stages, the men remaining longer and longer at each stage as they approach the normal pressure. The important fact in connection with decompression is that the absolute pressure can always be

halved forthwith without any risk. In the first air lock on leaving the working face of a caisson, for example, the pressure is at once reduced to one-half that of the working face, and in the remaining air locks the pressure is reduced by stages until zero is reached. The difficulty and danger is the tendency on the part of the workers to curtail these weary waits, and get away from work as soon as possible.

In the case of the diver, decompression is carried out by raising him to various levels in stages, and letting him remain at each stage a longer and longer period as the surface is approached. The Admiralty rules for divers require that a diver working, say at 140 ft. shall be first raised straightaway to a depth of 50 ft. where he waits 10 minutes, then to 40 ft. for 10 minutes, 30 ft. for 20 minutes, 20 ft. for 30 minutes, 10 ft. for 35 minutes and then he leaves the water abruptly.

In commercial aviation passengers should not be flown at altitudes above 18,000 ft. in unsealed cabins, and military flying should be restricted to this level where practicable. Even when using sealed pressure cabins altitudes above 30,000 ft. should never be exceeded because of the danger of decompression sickness in the event of cabin failure.

**CURATIVE.**—It was early discovered by the caisson workers themselves that the only remedy for the malady was to re-enter the high air pressure. A recompression apparatus in the form of a medical air lock is supplied at all caisson works, and on all ships engaged in deep salvage. On the appearance of any symptoms the worker is placed in the compressing room and the pressure is run up to the full pressure at which he has been working, when it is usual for the symptoms to ameliorate rapidly or disappear. After the recompression the decompression must be carried out very slowly, for the bubbles once formed in the tissues are not easy to get rid of, though they may be kept at a small size by the pressure. Cases apparently at the point of death with cyanosis and coma have many times completely recovered in a few hours by recompression. When symptoms have appeared, the decompression should take at least 5 hours. Caisson workers and divers should wear on the lapels of their jackets a metal tablet clearly inscribed with a notice stating both their occupation and the address of their place of work. They should sleep and live close to the medical air lock in order that they may be near aid during the first hours following decompression. The paralysis when once established is to be treated upon ordinary lines. Aseptic necrosis of articular cartilage may necessitate opening a joint for removal of necrotic material.

In aviation, recompression fortunately involves only descent to lower altitudes and higher atmospheric pressures. The descent should be started as soon as possible after the onset of symptoms and as rapidly as is consistent with the safety of the flight. For mild attacks a descent to about 25,000 ft. will generally relieve all the dangerous symptoms, although pruritus may persist. In a severe attack descent to sea level or slightly above should be made, and the flight discontinued at the first available landing point. In crashes following high altitude flights the possibility of coma or paralysis among the injured being due to decompression sickness should be borne in mind.

## ANOXÆMIA

**Definition.**—A series of phenomena which results from deficiency in oxygenation of the tissues in the absence of carbon dioxide retention.

**Pathology.**—The condition is due to lack of oxygen and lowered internal respiration. Anoxæmia is divided into three classes, with widely differing causal mechanisms :

1. *Arterial anoxæmia.*—This is due to a deficiency in the oxygen content of the arterial blood, the oxygen-carrying power being normal and the carbon dioxide discharge unhindered. It is apt to appear whenever the oxygen content of the arterial blood falls below the normal limit of 94 per cent. of its total capacity, and it may or

The picture presented is one of "shock" and represents a transformation within a period usually of several hours from a state of health and vigour to one of incapacity without any apparent trauma being inflicted upon the individual. It is this condition which not only frequently supervenes in divers when the premonitory symptoms of "bends" are ignored and treatment delayed, but may also be responsible for circulatory collapse and deaths which occasionally occur following too rapid decompression in the low-pressure chamber.

Vertigo ("the staggers") is a common symptom. The staggering gait may be accompanied by nausea, vomiting, tinnitus and nystagmus. When paraplegia occurs it usually extends as high as the ninth dorsal segmental level, but may reach the cervical region and involve the arms. It comes on rapidly and involves motor, sensory and sphincter functions. It may be of any degree of severity from a slight and transient effect to a complete and permanent loss of the functions of the spinal cord. It occurs with increasing frequency and completeness in proportion to the degree of pressure and the length of exposure to its influence. Hemiplegia or monoplegia of cerebral origin are less commonly seen.

The complications of decompression sickness are limited to certain lesions of the lungs, bones and joints which occur in caisson workers. Spontaneous pneumothorax is a rare complication of too rapid decompression. Where bone complications occur, the symptoms of onset are insidious and are delayed from 6 months to a year or more following repeated attacks of caisson disease. Various infarcts, possibly due to nitrogen emboli in end arteries of nutrient vessels, lead to aseptic necrosis of areas of bone and sometimes of articular cartilage. The bones of the lower limbs are commonly affected and the joints include hip, knee and shoulder. Where the diaphysis of a bone is involved the lesion results in an encapsulated calcified area. The joint lesion may lead to persistent pain and ultimately to osteoarthritis with disablement.

**Treatment.**—**PROPHYLACTIC.**—The ideal age for compressed air workers and aviators is between 20 and 40 years, since during these years the cardio-vascular system is at its greatest efficiency and therefore best able to withstand the hardship involved. All persons with disease of the heart, lungs, kidneys and peripheral vessels should be rejected. Obese men are bad risks because fat deposits act as a gaseous reservoir predisposing to bubble formation. Acute infections of the respiratory passages must temporarily disqualify a man for employment because the infection may involve the Eustachian tubes and the ostia of the sinuses with the risk that air will be trapped in the middle ear or sinuses with consequent infection or rupture of the tympanum. The workman, airman or air passenger avoids the consequences of unequal pressure on either side of the tympanum by opening the Eustachian tubes with repeated acts of swallowing or yawning. Dental supervision and treatment must be carried out in an endeavour to prevent aerodontalgia.

Since the malady is due entirely to the escape of nitrogen bubbles into the tissues during a too rapid return to normal pressures, it follows that it can always be prevented by adopting suitable limitation of exposure. The malady never arises from compression below 18 lb. to the square inch, or roughly 40 ft. of water, and those who work at such a pressure may do so for long hours and return to a normal pressure rapidly, and without any risk. At higher pressures the working shifts must be shortened as the pressure gets higher. The shifts should be not longer than 6 to 8 hours at a pressure of 30 to 35 lb., or 3 atmospheres; 2 to 3 hours at a pressure of 45 lb. and 1 hour only at a pressure of 50 lb. At higher pressures than this, which are only encountered by divers, a few minutes' exposure is allowed only.

Decompression sickness never occurs if the return to the normal atmospheric pressure be sufficiently slow. In the case of caisson workers a series of air-locked chambers is provided in which the air pressure is lowered in stages, the men remaining longer and longer at each stage as they approach the normal pressure. The important fact in connection with decompression is that the absolute pressure can always be

its presence is realised, that in Tissandier's balloon ascent in 1875, all three aeronauts, though provided with oxygen apparatus, were paralysed beyond movement before realising the necessity for using it, and two of them lost their lives. Diminution of auditory perception becomes so great at high altitudes that the *acroplane engine* becomes almost inaudible.

*Respiratory effects.*—At an altitude of 12,000 ft., nose-breathing ceases, and above this height the breathing deepens into hyperpnœa, which is periodic and may be most distressing. The dyspnœa is greatly increased on exertion and is accompanied by cyanosis. Even such acts as talking and using a pressure pump may greatly increase the dyspnœa.

*Muscular weakness.*—Accompanying the mental lethargy is an increasing condition of muscular weakness. The slightest exertion is hard work. The machine is difficult to fly at very high altitudes, the marksman shoots badly and the mountaineer becomes incapable of taking exercise.

Other symptoms which may occur are—(1) headache, which may be very intense and which is usually met with in prolonged exposure to high altitudes, as in mountain climbing; (2) *spasmodic gulping accompanying the hyperpnœa*; (3) *fainting on exertion*; (4) increased frequency of micturition; and, rarely, (5) vomiting and (6) epistaxis.

The mental effects were most conspicuous in aviators who had to make prolonged flights at very high altitudes before the regular use of oxygen apparatus. The dyspnœa, headache and muscular effects have been most troublesome in mountain ascents where exertion is unavoidable.

Death has occurred in balloon ascents to gain a great altitude. It occurs very rapidly and is preceded by general muscular paralysis. Glaisher and Coxwell survived 29,000 ft. by a lucky chance after complete paralysis of the limbs had set in. Sivel and Croce-Spinelli died at a height of 27,500 ft., while Tissandier, who was with them, survived. Exposure of airmen to high altitudes produces the following effects: The gait of the men on landing is unsteady and laboured. Reports are laboriously made out (there being a general disagreement as to what was seen and done). Tempers are short, everyone looks and feels tired, and the idea uppermost in the mind is to lie down and go to sleep. Severe frontal headache is common; it may persist until the following day and at times proves incapacitating. Appetites are poor and spirits are depressed. A repetition of this kind of work over any length of time rapidly produces deterioration of mental and physical well-being.

Remarkable individual tolerance to anoxæmia occurs in some subjects, but this tolerance tends to disappear with repeated long exposure. Physical fitness and training increase tolerance up to a certain point, whereas unfitness and especially digestive disturbances lower tolerance, and the latter are apt to induce vomiting.

*Treatment.*—Since the symptoms are due solely to lack of oxygen they can be entirely avoided by the use of a portable apparatus to deliver the necessary oxygen by all those who have to encounter an altitude of over 15,000 ft. The essential feature of such an apparatus is the regulation of oxygen delivery by an aneroid controlled valve, so that the amount of oxygen delivered varies in inverse proportion to the barometric pressure of the atmospheres surrounding the instrument, and consequently, in direct proportion to the altitude.

When symptoms have developed, the immediate treatment requisite is the cessation of exertion, the provision of oxygen if available and a speedy return to a lower altitude.

## TRAVEL SICKNESS

Under this heading can be included sea-sickness, air, train and car sickness. By far the most disabling form of travel sickness is sea-sickness. It is a disorder of

may not be associated with cyanosis. It is the usual result of breathing a rarefied atmosphere in which the partial pressure of oxygen is lowered, and in this connection is known as "mountain sickness" or "altitude sickness" when heights approaching 20,000 ft. are reached. The characteristic phenomena can be produced at will by respiration within a partially exhausted chamber, and they can be obviated at high altitudes by adequate oxygen addition in respiration. Arterial anoxæmia is also present to some extent in those pulmonary diseases in which there is damage to the respiratory epithelium, obstruction to the air passages and when prolonged shallow breathing occurs, as in pulmonary œdema, emphysema and pneumonia, and in these conditions oxygen addition is valuable if its administration can be very prolonged.

2. *Stagnant or passive anoxæmia.*—This results when, on account of some fault in the circulatory mechanism, the passage of the blood through the tissues is too slow to provide for adequate oxygenation. It is the common happening in the circulatory failure of cardiac disease. There is here no fault with the oxygen content of the arterial blood. The oxygen saturation of the venous blood falls lower than 65 per cent. of the normal, and the normal difference between the oxygen saturation of the arterial and of the venous blood, which is 20 to 30 per cent., is exceeded, and there is always cyanosis, which appears when the reduced hæmoglobin content reaches 40 per cent. of the total hæmoglobin. Since the arterial blood oxygen content is not at fault, oxygen administration is useless to relieve this condition.

3. *Anoxic anoxæmia.*—This results from a deficiency in the oxygen-carrying power of the blood, either by reason of deficient hæmoglobin content, as in the anæmias, or by fixation of some of a normal hæmoglobin content, as methhæmoglobin, sulphæmoglobin, or carbon monoxide hæmoglobin. In the anoxic varieties, cyanosis does not occur, however severe the anoxæmia, for the reason that cyanosis only appears when 40 per cent. of a normal hæmoglobin content exists as reduced hæmoglobin. Therefore, an anæmic patient with 50 per cent. hæmoglobin would require 90 per cent. of the total hæmoglobin present to be reduced for the appearance of cyanosis. Oxygen administration is of no avail in anoxic anoxæmia.

**ALTITUDE SICKNESS; MOUNTAIN SICKNESS.**—There is considerable difference among individuals as regards liability to the appearance of symptoms at low atmospheric pressures, some suffering earlier and more than others. The immediate effect of exposure to such pressures is to cause rapid concentration of the blood and therefore a relative increase of the ratio of the hæmoglobin to the volume. A 10 per cent. rise in the hæmoglobin ratio may occur after 20 minutes' exposure. This is in part produced by the rôle of the spleen in acting as a reservoir for the erythrocytes, which are discharged rapidly into the general circulation under these circumstances. This serves as a compensation for the oxygen-want of the tissues, and its occurrence is associated with a disappearance or amelioration of the initial symptoms of oxygen-want. In those who remain at a bearable high altitude many weeks, some degree of acclimatisation occurs, and this is associated with hyperactivity of the blood-forming organs and an erythrocytosis. The anoxæmia produces hyperpnœa, and there is at first an alkalosis from increased ventilation, which subsequently lessens.

**Symptoms.**—*Mental effects* are most important when rapid ascents to high altitudes are made in aviation, and consist of a gradually increasing dulling of perception, of which the subject is usually unaware. There is an increasing inaccuracy and lethargy of mental functions, with a tendency to torpor and loss of memory. The skilled photographic observer takes many photographs upon the same plate, the observer throws his valuable notes overboard, the navigator makes for a wrong destination or goes to sleep, and the fighter pilot forgets to go into action. On return to land a muddled and confused memory of what has happened during the flight is all that remains. Lesser degrees of this condition have led to great errors in judgement, foolhardiness, apparent cowardice and irresponsibility in military aviation. So insensibly does this mental paralysis come on and so deep may be its effect before



its presence is realised, that in Tissandier's balloon ascent in 1875, all three aeronauts, though provided with oxygen apparatus, were paralysed beyond movement before realising the necessity for using it, and two of them lost their lives. Diminution of auditory perception becomes so great at high altitudes that the aeroplane engine becomes almost inaudible.

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## TRAVEL SICKNESS

Under this heading can be included sea-sickness, air, train and car sickness. By far the most disabling form of travel sickness is sea-sickness. It is a disorder of

gastric and intestinal function brought on in susceptible subjects by travelling on the sea. A similar disorder occurs in many persons under various other conditions in which they are subjected to repetitive irregular motion as in an aeroplane, a swing, a roundabout and, to a less degree, in a railway train, a motor car, a lift or even during dancing.

**Ætiology and Pathology.**—It is well known that irregular and unaccustomed stimulation of the labyrinth causes nausea and vomiting, and also other disorders of function in the structures innervated by the vagus or parasympathetic system. In travelling through rough seas the roll and pitch of the ship cause excessive stimulation of the labyrinth. In the case of car and aeroplane travel the labyrinth is subjected not only to the effects of rotation of the body through planes to which it is unaccustomed, but also to rapid accelerations and decelerations as well as to altitude changes. Another influence is the reception of irrelative impressions from the other afferent organs, which subserve the orientation of the body in space and the appreciation of movement, namely, the eyes, and the postural sensory system of muscles and joints. Psychological factors, especially apprehension, also play a part. Train and car sickness are mainly concerned with the visual factor and are brought about by the difficulty experienced in adjusting vision to the rapidly passing landscape. A receding landscape imposes such disability on certain individuals travelling by train that they can only travel facing the engine.

The degree of susceptibility varies greatly in different individuals. Early infancy is immune from the affection, since the orienting mechanism has not attained full physiological activity, and old age is relatively immune, probably from lessening irritability of the nervous system. Individual hypersusceptibility and individual immunity are very common, and the readiness with which tolerance is acquired by training varies greatly in different people. Personal immunity is, for the most, relative only, for there are few who can pass through excessive and prolonged stimulation without developing some of the characteristic symptoms. The development of tolerance by habitude varies greatly. Some develop tolerance readily, and others with great difficulty. Years of continuous sea-going may pass before any tolerance is developed, and many sailors never acquire any, as was the case with Admiral Nelson. Of the many adjuvant factors the more important are apprehension, or the full expectation of being sick, the smell of the ship and especially of oil, heat, a stuffy cabin and the presence of others who are sick.

**Symptoms.**—The initial symptoms are a loss of the usual feeling of well-being, accompanied by a feeling of abdominal or visceral discomfort. Salivation, gaping and yawning follow, with irregularity of respiration, flatulence, pallor of the face and a sense of squeamishness as though at any moment vomiting might occur. Many subjects at this stage have a desire to defæcate. These early symptoms are followed by severe nausea, retching and vomiting. In many cases the vomiting is of brief duration, but in others the gastric symptoms may become most violent and distressing, the vomit ultimately consisting of thin bile-stained fluid; there is complete anorexia, and in severe cases nothing can be retained in the stomach. In nearly all cases of any severity the visceral symptoms are accompanied by headache, giddiness, continued pallor, apathy, lassitude, weakness, dehydration and prostration. These general constitutional effects may be serious, and may lead to a condition of collapse. The eyes are dull, the facies becomes shrunk, perhaps greenish in hue and inexpressive or dejected. The skin is cold and usually clammy, the tongue is coated, and both the breath and urine may contain acetone bodies. Pulse and respiration are quickened, and the blood pressure lowered. Little urine is passed, and constipation, after an initial bowel action, is usual.

**Diagnosis.**—This is seldom in doubt, but the possibility of other abdominal disorders must not, of course, be overlooked.

**Course and Prognosis.**—The symptoms usually subside rapidly when the voyage

or other movement causing the condition is over, but sometimes dizziness, headache and gastric symptoms persist for a long time, and the patient is "good-for-nothing" until he has had a night's sleep. In persons taking long sea voyages, the symptoms usually lessen in a few days, reaction sets in, accompanied by a return of appetite, and convalescence is complete within a week, but symptoms are liable to return with an onset of rough seas. Some persons, on the other hand, never lose the symptoms until the voyage, however long, is over, and these may be reduced to a piteous condition of bodily weakness, from which subsequent convalescence is slow. Death appears rarely, if ever, to have occurred even in the most severe condition of bodily depression and starvation from sea-sickness alone. Apart from the long convalescence which may be required in severe and long-lasting cases, there seem to be no harmful results.

**Treatment.**—Securing an airy cabin amidships with pleasant distractions during the voyage may prevent symptoms. Even unpleasant distractions such as fear and excitement in troops about to land on a hostile shore are often effective. Many drugs are valuable in the control of sea-sickness. They include hyoscine, diphenhydramine (Benadryl), dimenhydrinate (Dramamine), chlorcyclizine (Histanin), promethazine (Phenergan) and benzhexol (Artane). Their mode of action is not known; it may either be a direct sedative effect on the vomiting centre or a central anticholinergic effect. Not one of these drugs is outstanding, but hyoscine hydrobromide 1 mg. taken an hour before sailing will prevent sickness during short sea journeys in the majority of susceptible people. On long voyages, taken in the effective dose of 0.75 mg. t.d.s., it may cause unpleasant side-effects and promethazine (25 mg. t.d.s.) is to be preferred.

## ELECTRICAL INJURIES

Electrical injuries may be received from lightning-stroke, from accidental contact with high-tension conductors, on railways or in factories, mines and shipyards, from faulty household electrical appliances, or from judicial electrocution where this obtains.

**Ætiology.**—In Great Britain electricity is usually supplied to householders at voltages under 250. The severity of the injuries sustained in any given case depends upon other factors than the voltage of the discharge received, and thus it is that fatal injuries may be received from currents of comparatively low voltage (120 volts), and survival may follow the reception of currents of higher potential. A current of 500 volts is commonly fatal, and alternating currents are usually more dangerous than direct. Voltages of over 1000 are spoken of as "high tension". The quantity of the current is also of importance. A current of 100 amperes is dangerous, one of 500 is likely to be fatal. The lightning flash is a rush of protons and electrons through the air in a path which may be more than a mile long and about 20 ft. wide. The current is direct, not alternating, of the order of 1000 million volts and perhaps 20,000 amperes. The duration of a single stroke is about a thousandth of a second. In judicial electrocution the victim is subjected to repeated discharges (4 to 8), each lasting some seconds (5 to 50), of alternately low and high potential (500 and 2000 volts).

**Pathology.**—In death from lightning-stroke the head is invariably struck. The body surface shows burns of various forms. In the nervous system there are abnormal rents and fissures in the brain, the cerebrospinal spaces are distended, the perivascular spaces enlarged and the arteries at the base of the brain may show rupture of their muscular coats. In various situations the nerve cells show severe disruptive changes. The passage of the current through and over the body is inadequate to account for the lesions found in the nervous system: they are due to the charging of the body itself with electricity.

If a man makes contact with a conductor at high potential, or if he be struck by lightning, he will suddenly become highly charged with electricity. A current

will pass through him only if he is in a position to lose this charge. If he be earthed the charge will pass rapidly through and over him, and will not accumulate upon him. If he be more or less effectively insulated from earth, his body surface will become highly charged, and electrostatic forces will develop from the mechanical repulsion which is exerted between similarly charged particles or bodies. A charged body will be repelled from all similarly charged bodies, and all the constituent elements of the body which carry the charge will be repelled from one another.

Thus it is that when more than one object is struck by lightning, they are flung apart; a man is flung several yards from a tree under which he has been standing; or two men simultaneously struck are flung away from each other; a parcel held by an individual struck is hurled out of his grasp, and also his clothes, belt and boots are burst and torn off him in fragments, and he may be stripped naked. Within his body the same disruptive forces are at work, and produce lesions in proportion to the rigidity and cohesion of the tissues. This accounts for the characteristic disruptive lesions found in the brain. In addition to these mechanical effects the current also produces heating and electrolytic effects but these are probably negligible as far as the morbid anatomy is concerned.

**Symptoms.**—The effects of lightning-stroke include burns, lacerations, fractures, conjunctivitis, paresis of accommodation, cataract, partial alopecia, flaccid paralysis of the lower limbs and hysteria. Of all these lesions the burn is the most common. It may occur in an unusual pattern as an arborescent marking ("brushburn"), or a series of long narrow lines on the skin. It is not a true burn for it is painless and without inflammatory reaction. Metal objects in the pockets or in contact with the body such as buckets and iron rods, may determine the site and severity of the lesions.

A person struck by lightning usually falls unconscious at once. Retrograde amnesia is common. Sometimes he speaks of having received a tremendous blow on the head, or of intense visual or auditory sensations, of pain in the trunk and limbs, or of giddiness. The subject is unconscious, pale and pulseless, and respiratory movements are suspended. This initial state of suspended animation or apparent death is common after lightning-stroke, but not so frequent after accidental electrical injuries from contact with conductors. There may be powerful and generalised muscular spasm for a brief period and the limbs may be in flexion. It is because of similar spasm in the heart and muscular arteries that the victim is pulseless and pale. Surface burns of varying severity are seen, and examination of the scalp will reveal a localised swelling at or near the vertex, with no cutaneous abrasion.

As respiration becomes re-established—either spontaneously or after artificial respiration—the subject may become restless and resistive, crying with the pain of muscular spasm. Later, he becomes drowsy, has headache and for 1 or more days may not be fully alert.

If an individual merely touches a conducting element or a part of an electrical appliance which is not insulated, he receives a shock which causes a violent and unpleasant tingling sensation in the limb concerned or throughout his body, and this is quickly cut short by withdrawal of the part of his body from contact with the "live" object. The subject may feel faint but has no external injury.

The serious cases are those in which the individual grasps a metal lamp-standard or other object which has become electrified as a result of a defect in the wiring. The flexor muscles of the grasping hand are at once thrown into strong spasm by the electrical stimulation, with the result that the patient cannot let go. The spasm quickly extends up the affected arm. Usually he brings up his other hand and tries with it to release his first hand, and if he again catches the object by an electrified part, the muscles of both arms are quickly tetanised, and the spasm spreads to his chest and other parts of his trunk. The patient becomes speechless and pale, then cyanosed and convulsed, he loses consciousness, and may stop breathing. Unless

the current can be switched off quickly death may result, but the degree of electrocution varies considerably according to the degree to which the patient is insulated. If the current is switched off within a few minutes the patient usually recovers consciousness quickly, but suffers from a variable degree of shock and muscular spasm.

In another group of cases persons are electrocuted whilst taking a bath. An individual standing or sitting in a bath may pick up an electric hair-dryer or touch an electric heater, probably with a dripping hand. Instantly electricity passes over the patient's wet body, and the water and the bath become charged with it. The symptoms which ensue in the occupant are those already described, and unless the contact is broken, death may follow rapidly.

**Diagnosis.**—Where death has occurred from lightning-stroke, the following signs are found. There is an effusion beneath the scalp without superficial abrasion, and streaks of "brushburn" will be found upon the skin. The body will be more or less stripped of clothes. If a hat was worn, a hole will probably be found in it over the site of the scalp lesion. Leather garments, boots and belts are burst. Of course, if the victim was hurled or flung down some other signs of injury caused in this way may be found.

**Prognosis.**—Following lightning-stroke the number of deaths is small in proportion to minor injuries; out of 300 persons in a church which was struck, 100 were made unconscious and injured, 30 had to take to bed and only 6 were killed. Recovery from the average burn, laceration and fracture is prompt. Conjunctivitis and paresis of accommodation rapidly disappear. Flaccid paralysis of the lower trunk and limbs is temporary, power and sensation usually returning to normal after 12 hours. In cases of alopecia the hair grows again after 6 months. Hysterical deafness, blindness and aphonia should recover with adequate treatment. The only lesions which ever remain permanent are both rare, namely, cataract and a condition called spinal atrophic paralysis. This consists in muscular atrophy with fibrillation without sensory disturbance, in the distribution of the fourth to sixth cervical segments of the cord. It may progress and cripple the patient.

**Treatment.**—**PROPHYLACTIC.**—Thunderstorms are less common in high latitudes than nearer the equator. On mountains and in open country, especially in the tropics, it is important to know what to do when lightning comes near. It is safest to be inside a house, in a room with all the doors and windows closed, and away from the fireplace. In Great Britain telephones are fitted with lightning arresters and so may be used without danger. If there is no house, shed, cave or closed motor-car available the protection of a ditch or hollow should be sought. Crowds of people and the neighbourhood of domestic stock should be avoided, as should trees standing alone, wire fences, hedges, walls and the banks of rivers and ponds. The centre of a wood is fairly safe. If one has to be struck it is better to be wet through, for wet clothing may short-circuit most of the current.

In factories, mines and shipyards safety must be secured by the proper design of electrical apparatus, an active inspectorate and adequate safety-first propaganda. The generators, transformers, motors and switchboards should be placed on a floor itself made of some insulating material and covered with insulating mats which must be kept dry and free from oil. No circuit should be worked upon until the power has been cut off and the switch padlocked. If it becomes absolutely necessary to handle a live circuit, care should be taken to work upon but one wire at a time and to wear rubber gloves.

Pylons carrying live wires must be provided with danger notices and fitted with metal spikes to discourage attempts to climb them. Where roads cross electric railways fitted with overhead conductor wires, screens must be erected in such a way as to prevent the electrocution through the stream of urine of small boys who engage in the ingenious but deadly pastime of aiming at the wires in this particular way from the bridges. In the home, bathrooms must never be fitted with electric power

points because of the danger involved in touching a defective electrical appliance with wet hands while standing in water in a metal bath.

**CURATIVE.**—When the victim is unconscious, white and pulseless, artificial respiration must be undertaken at once, and persevered with for at least 8 hours before abandoning the patient. In factories the majority of recoveries when artificial respiration is applied occur in the first 10 minutes, a good proportion in the second 10 minutes but fewer after this period. There are few records of artificial respiration having been carried on in fatal cases for much longer than an hour, while many attempts are abandoned within half that time. Swallowing is the most reliable sign of the return of spontaneous breathing. Even when respiration is first resumed, it may fail again and artificial respiration must be kept up until normal breathing movements are fully established. The usual restorative measures employed in severe shock must also be used. When consciousness is regained, the patient may complain of severe headache and of painful muscular cramp. The latter should be treated by massage.

The superficial linear burns of lightning-stroke are best covered by aseptic dressings, when they usually heal without scarring. The deeper burns related to metallic objects carried by the victim, or to the points of entry and departure of the current in accidental injuries from contact with conductors, will require the ordinary treatment of burns according to their depth and extent. Neurological symptoms and disabilities have to be dealt with according to their character and severity.

## THE EFFECTS OF HEAT

Under this heading are included those important conditions which result from exposure to high temperature. They are (1) heat exhaustion; (2) heat cramps and (3) heat hyperpyrexia (heat-stroke, sun-stroke, heat retention).

**Ætiology.**—The factors which lead to these affections are divided into the environmental and the individual.

Exposure to heat is the environmental necessity. Naturally, cases are most common in the tropics where there is danger in any shade temperature above 110° F., though heat exhaustion is not rare on a hot English summer day. There is, however, no special quality of solar rays to blame, for in experimental work direct exposure of the head to the sun is well tolerated if other factors are favourable, while heat-stroke is common in the gloom of a ship's stoke-hold. Those who live well exposed to the sun at high altitudes do not suffer like those on the plains. In tropical campaigns the rise in case incidence appears to lag behind the rise of atmospheric temperature by a few days. In individual instances illness follows exposure by some hours, suggesting some cumulative effect.

Furnacemen, foundrymen, forge hammer workers, ships' firemen, iron and glass workers, and miners in deep mines run the risk of undue exposure to heat, and it is in these men that heat cramps are to be expected. In tropical countries, laden troops on the march readily succumb to heat-stroke.

Climate, atmosphere and, in particular, humidity must be considered. A heat wave in any country leaves its quota of cases: in deserts without shade, and countries where day and night temperatures are both high, there is more danger. Most important of all, an atmosphere with a high humidity hinders heat loss from the body, and in motionless air where the wet-bulb thermometer reads 83° F. there is considerable chance of heat-stroke; still and poorly ventilated atmospheres themselves predispose to it, and the value of fans is self-evident.

**Dwellings** must be made of thick non-conducting material if they are to be protective, and in this respect a tent is of little use. Buildings should be well ventilated, and it has become almost instinctive for people in tropical climates to open their windows only in the cooler parts of the day.

*Clothing* needs to be light and loose-fitting; experienced workers in hot damp places have found that they are more comfortable if they wear a cotton shirt than if they are stripped to the waist and bathed in sweat.

Deficiency of salt in the body is just as important as any of the above factors and is thought to be the basis of all conditions attributable to heat. Sweat contains about 0.25 per cent. of sodium chloride, and by sweating a man may lose as much as 30 g. of salt in a day. In the absence of added salt, such a depletion may predispose to heat-stroke, and is certainly the principal cause of heat cramps. This fact was discovered by J. S. Haldane in the deep South Staffordshire coal-mines. He was the first to suggest that the cramps would follow the drinking of water, but that they could be avoided if salt were added to the water. Directly linked with sweating is the amount of exertion undergone, so that heavy work in a hot and unfavourable atmosphere is particularly dangerous.

Predisposing factors include malaria, fatigue, alcoholism, metabolic diseases, gastro-intestinal disorders in which water and salt are readily lost, and the previous use of strong purgatives, thyroid or atropine. Native races are usually immune unless there is other disease present; old people are susceptible, so are those who have previously been affected. Some people have a constitutional inability to perspire. What is especially noteworthy is that an unacclimatised man is more susceptible than a veteran, for, during acclimatisation, there is physiological conservation of salt and the salt content of the sweat falls to 0.09 per cent.

**Pathology.**—In heat exhaustion a direct heat action upon the brain probably occurs in addition to the salt loss, and the picture is akin to that of surgical shock. In heat cramps there is loss of salt and the serum sodium is lowered. It may be that the corresponding ionic changes at the myoneural junctions initiate the cramps, particularly as the muscles most in use are affected.

In heat hyperpyrexia there is derangement of the heat regulating centre, but salt depletion is also important, for the urinary chloride figure is very low. There is some evidence of increased metabolism in addition to indicanuria. That experimental hyperpyrexia can be induced with *beta*-tetra-hydro-naphthylamine has been used as evidence to support a theory of auto-intoxication by katabolites as the basis of heat-stroke.

After heat hyperpyrexia rigor mortis occurs early and so do putrefactive changes. Oedema and hyperemia of the brain and lepto-meninges occur, and the nerve cells in the grey matter show degenerative changes. In severe cases petechiæ occur in the skin and mucous membranes, and venous congestion is present in all organs.

## 1. HEAT EXHAUSTION

*Acute symptoms may overtake a man at his work.* There is an attack that suggests syncope, he becomes weak and faint, pale and prostrated, giddy and sweating. The pulse is weak and rapid, the blood pressure very low and the signs resemble those of shock. He may become unconscious. The temperature is normal or subnormal, respirations shallow and sighing, and the pupils dilated. Recovery may be quite rapid, but there is danger of hyperpyrexia later if the patient is not carefully treated for some days.

**Treatment.**—Lay the patient on his back in a cool place, loosen the clothing and apply massage or local heat to the limbs. A warm bath may do good; give saline drinks, perhaps intravenous saline, and keep him under observation.

## 2. HEAT CRAMPS (See p. 416)

In the second half of his shift at work a man may be seized with violent cramps. He is often of poor physique. The symptoms are more likely to occur should he have

slow and obstinate, and has a tendency to progress and to resist treatment in a remarkable way. It is at times very painful.

In chronic X-ray dermatitis the changes in the hands begin round the base of the nails as a peculiar erythema and gradually increase. Transverse and longitudinal ridges appear on the nails, which become brittle, assume a characteristic dirty brown appearance, tend to separate from the matrix and eventually thicken and form shapeless masses. The skin becomes uniformly red and atrophied; small warts appear, increase in size and number, and, when situated over the knuckles, crack and cause much pain. Later the dry thickened skin shows telangiectases, absence of hair, paronychia and ulcers which are slow to heal and prone to break down. The hair follicles and the sebaceous and sweat glands completely disappear in cases of long standing. The freedom of the palms of the hands may be due to the naturally thicker skin there, but the greater liability to exposure of the backs of the hands and fingers is probably the more important factor. The lesions are, as a rule, slowly progressive. Post-irradiation telangiectases, which have been regarded as compensatory for obliteration of the vessels in the corium, usually appear within 2 years, and sometimes in the absence of an initial erythema; in some instances the interval between irradiation and the appearance of telangiectases is prolonged, even to 15 years. If exposure is continued the lesions may progress to involve the tendon sheaths and joints. There may be intense pain, of which the severity is out of proportion to the size of the lesions; it is caused by the exposure of nerve-endings.

Squamous-celled carcinoma is almost always the form of malignant disease which has followed excessive X-ray exposure and long-continued X-ray dermatitis in man. Although most often seen in radiologists and manufacturers of X-ray apparatus, X-ray carcinoma may also occur in patients who have undergone treatment by X-irradiation. The interval between the onset of chronic X-ray dermatitis and the appearance of malignant disease varies from 3 to 27 years. The average of 35 cases was 7 years. The age incidence from 35 to 50 is comparatively early, that of ordinary carcinoma of the skin being between 55 and 58. The most frequent site of the growth, which is not uncommonly multiple, is on the backs of the hands and fingers, and the hand more exposed appears to be the one more severely affected, the left in radiologists and the right in those engaged in the manufacture of apparatus. Among radiologists carcinoma usually develops in an ulcer, less often in keratotic areas. The predominating symptom is pain, which may be constant and very severe, and has been ascribed to invasion of the terminations of nerves by the growth and to neuritis. Occasionally basal-celled carcinoma results from X-irradiation. In one case a basal-celled carcinoma of the scalp appeared 18 years after epilation for ringworm. A case has also been recorded of multiple basal-celled carcinomas on the trunk of a radiographer.

Constitutional symptoms only became prominent after the introduction of deep X-ray therapy, in which massive doses of deep penetrating rays were given. Severe constitutional symptoms may occur. They are nausea, uncontrollable vomiting, sometimes with hæmatemesis, diarrhœa, with the passage of blood, abdominal pain and distension, fever up to  $104^{\circ}$  F., restlessness, profound prostration, progressive cardiac failure, small rapid pulse and dyspnœa. When death has occurred it has usually taken place about the fourth day from the onset. Both animal experiments and necropsies of human victims show that the application of X-rays to the abdomen may result in necrosis of the intestinal mucosa. As long ago as 1905 unsuspected sterility was found in 18 persons who had for various periods been exposed to X-rays. The acute degenerative changes in the testes are followed by fibrous atrophy. Anæmia occurs in X-ray workers. After small doses of X-rays, the lymphocytes are first increased in number, then diminished. The red cells may also be increased at first, but anæmia sets in later and may become extreme. In patients who recover, the anæmia is slower to disappear than is the leucopenia. True aplastic anæmia does not occur.



**Diagnosis.**—The possibility of exposure to radium should always be excluded before attributing what appears to be aplastic anæmia in an X-ray worker to X-irradiation.

**Treatment.**—**PROPHYLACTIC.**—Within the first few months after their discovery it was found that X-rays were stopped more effectively by lead than by any other common metal. Hence lead for protection came into use very early. To-day lead, lead glass, lead rubber and lead bakelite are extensively used. Transparent lead glass windows in tube containers were first employed about 1900. At that time the need for protecting both operator and patient during X-ray exposure was very great, because low voltages were used, with consequent long exposure to a very soft and easily absorbed radiation. For example, to radiograph the spine required exposures up to 1 hour. That the radiologist was not more frequently affected by the scattered radiation of such exposures was due to the fact that during them he might retire to another room to see other patients. About 1903 there appeared a multitude of protective devices to be worn by the radiologist, including apron, jacket, gloves and goggles. This type of protection gradually reached its peak about 1914, when necessity threw caution to the winds, and the more elaborate devices gave place to means of protection which were built into the apparatus.

To-day there is international agreement as to the most effective methods of prevention. In Great Britain such methods have been widely adopted, and although they have no strictly legal recognition, powers of inspection and approval have been placed in the hands of the National Physical Laboratory. A service has been organised whereby the radiation received by a worker can be assessed by means of the blackening of a small wrapped photographic film worn on the coat lapel during working hours for a week. If the film, when developed, indicates a higher dose than 0.3r per week the laboratory immediately follows up with an inspection of the department concerned. The results of film tests carried out on several thousand radiological workers from 1943 to 1948 indicated that about 80 per cent. received less than 0.1r per week from external sources of radiation. Repeated periodical blood counts must be carried out in all doctors, nurses, research workers, students, technicians and workshop employees exposed to X-rays.

It is important that the industrial physician should plan measures for the protection of employees against the dangers of X-irradiation, for in large manufacturing establishments there are X-ray departments for diagnosis as extensive and as much used as the average hospital department. Here the problem may include protection of workers in neighbouring rooms, for unless walls and floors are very thick or are rendered impermeable by the use of lead or barium concrete, X-rays may pass through them and cause injury.

**SYMPTOMATIC.**—X-ray carcinoma should be treated by radical excision when this is possible, such as amputation of a finger, by diathermic coagulation under local anæsthesia, or by radium. Slight degrees of anæmia recover on removal from exposure. In more severe degrees iron must be used, and when this fails blood transfusion is necessary.

## INJURIES FROM RADIOACTIVE SUBSTANCES

**Ætiology.**—The gamma rays of radium appear to have a greater tendency than X-rays to cause aplastic anæmia; this impression is supported by the experimental evidence that the penetrative gamma rays of radium reach the bone marrow more readily than do X-rays. Three fatal cases of aplastic anæmia were reported in the London Radium Institute in 1920, one in a nurse and two in laboratory assistants. The late effects of internally deposited radioactive materials in man were studied from 1925 onwards. Paints consisting of crystalline phosphorescent zinc

sulphide, rendered permanently luminous by the addition of a very small proportion of insoluble sulphate of radium, mesothorium and radiothorium, came into use about 1908. Such paints are applied to the figures of clocks and watches, and certain important parts of the machinery of aeroplanes. At two factories, one in New Jersey and the other in Connecticut, 38 deaths occurred among factory girls, chemists and physicists. The girls affected introduced the paint into their mouths through the habit of pointing the brush between their lips and swallowed it for periods of from 1 to 4 or more years. The insoluble radioactive materials became deposited in the body to such an extent that even during life radioactive emanations could be detected in the expired air. Pointing the brush with the lips was prohibited in 1924.

**Pathology.**—After death, bone was found to be the tissue in which the materials had mainly accumulated. Aplastic anæmia resulted from the continuous bombardment of the hæmatogenous marrow by alpha particles, and it was found that these changes were quite different from those due to external irradiation with beta and gamma rays only. Radioactivity in the bones and teeth was demonstrated by autoradiography. The bones when placed directly on photographic plates produced impressions in as short a period as 3 days. By 1952 there had been 14 deaths from sarcoma of bone which had appeared on an average 23 years after cessation of exposure to the luminous paint. In 3 cases deaths occurred from carcinoma of the paranasal sinuses, one of them 34 years after removal from exposure. The total amount of radioactive material necessary to produce fatal results is extremely small. It is sufficient for 0.01 mg. to be distributed over the whole skeleton to produce a terrible death years after it has been ingested. Radium is thus the most deadly poison known; tetanus toxin previously held the record with a lethal dose of 0.22 mg.

It is dangerous to use injections of thorium compounds for diagnostic or other purposes. Thorotrast, a thorium dioxide sol, was used for diagnostic radiography in doses which were carcinogenic. The alpha ray activity of 25 ml. of thorotrast has been found equivalent to a maximum of 1 microgram and a minimum of 0.5 microgram of radium. Thorotrast has been employed in hepatolienography, retrograde pyelography and arteriography; its elimination from the body is insignificant. In the diagnostic procedures mentioned it may be retained indefinitely in the liver, renal pelvis or subarachnoid space. By 1953, 7 deaths from its use had been recorded either from aplastic anæmia or from malignant neoplasms found to contain thorium concentrated in their substance.

**Symptoms.**—Dermatitis due to radium, isolated by the Curies in 1898, was reported in October 1900. Insufficiently protected tubes of radium salts kept in the waistcoat pocket for 6 hours produced reddening of the skin and within 10 days or so ulceration. Dermatitis has been reported in a number of persons engaged in making radium preparations, and less often in medical men. The ill-effects of ingestion of radioactive substances include severe anæmia, sometimes aplastic, necrosis of the jaw, spontaneous fractures, sarcoma of bone and carcinoma of the paranasal sinuses. The changes in the blood have been referred to as *anæmia radiotoxica*. The red cell count may drop below one million and the hæmoglobin below 20 per cent. Leucopenia, granulocytopenia and thrombocytopenia all occur. Purpura is followed by more serious bleeding, such as menorrhagia, hæmoptysis, hæmaturia and retinal hæmorrhages. Necrosis of the jaw occurs. It is similar to that produced by phosphorus, and is attributed to infection supervening upon changes in the bone. In certain cases necrosis of the jaw does not occur, but after a number of years generalised changes in the bones develop with deformity and sometimes spontaneous fracture, a condition known as *radiation osteitis*. Bone sarcoma occurs in 25 per cent. of the cases of occupational mesothorium and radium poisoning.

**Treatment.**—**PROPHYLACTIC.**—Though medical practice is now almost safe so far as X-irradiation is concerned, matters are very different in the case of radium. There is no doubt that many people are affected by handling radium, chiefly by the

gamma rays. Their penetrative powers are so great that it is not practicable to secure complete protection. In the case of persons who carry radium about, the weight of lead they can bear to carry only partly protects them. Surgeons handling radium are also ill-protected. In the case of a man using 120 mg. of radium in the treatment of carcinoma of the cervix uteri, protection is very difficult as each time he has to handle the substance closely and carefully. In such circumstances the best protection is to keep the radium at as great a distance away as possible until it must actually be handled. It is obvious that ingestion or inhalation of radioactive materials in industry is highly dangerous, and that all occupations involving the handling of such substances should be strictly controlled and supervised. In the watch industry, outside New Jersey and Connecticut, the practice of pointing the brush with the lips is unknown, and no ill effects have been observed in other countries. In the luminous dial painting industry safety measures fall into two groups. First, there are precautions designed to reduce unavoidable exposure to a minimum and to improve the general conditions of work. These include protective gowns, rubber gloves and aprons, lead glass screens in front of the operatives and local exhaust ventilation. Secondly, examination of the operatives for over-exposure is necessary. In routine blood examinations, leucopenia, granulocytopenia or thrombocytopenia call for a change of occupation in the worker concerned. The hands must be repeatedly inspected for dermatitis. Workers must wear beta- and gamma-ray sensitive photographic films, and the radon appearing in the expired air must be repeatedly measured.

**SYMPTOMATIC.**—Like lead, radium has been shown to be stored largely in the bones. A course of treatment with calcium versenate (p. 371) may prove successful in reducing the amount of retained radium as indicated by the amount of radon in the expired air. For aplastic anæmia repeated blood transfusions will be necessary.

## INJURIES FROM FISSION PRODUCTS

Fission of the uranium nucleus has led to an industry concerned primarily with the development of bombs. The stable and radioactive isotopes are essentially by-products of work on atomic energy, but they are assuming increasing importance in research, therapeutics and industrial processes, and radiation hazards in peace-time are therefore not confined to establishments concerned with atomic energy research and production. Ionisation may be produced directly by charged particles such as electrons or protons, or indirectly by the passage of uncharged neutrons, which cause ionisation by collision with some of the atoms of the tissues.

**Dangers of exposure.**—Danger may arise from direct radiation or from the inhalation or ingestion of radioactive materials. Neutrons and gamma rays are exceedingly penetrating, alpha particles can be stopped by a sheet of tin foil and beta particles by a tenth of an inch of aluminium. Alpha and beta particles when taken into the body can cause an immense amount of damage although absorbed in a comparatively small thickness of tissue. Radioactive substances which are particularly dangerous are those which are selectively retained in the skeleton. Thus uranium, thorium, plutonium and the isotopes of strontium and yttrium are bone seeking. Since some of these elements are excreted very slowly they will irradiate both bone and bone marrow continuously for many years.

**Pathology.**—The essential effect of irradiation is cellular injury leading to tissue necrosis. The erythron, lymphoid tissues and immature germ cells are the most sensitive, and highly differentiated tissues such as bone, nerve and muscle are less severely affected. Haemorrhage results from vascular injury, thrombocytopenia and possibly from the presence of an anticoagulant substance in the blood. Secondary infection with ulceration of the gut and urinary tract and acute haemorrhagic necrotising pneumonia are common. Sterility may be temporary or permanent and radiation

cataract may appear years after exposure. Little is yet known as to the carcinogenic and mutagenic effects of ionising radiations. Contamination of residential areas by radioactive dusts might cause cancer, and the bone-seeking isotopes would constitute a special long-term hazard. An increased incidence of hereditary defects in future generations is also a danger.

*Effects of atomic warfare.*—The most destructive effects of an atomic explosion are due to blast and to the release of thermal radiation. Casualties from blast, flash burns, debris and fire comprised 85 per cent. of the deaths at Nagasaki and Hiroshima. Ionising radiation arises in several ways during the explosion and includes neutrons, gamma rays and beta rays. A small proportion of the energy of the explosion appears as fast neutron radiation, which has great penetrating power but which rapidly loses its energy in traversing matter. It is of secondary importance to the gamma radiation which is also highly penetrating. Beta rays come to rest completely after passing through a few yards of air. When an atomic bomb explodes high in the air fission products are dispersed and contamination does not occur unless they are carried down by rain. In ground or underwater explosions there is a risk of direct exposure, ingestion and inhalation. The risk diminishes rapidly during the first 24 hours and its total duration depends on the prevailing weather conditions, the half-lives of fission products and other complex factors.

*Symptoms.*—In atomic warfare casualties can be divided, according to the degree of severity, into four groups, but the clinical picture in all the victims may be complicated by the effects of burns and other injuries.

Group I. Following exposure to intense radiation, nausea, vomiting and shock occur within a few hours and there is progressive weight loss, fever and diarrhoea leading to death from toxæmia within 2 weeks.

Group II. With less severe exposure symptoms do not appear until about the third week, when loss of hair, aplastic anæmia, pneumonia and severe gastro-enteritis result in death in the majority within 6 weeks.

Group III. In those who survive beyond the sixth week aplastic anæmia may become chronic, although many will still die from pneumonia, enteritis and other forms of secondary infection. Complete recovery is possible within 6 months but weakness and fatigue are common during convalescence.

Group IV. In mild cases leucopenia, diarrhoea and loss of hair may be the only abnormalities.

*Protective Measures.*—In atomic energy establishments, plutonium factories and research laboratories sources of intense radiation such as reactors and cyclotrons are surrounded with screens of thick concrete. Inhalation of radioactive gases is prevented by the use of gas masks or more elaborate air conditioning devices, and protective clothing is worn to prevent direct contact. When materials are exceedingly active they are encased in screened cells and are manipulated by remote control, often with the aid of periscopes or by television. Pollution of the atmosphere with radioactive dusts is prevented by means of filters fitted to the stacks, and contaminated waste water is rendered inactive in special delaying and treatment tanks before it is released into the rivers and seas. Many forms of monitoring devices are used to ensure the effectiveness of precautions. All workers carry film badges, fountain pen monitors or other forms of electrometers; they also undergo medical examination with blood counts at regular intervals. The radiation levels of the environment are estimated with continuously running dust monitors, Geiger counters and other instruments which are either portable or fixed.

DONALD HUNTER.

## SECTION V

### DISEASES OF METABOLISM

#### BASAL METABOLIC RATE

By basal metabolism is meant the metabolism of an individual when he is lying down completely relaxed and in the post-absorptive state, *i.e.* about 12 hours after the last meal.

Food, particularly protein, will increase the metabolic rate, this increased metabolism being almost entirely due to increased activity of the liver. The metabolic rate of an individual is usually estimated by causing him to breathe into, and from, a closed system containing oxygen and also soda-lime to absorb the exhaled carbon dioxide. The rate of oxygen consumption is recorded, and the heat produced when this amount enters into the combustion of foodstuffs is calculated. This is then, conventionally, divided by the surface area of the individual, expressed in square metres and calculated from the height and weight. This figure is finally expressed as *plus or minus "x" per cent. as compared with a normal average value.*

Recent work has shown that there are several fallacies in expressing metabolic rate as a function of the surface area. In the first place, even in the normal, metabolic rate is not strictly related to surface area, and secondly, variations in the ratio between surface area and the weight of metabolically active tissue frequently occur in abnormal states. This is well illustrated by subjects who are severely undernourished, for their basal metabolic rate expressed conventionally in terms of surface area is very low, whereas when expressed in terms of metabolically active tissue it is only slightly below normal. In such subjects, the discrepancy seems mainly to be caused by a greatly increased extracellular fluid volume (shown, when extreme, as famine œdema) which increases the calculated surface area without contributing anything to the metabolic rate.

Determination of metabolically active tissue is, however, difficult and is in itself somewhat arbitrary. It is very unlikely to be used in routine clinical practice with the existing methods of estimation.

#### DISTURBANCES OF WATER AND ELECTROLYTES

Normally water constitutes 60 to 70 per cent. by weight of the body. Approximately 20 per cent. of the body weight is due to extracellular water and 40 to 50 per cent. to intracellular water. About one-quarter of the extracellular fluid is composed of plasma and the rest constitutes the interstitial fluid. The main electrolytes in the extracellular fluid are the basic ions, sodium, potassium and calcium, and the acidic ions, chloride and bicarbonate. In the intracellular fluid, potassium and magnesium are the main anions and phosphate, bicarbonate, sulphate and protein are the main cations. When considering these substances it is more convenient to express them in milliequivalents (meq.) than in mg., since 1 milliequivalent of a basic ion is equivalent to 1 milliequivalent of an acidic ion and thus in any solution the total concentrations of basic and of acidic ions are equal when expressed in this way. One milliequivalent of an ion is the ionic weight expressed in mg. divided by the valency. Thus 23 mg. of sodium is 1 milliequivalent and this would combine with 35.5 mg.—or 1 milliequivalent of chloride and so on. The following are the

normal mean concentrations of the main electrolytes of plasma and of intracellular fluid :

Plasma				Intracellular Fluid			
Cations	meq/l	Anions	meq/l	Cations	meq/l	Anions	meq/l
Sodium	140	Chloride	100	Potass.	153	Bicarb.	11
Remaining		Bicarb.	28	Magnes.	43	Organic Phos-	
Cations	10	Protein	18			phate	100
		Remaining				Protein	67
		Anions	4			Sulphate	18
Total	150		150		196		196

### DEHYDRATION

Dehydration is the body state which results from an abnormally low water content. This lack of water may affect both intracellular and extracellular compartments, or the major deficiency may occur in only one of them.

In the last resort, too little body water must occur as a result of a negative body water balance, hence it arises from any condition resulting in the loss of water being greater than the intake. The intake of water is controlled largely by the sensation of thirst, the precise stimulus for which is not fully known. Water loss can be considered under two categories, namely, insensible loss and loss composed of urine, faecal water and the water content of any other bodily losses such as vomitus, intestinal contents from fistulae, etc. Insensible loss is normally of the order of 1,000 ml. per day, but the precise amount can only be measured with the greatest difficulty. The loss from the other sources can be precisely measured.

Urinary water loss is controlled to a very great extent by variations in the secretion of anti-diuretic hormone (A.D.H.) by the posterior pituitary. These variations occur as a result of impulses from cells in the hypothalamus called osmo-receptors which are sensitive to changes in the osmotic pressure of extracellular fluid. When this rises above normal there is an increased secretion of A.D.H. with the result that only small quantities of highly concentrated urine are produced—so lowering extracellular osmotic pressure. With too dilute an extracellular fluid the opposite occurs and large quantities of dilute urine are secreted.

The concentration of sodium ion in extracellular fluid is the major factor in controlling its osmotic pressure. Over 90 per cent. of the osmotic effect of the basic ions is due to sodium and the total quantity of acidic ions follows that of the basic ions, bicarbonate being controlled rapidly by means of metabolic processes and respiration. It can be seen, therefore, that, if for any reason the body becomes deficient in sodium, extracellular water is regulated so that the osmotic pressure of extracellular fluid remain as normal as possible. Hence a deficiency of sodium leads to an extracellular water deficiency, one form of dehydration. By contrast, excessive quantities of sodium in the body lead to retention of water and to oedema production, if the quantities involved are great enough.

If the body loses water directly and not as a result of sodium loss, this results in a shift of water from the intracellular to the extracellular water compartment. Loss of water only is thus reflected in a general increase in osmotic pressure in both compartments.

The mode of origin, symptoms and signs and the treatment of these two forms of dehydration are different so that the differential diagnosis is important.

"SODIUM" DEHYDRATION.—This occurs whenever the loss of sodium from the body is greater than the intake, e.g. vomiting, diarrhoea, profuse sweating. Thirst is not a feature of this form of dehydration. More characteristically patients suffer from languor, apathy, muscular cramps, weakness and fatigue. Headache may be

present and also a tendency to syncope on standing. Nausea and vomiting also occur and this accentuates the dehydration. The skin is wrinkled and lacking in the normal elasticity. Reasonable quantities of urine are passed until the dehydration becomes extreme. With severe degrees of salt dehydration the patient enters a phase of oligemic shock, with cold, clammy skin and peripheral cyanosis. Stupor and even sudden death may then ensue. The hæmoglobin and hæmatocrit are markedly raised owing to the hæmoconcentration and the plasma sodium tends to be low, though not markedly so until the condition has become very severe. Gastro-intestinal function seems to be impaired as a result of salt depletion, and such considerable periods elapse before adequate amounts of salt have been absorbed from the alimentary tract that it is often advisable to correct the condition by giving salt solutions intravenously.

**WATER DEHYDRATION.**—Water dehydration in which there is lack of water without corresponding lack of sodium occurs when a patient is too weak or ill and so cannot ask for drinks, and also in special conditions such as on rafts after shipwreck.

Intense thirst is a prominent feature of this form of dehydration, but the loss of intracellular fluid is greater than that of extracellular fluid, and, until the dehydration is severe, there is only a relatively slight increase in the hæmatocrit and hæmoglobin values. There is, however, a great diminution in urinary output and the urine which is produced is highly concentrated. The mouth becomes dry and thirst intense. When the water deficiency is becoming severe the face becomes pinched and grey and there is a diminution in muscular power. There may also be emotional lability and, when the dehydration is very severe, confusion and hallucinations.

Water taken by mouth is rapidly absorbed and produces improvement in the general condition in a matter of a few minutes.

**OVERHYDRATION.**—By contrast with dehydration, overhydration occurs where the body water content is too high. By the mechanisms discussed above, it can occur either primarily as a result of too much water alone or secondarily to an abnormally great body sodium content, which itself results from a greater sodium intake than elimination (mostly by the kidney). As with dehydration, the two forms of overhydration produce quite different clinical pictures.

**PRIMARY OVERHYDRATION—WATER INTOXICATION.**—This occurs as the result of an excessive quantity of body water, relative to sodium. It usually arises only in the presence of deficient renal function whether this be due to renal disease or occasionally in some general metabolic disturbance such as Addison's disease. It has been noted to follow the administration of large watery enemata to children with megacolon and to follow over-enthusiastic efforts to produce sodium depletion in patients with cardiac failure. Restlessness, muscle twitchings and later convulsions and coma are the main clinical features. It seems probable that these effects are mainly due to excessive intracellular water, since treatment by the injection of hypertonic saline (50 to 100 ml. of 5 per cent. solution) causes a rapid improvement.

**OVERHYDRATION SECONDARY TO SODIUM RETENTION.**—This form of water retention is that which, if it is great enough, gives rise to oedema, the excess being contained in the interstitial spaces. It is most commonly found in congestive heart failure, in certain renal diseases associated with massive proteinuria and in liver disease. In these conditions the kidney conserves sodium and, associated with this, a corresponding amount of water. Because oedema is secondary to sodium retention it is treated by measures which deplete the body of sodium, such as sodium restriction to a daily intake of less than 20 mcq. (0.5 g.), large quantities (about 15 g. with each meal) of resins which absorb sodium from the alimentary canal and, where indicated, organic mercurial compounds. The latter act by preventing the renal tubules from reabsorbing sodium and, because of the osmotic effect of sodium in the tubular lumina, less water is reabsorbed so that a so-called saline diuresis occurs.

## ACIDÆMIA AND ALKALÆMIA

The normal reaction of the plasma is  $pH\ 7.4 \pm 0.05$ . When the hydrogen ion concentration is greater than this (the pH lower) a state of acidæmia exists; conversely, alkalæmia occurs when the pH is higher than the above levels.

Owing to the efficient buffering action of the blood and body fluids, considerable alterations in the electrolyte levels can occur with comparatively small changes in pH, though it should be noted that a change of 1 pH represents a tenfold change in hydrogen ion concentration. Since, however, bicarbonate is the most labile ion (owing to its rapid turnover and to the rapidity with which it may be retained or excreted as  $CO_2$  by the lungs), and since its concentration depends upon the difference between the other acid and the basic radicles, its plasma level is usually estimated in determining what degree of acidæmia or alkalæmia is present. The fundamental consideration is that carbonic acid reversibly dissociates into hydrogen ions and bicarbonate ions thus :



In accordance with the Law of Mass Action

$$k[H.HCO_3] = [H^+] \times [HCO_3^-]$$

where [ ] denotes "concentration of" and  $k$  is a constant. From this it follows that

$$\frac{1}{[H^+]} = \frac{1}{k} \times \frac{[HCO_3^-]}{[H.HCO_3]}$$

$$\text{Since } \text{Log } \frac{1}{[H^+]} = pH$$

$$pH = \text{Log } \frac{1}{k} + \text{Log } \frac{[HCO_3^-]}{[H.HCO_3]}$$

$$\text{Log } \frac{1}{k} = 6.1 \text{ for these circumstances}$$

$$\therefore pH = 6.1 + \text{Log } \frac{[HCO_3^-]}{[H.HCO_3]}$$

It can thus be seen that the pH is linearly related to the logarithm of the ratio of bicarbonate to carbonic acid; it is not dependent upon the concentration of bicarbonate alone or of carbon dioxide alone. Normally the ratio of  $[HCO_3^-]$  to  $[H.HCO_3]$  is 20 : 1. Thus normal  $pH = 6.1 + \text{Log } 20 = 6.1 + 1.3 = 7.4$ .

A disturbance of the acid-base balance can arise either from metabolic causes, such as failure of correct renal acid-base regulation, or the production of large quantities of organic acid radicles as in diabetic ketosis, or from lack of proper respiratory function as in hysterical over-breathing or in severe emphysema. In an acidæmia of metabolic origin, either a larger quantity of basic ions (largely  $Na^+$ ) than acidic ions have been excreted by the kidney, or, by processes of metabolism or deficient renal function, an abnormal concentration of acid radicles has accumulated. In either case there is a smaller difference between the total ionic concentration of base and of non-bicarbonate acid than usual. Thus the bicarbonate concentration will be lower than normal; usually, under these circumstances respiratory ventilation increases, so lowering the plasma carbonic acid concentration and tending to restore the pH to normal. In addition, owing to the loss of base there will be a loss of water and dehydration. By contrast, if an acidæmia is of respiratory origin, e.g. emphysema, it arises because carbon dioxide cannot be expired at a normal tension and hence the concentration of carbonic acid in the plasma becomes abnormally high. Owing to the relationship between this, pH, and bicarbonate concentration shown earlier, the level of bicarbonate must also rise if the pH is to be kept within the range compatible



with life. The total electrolyte balance under these circumstances is maintained largely by the excretion of chloride by the kidney. Hence in respiratory acidæmia, the concentration of plasma bicarbonate is higher than normal.

It can be seen from the foregoing that, in order to obtain a reasonably correct interpretation of acid-base balance, it is really necessary to estimate two of the three related factors  $pH$ ,  $(HCO_3^-)$ , and  $(H.HCO_3)$ . However, if it is known whether the primary fault is metabolic or renal on the one hand or respiratory on the other, an estimation of  $(HCO_3^-)$  alone should reveal any tendency towards acidæmia or alkalmia.

**ALKALI RESERVE.**—In the above discussion this term has been carefully avoided, since it has no really precise meaning and it may actually be misleading. Originally applied to the plasma bicarbonate concentration, and implying that the amount of alkali (largely sodium ion) corresponding to this was available in reserve to deal with any increase in acid radicles which might occur, the term is now sometimes referred to the plasma  $CO_2$  content. Actually the alkali corresponding to the bicarbonate cannot all be considered as a physiological reserve, since death occurs before the bicarbonate is all replaced; furthermore, as previously shown, in respiratory acidæmia the total amount of bicarbonate is greater than normal.

#### ACIDÆMIA

The main conditions encountered in practice which give rise to acidæmia are chronic renal deficiency, where the kidney cannot excrete the excess of acid over basic radicles which are present in a normal diet, acute diarrhœa where a large amount of base is lost in the stools, diabetic acidosis where, in association with defective carbohydrate metabolism, a grossly excessive quantity of organic acids is produced, and acute starvation where carbohydrate is not metabolised in normal amounts and there is a secondary production of organic acids. Prolonged vomiting may or may not produce acidæmia depending on whether the acid lost in the vomitus either is not or is great enough to be balanced by the organic acid production which results from the lack of food intake. As explained above, acidæmia also accompanies insufficient respiratory function from whatever the cause and it also occurs after profuse hæmorrhage.

The main symptom of acidæmia is an increase in the depth and rate of respiration, though this only becomes apparent when the degree of acidæmia is quite severe. The breathing is deep and relatively quiet, though owing to the rapid air flow there may be a hissing sound. This type of breathing is known as *acidotic breathing* or Kussmaul's respiration. Signs of sodium dehydration are usually also present.

In severe degrees of acidæmia the  $pH$  of the blood may exceptionally fall to 7.0 and, if the cause is renal or metabolic, the bicarbonate may fall as low as about 5 meq. per litre (11.0 volumes of  $CO_2$  per cent.).

#### ALKALÆMIA

Most commonly this condition occurs as a result of the ingestion of excessive quantities of alkali often because of peptic ulcer. It also occurs in patients with pyloric stenosis who vomit large quantities of acid fluid. It is sometimes found associated with renal failure, but here there has usually been an excessive intake of alkali, given to combat the acidosis which is commonly present initially. Hyperventilation by hysterical individuals can also give rise to quite serious degrees of alkalmia. A mild alkalmia is often found in Cushing's syndrome.

**Symptoms.**—There may be no symptoms even in the presence of a severe alkalmia. However, loss of appetite, nausea and vomiting may occur and may be accompanied by headache and mental abnormalities. Many of these symptoms,

If the high potassium results from adrenal deficiency then deoxycortone acetate (D.O.C.A.) 10 mg. intramuscularly should also be given at once, and the underlying condition subsequently treated in the usual way (see Addison's Disease). If, however, as is usual, the hyperpotassaemia is due to deficient renal function, potassium must be removed by means of peritoneal dialysis, by the use of an artificial kidney, or by taking 50 to 100 g. per day by mouth of a kationium resin charged with ammonium or sodium.

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## DIABETES MELLITUS

**Definition.**—Diabetes mellitus is not a disease entity, but includes a variety of related disorders of metabolism, having in common an increase in blood sugar, usually accompanied by glycosuria. In most of these there is also a greater or lesser tendency to ketosis, which is the most important immediate danger; and an increased liability to various forms of vascular degeneration, which are the most serious long-term risks.

**Prevalence.**—It is estimated that there are between 150,000 and 200,000 known diabetics in Great Britain and the incidence as everywhere is rising. Further, "detection drives" in the U.S.A. and elsewhere have shown fairly constantly that there are nearly as many mild undiagnosed cases as there are known ones; and the same may well be true in this country. Since the majority of diabetics are over the age of 40, and since the proportion of the population over the age of 40 is rising rapidly, it is likely that in 20 years' time 500,000 or nearly 1 per cent. of the population will be diabetic.

Though insulin has revolutionised the outlook for the diabetic in certain respects—the expectation of life of a 10-year old diabetic child is now 45 years instead of 1·3 years in the pre-insulin era—it has not prevented an alarming incidence of complications, particularly retinopathy, nephropathy and arteriopathy in those who have had the disease for some years. How far these complications are due to factors which cannot be controlled by insulin and diet, and how far to avoidable poor control of the diabetic state is not yet known, but the question must be regarded as one of the major problems of modern medicine.

**Aetiology.**—Knowledge of the aetiology of diabetes is quite incomplete, but two factors of importance have been recognised, an inherited tendency and overnutrition.

There are two kinds of evidence for an hereditary tendency. First a history of diabetes in one or more blood relatives is much commoner in diabetics than in non-diabetics; and secondly, concordance (i.e. both twins developing diabetes) is five times as common in identical twins as in fraternal twins. Identical twins indeed often develop diabetes of about the same severity, within a short time of each other. How far diabetes mellitus is genetically homogeneous and how the tendency is inherited is uncertain. It has been suggested that it is homogeneous, that the tendency is inherited in a simple recessive manner and that if all potential diabetics lived to the age of 90, the numbers actually developing the disease would be in accordance with this hypothesis. On the other hand, it has been suggested that the disease is heterogeneous, the severe early-onset cases being determined by recessive genes and the mild late-onset cases by dominant genes. If the assumption of recessive inheritance is correct for all diabetics, it appears that the number of carriers of the gene in the population is in the order of 25 per cent. Further, if it is proved that a considerable proportion of cases of diabetes are hereditary, this affection must rank as the most important, numerically and socially, of all hereditary diseases.

The importance of overnutrition is shown by the fact that over the age of 40 some 80 per cent. of patients developing diabetes are, or have been, considerably overweight. Broadly speaking, both the incidence and mortality of diabetes after middle

age vary directly with the degree of obesity; and in the War of 1914-1918 and the War of 1939-1945 both incidence and mortality fell with rationing.

It appears likely that when the inherited tendency is strong enough, the subject develops diabetes in childhood or youth without becoming fat; though the onset often follows a period of active growth, and children tend to be above average height when they develop the disease. If the inherited tendency is less strong, the disease becomes manifest only when precipitating factors "bring out" the inherited predisposition. The most important of these is obesity, though infection may act temporarily in the same way, and so possibly may nervous shock.

The disease is apparently commoner in urban than in rural communities, and in Jews than in Gentiles. These differences may well be due to habits as regards diet and physical exercise. It is possible that trauma, like any other form of shock, might hasten the time at which a person with latent diabetes manifests symptoms. The absence of an increased incidence of the disease in the battle casualties of the War of 1914-1918 and the War of 1939-1945 indicates that trauma can play no more important part than this, except in excessively rare cases in which a large part of the pancreas is destroyed.

**Pathology.**—In 1889 Minkowski produced diabetes experimentally by removing the pancreas from a dog. Langerhans had described his islets in 1869, and the hypothetical internal secretion of the pancreas was named "insuline" long before it was isolated. How it was finally isolated in 1921 after only a few months' work by Banting, then a young orthopaedic surgeon, and Best, a junior graduate assistant, is one of the medical romances of the century.

The pathogenesis at that time appeared deceptively simple. Lack of insulin due to a defect of the islets reduced the ability of the tissues to utilise glucose, which therefore accumulated in the blood, and was excreted in the urine. Impaired oxidation of glucose led to a hold-up in the metabolism of fat, so that intermediary products accumulated in the blood and led to ketosis. It soon became apparent, however, that this was an oversimplification. Histological studies on the pancreas showed that whereas in some human cases various changes, including fibrosis, hyaline changes and hydropic degeneration of the  $\beta$  cells are found in the islets, in at least 25 per cent. these are quite normal. Further, a number of patients have now survived total pancreatectomy and presumably have no insulin secretion of their own. They have been found to develop a moderate degree of diabetes easily controlled by 40, or at most 60, units of insulin a day. Since many "idiopathic" diabetics require well over 100 units a day, their diabetes cannot be due to a simple lack of insulin secretion.

A great deal of experimental evidence has implicated other endocrine glands, particularly the anterior pituitary. Indeed, the condition has been produced in suitable animals by injections of crude anterior pituitary extracts, and more recently of purified growth hormone. This fits in with the clinical observation that mild diabetes is seen in some cases of hyperpituitarism. It also might explain why diabetic women not only tend to have large babies, but sometimes give a history of having given birth to large babies long before they developed diabetes. It has been suggested that the growth hormone leads to growth as long as adequate insulin is available (and may increase the secretion of insulin for this purpose) but to diabetes where the supply of insulin is inadequate.

The explanation of the hyperglycæmia and glycosuria as due to the failure of the tissues to oxidise glucose has also been untenable for many years, at least in the simple form in which it is usually propounded. In 1923 Mann succeeded in removing dogs' livers. Such animals rapidly use up their available glucose and die in hypoglycæmic convulsions. It was soon shown that this is also true of diabetic dogs, who in the absence of the liver, die in hypoglycæmia as rapidly as non-diabetic ones; an observation which is incompatible with "under-utilisation" of glucose as the sole explanation of hyperglycæmia. Indeed it appears from the experimental work

of Soskin, amongst others, that one factor in the hyperglycæmia is the "overproduction" of glucose by the liver. In the normal animal there is a kind of "thermostatic" mechanism whereby a fall in blood sugar leads to an increased output of glucose from the liver and vice versa. In diabetes the "thermostat" is set at a higher level than normal, for indeed the liver goes on putting out glucose in an uncontrolled fashion to the limit of its capacity. Recent studies with radioactive glucose show, however, that underutilisation in the tissues is also important.

Similarly the "oxidation" of glucose in the tissues is an oversimplification. Molecular oxygen does not react directly with foodstuffs. The oxidative breakdown of energy materials in the tissues occurs by a series of reactions, including oxidation-reduction, decarboxylation, addition of  $\text{CO}_2$ , phosphorylation, hydrolysis and transamination. The most important step is the formation of glucose-6-phosphate from glucose, and this reaction is catalysed by an enzyme hexokinase. It has been suggested that hexokinase is inactivated by anterior pituitary hormone in the absence of insulin, and that this is the point at which insulin exerts its main effect. Fortunately ability to use insulin therapeutically has not had to await the exact elucidation of its pharmacological actions, which is still far from complete.

It does seem, however, that our concept of diabetes is approaching a new synthesis. It may be said that we depend for survival among other things on a delicate homeostatic mechanism which keeps the blood sugar in normal persons in a narrow range from about 70 to 160 mg. per cent. The most vital part of this mechanism is that which raises the blood sugar and prevents hypoglycæmia and unconsciousness in starvation, and this seems to be a function of the anterior lobe of the pituitary and the adrenal cortex. Insulin, which alone of the hormones lowers the blood sugar, is less immediately important.

Diabetes may be regarded as an imbalance in this mechanism, in which the blood sugar-raising factors predominate over blood sugar-reducing ones. Exhaustion of the islets of Langerhans with permanent changes in their structure may follow. Meanwhile the organism starves in the midst of plenty, and many features of its metabolism, including the tendency to ketosis, can be explained as analogous to those of starvation. It may well be, as Harold Wolff has recently suggested, that diabetes mellitus should be regarded as an inappropriate use of an adaptive-protective reaction, the anterior pituitary-adrenal mechanism which prevents hypoglycæmia in starvation.

**Clinical Picture.**—The classical onset with severe thirst, polyuria and loss of weight is seen in a minority, perhaps one-third of cases. Lack of energy, muscular weakness, mild thirst and some loss of weight are found in perhaps another third, if enquiry is made about them. Definite increase in appetite is unusual, though it is a safe generalisation in this country that real loss of weight with an increased appetite means either thyrotoxicosis or diabetes mellitus. Pruritus vulvæ and varying degrees of vulvitis are common in women, but generalised pruritus due to diabetes must be excessively rare, if it ever occurs. Men occasionally notice that spots of urine on their trousers dry leaving a white deposit, and some complain of impotence.

A few patients are virtually symptomless, the glycosuria being discovered when the urine is examined as a routine for life insurance or other purposes. Almost one-fifth present with symptoms of complications. Of these a very few patients are first seen in diabetic coma, or with severe neuropathy. Others are detected by ophthalmologists who see micro-aneurysms or other evidence of diabetic retinopathy, in antenatal clinics and by gynaecologists among women referred for vulvitis. A few are discovered by testing the urine of patients with boils and other staphylococcal skin infections.

It may be said that a majority of diabetics fall into one of two groups. The older and fatter tend to have mild symptoms with an insidious onset, more often present with a complication, have little tendency to ketosis and are relatively insensitive to insulin. The younger and thinner more often have severe and classical

symptoms, with a definite onset, are very liable to ketosis and are sensitive to insulin.

Physical examination shows nothing in mild uncomplicated diabetes. In severe cases there may be weakness and wasting with some degree of dehydration. In more severe cases a dry brownish tongue, the odour of acetone in the breath and an enlarged tender liver may indicate that the patient is in impending coma. As many patients have complications by the time they consult a doctor, no initial examination of a diabetic is complete without examination of the eyes for lenticular opacities and retinopathy; of the chest for signs of tuberculosis (and a radiograph of the chest should be taken, even if no signs are found); of the skin for septic infections; of the legs for loss of knee and ankle jerks and other signs of diabetic neuropathy, and of the feet for loss of pulsation in the dorsales pedes and posterior tibial arteries or other signs of impaired blood supply.

**Diagnosis.—Urine testing.**—The importance of routine urine testing for sugar will be evident from what has already been said. Benedict's test is preferable to Fehling's, but must be correctly performed. "Clinitest" and "Glucotest" are satisfactory and trouble-saving substitutes, provided the makers' instructions are followed exactly. A positive result with any of these tests indicates that a reducing substance is present in the urine, but not that the substance is glucose. "False positives" may be due to drugs such as aspirin, salicylates, chloral hydrate and ascorbic acid, or to the presence of other sugars, of which lactose in pregnant and lactating women is the only one of clinical importance.

In practice slight colour changes (*i.e.* a green colour) with Benedict's test should be ignored, or left for elucidation by a biochemist. A definite reduction (*i.e.* a yellow or red deposit) in an untreated patient with definite thirst and polyuria, is for practical purposes diagnostic of diabetes, and further investigations are unnecessary. If a definite reduction is found in a patient with no symptoms or with doubtful symptoms, it is best to proceed to the determination of a single blood sugar taken 1 to 1½ hours after a meal containing at least 80 g. of carbohydrate or to a sugar tolerance test.

The urine should also be tested in every case of suspected diabetes by Rothera's sodium nitroprusside test and Gerhard's ferric chloride test for the presence of ketone bodies. The clinical significance of these two tests is often not understood. The nitroprusside test is specific for ketone bodies, but is extremely sensitive so that it may be positive in the presence of a clinically very mild ketosis. A red or purple colour with the ferric chloride test may be produced by ketone bodies or by drugs, notably aspirin and salicylates and sodium aminosalicylate. In the former case the test will be negative if performed on boiled urine, since ketone bodies are volatile. The ferric chloride test, however, is relatively insensitive, and therefore if both tests are positive a ketosis of some severity is present. The practical significance of different findings with these tests is summarised in the table on p. 426.

**Blood sugars and the glucose tolerance test.**—In each case the patient should have been eating a normal amount of carbohydrate for at least a week before the test, since a normal person after a few days on a reduced carbohydrate diet may show an abnormal blood sugar curve. For this reason patients found to have glycosuria, without definite diabetic symptoms and without ketosis, should never be put on a diet until the diagnosis has been confirmed by further investigations.

A clinically probable diagnosis of diabetes mellitus can be confirmed by estimating a single blood sugar 1 to 1½ hours after a meal containing at least 80 g. of carbohydrate. If this is over 180 mg. per cent., the diagnosis is confirmed.

In symptomless glycosuria and in any case in which the diagnosis is really in doubt, it is wise to perform a glucose tolerance test. A normal blood sugar curve (*i.e.* a fasting blood sugar of under 110 mg. per 100 ml., rising to less than 180 mg. per 100 ml. in half an hour and returning to the fasting level within 2 to 2½ hours) with sugar in one or more corresponding specimens of urine indicates a lowered

renal threshold or renal glycosuria. This is a harmless anomaly and requires no treatment. The so-called "lag storage" or "steep" curve in which the blood sugar at half an hour rises to above 180 mg. per 100 ml. but returns to the fasting level within the usual time is also usually regarded as a harmless anomaly. In frank diabetes the fasting blood sugar is above 110 mg. per 100 ml., rises above 180 mg. per 100 ml. and either continues to rise or fails to return to the fasting level in 2 to 2½ hours. Provided the carbohydrate intake over the previous week has been adequate, and provided other causes of abnormal sugar tolerance, *i.e.* sepsis, thyrotoxicosis,

Sugar.	Nitroprusside test.	Ferric chloride test.	Significance.
+++ <i>i.e.</i> 2 per cent. or more	—	—	Probably D.M. but no immediate danger or urgency.
+++	+	—	D.M. with mild ketosis.
+++	++	++	D.M. with severe ketosis requiring urgent investigation and treatment.
+++	—	+	Probably a diabetic who has taken aspirin or salicylates.
—	+	—	Mild ketosis due to other causes, <i>e.g.</i> vomiting in children or starvation.

severe liver disease, hyperpituitarism and hypercortico-adrenalism can be excluded, a curve in which the blood sugar rises above 180 mg. per 100 ml. at half an hour and does not return to the fasting level at 2 to 2½ hours should be regarded as indicating diabetes mellitus. It may be added that the chief value of the glucose tolerance test is in excluding diabetes mellitus, and there is never any indication to perform it on a known diabetic under treatment with insulin.

**Treatment.**—The decision whether to treat a patient by diet alone or with insulin depends on the severity of the symptoms, the presence or absence of complications and the patient's age and weight, and not on the results of special investigations such as the glucose tolerance test. Obese adult patients with mild diabetes and no ketosis nearly always can and should be treated with a diet which will reduce their weight. Underweight patients with severe symptoms and especially with ketosis should always be treated with insulin, and so should children. In the case of adult

patients whose weight is in the normal range and who have no ketosis and no complications, it is justifiable to try the effects of a moderate reduction of the carbohydrate in the diet, but this form of treatment should not be continued for long unless control is good without progressive loss of weight.

Treatment will therefore be described under the following headings:

a. Treatment of obese patients by diet alone.

b. Use of insulin.

c. Treatment of patients with severe ketosis.

a. *Treatment of obese patients by diet alone.*—Such patients are usually over middle age and have mild diabetic symptoms or no symptoms. They quite frequently, however, have some complication, such as retinopathy, by the time they come for treatment. The treatment is that of obesity (*q.v.*). If such patients adhere to a diet of C. 1,200 to C. 1,400, diabetic symptoms, such as thirst and polyuria, disappear, and the hyperglycemia and glycosuria are usually rapidly controlled. If the weight is substantially reduced or reduced to normal, such patients are often able to eat a more liberal diet without a return of the diabetic state. But if the weight is allowed to increase again, the diabetic state returns. Amphetamine or dextroamphetamine 5 to 10 mg. in the morning and at midday may be prescribed to assist those who genuinely try to diet, but whose appetite defeats them. It is useless in the case of those who will not even try to diet.

Difficulty arises with overweight patients who fail to lose weight, especially if they have complications such as retinopathy or obliterative arterial disease. Insulin should be avoided if possible, since such patients are usually insulin resistant, and if treated with large doses of insulin, their weight only increases further.

b. *Use of insulin.*—Underweight patients must be treated with insulin since a diet of low calorie value would only lead to further loss of weight. It is important that the objectives of treatment with insulin should be understood. These are:

- (1) To enable the patient to live as normal a life as possible, earn a living and take part in ordinary activities. To achieve this it is necessary for him to learn more about the management of his own illness than is considered wise in any other condition. The main part of the work of a physician treating diabetics is to teach them how to look after themselves.
- (2) To keep the patient free from any symptoms of diabetes and from anything more than minor and occasional symptoms of hypoglycemia throughout the 24 hours; and free from ketosis at any time.
- (3) To keep the urine as free from sugar as possible and the blood sugar as near normal as possible, provided the attainment of this does not interfere with (1) and (2). It is, for instance, misguided to achieve a sugar-free urine for most of the day, if this means that the patient has hypoglycemic attacks so frequently that he is unable to earn his living, or that he has to spend most of his spare time testing his own urine and weighing out his food. There is, however, considerable room for skill in attaining (3) within the limits set by (1) and (2).

Insulin is a protein of molecular weight of 35,200. It is destroyed by the gastric secretion, and therefore cannot be given by mouth. It is usually injected subcutaneously, though it can also be given intramuscularly and intravenously.

It is biologically standardised and the international standard preparation is a quantity of pure dried crystalline insulin hydrochloride, 1 mg. of which contains 22 units of activity. It is supplied in strengths of 20 units per ml. (single strength); 40 units per ml. (double strength) and 80 units per ml. (quadruple strength). Since on most syringes 1 ml. is divided into ten divisions, each division corresponds to 2, 4 or 8 units. Insulin should, therefore, be prescribed in multiples of 4 or 8, and not of 5 and 10.

There are unfortunately seven different preparations available in different strengths in Great Britain at the present time. The important ones are :

**INJECTIO INSULINI (B.P.).**—"Soluble", "Regular" or "clear" insulin. Available in strengths of 20, 40 and 80 units per ml. Acts quickly and strongly. Action starts within half an hour and lasts 6 to 8 hours with doses up to 40 units, but up to 12 hours with very large doses. Hypoglycæmic symptoms most commonly occur 2 to 4 hours after injection, but may be delayed up to 8 hours or more with very large doses.

Soluble insulin is used :

1. In diabetic coma and severe ketosis (*q.v.*).
2. Three doses of soluble insulin a day, *i.e.* one dose before each main meal is often employed temporarily when specially strict control is necessary, *e.g.* at the beginning of treatment, during infections, before and after operations, in the latter months of pregnancy and in patients with active pulmonary tuberculosis.
3. Two doses of soluble insulin a day, *i.e.* before breakfast and before the evening meal, was for many years the standard treatment for all diabetics on insulin. It is still a useful method for those who are used to it and prefer not to change, for a few diabetics who are difficult to control on a single dose of any insulin and for those requiring very large doses. (More than 80 units of any insulin in one dose should be avoided if possible, on account of the danger of severe hypoglycæmia.) On this régime one-third of the carbohydrate should be taken at breakfast and one-third in the evening meal, with a small lunch and tea and a snack at mid-morning and last thing at night.

**INJECTIO INSULINI PROTAMINATI CUM ZINCO (B.P.).**—Protamine Zinc Insulin, "cloudy" insulin. Available in strengths of 40 and 80 units per ml.

Is prepared as a suspension which must be shaken before use, consisting of insulin hydrochloride combined with protamine, derived from the sperm of the rainbow trout, and zinc. It is slowly liberated and absorbed from the site of injection. Its action does not begin for 3 or 4 hours but lasts from 12 to 24 or more, according to the dose. When it is given before breakfast, hypoglycæmic attacks occur in the second half of the day or during the following night. It is, therefore, generally considered wise that the dose of P.Z.I. should be adjusted so that the specimen of urine passed on rising should contain a small amount of sugar. Some diabetics are satisfactorily controlled on a single dose of P.Z.I. given before breakfast. In these cases the action of the insulin must presumably be lasting for more than 24 hours. Others require a mixture of P.Z.I. and soluble insulin. The carbohydrate in the diet should be distributed in the proportion of approximately one-fifth at breakfast, at lunch, at tea and at supper, with a snack during the morning and last thing at night.

The usual method is to start with P.Z.I. and increase the dose until the urine passed on rising contains a small amount of sugar. If, when this is achieved, urine passed in the morning or early afternoon contains large amounts of sugar, soluble insulin is added to the morning injection. Theoretically the P.Z.I. and soluble insulin should be given in separate injections since P.Z.I. contains an excess of protamine, and mixed with the soluble this converts an unknown amount of soluble insulin to protamine insulin. In practice, satisfactory results are often obtained by mixing the two in the same syringe according to the following technique :

1. Inject air equivalent to dose of P.Z.I. into P.Z.I. bottle; withdraw needle and
2. Inject air equivalent to dose of soluble into soluble bottle and draw required amount of soluble into syringe.
3. Transfer needle to previously prepared P.Z.I. bottle and draw into syringe the amount of P.Z.I. required.



4. Withdraw needle from P.Z.I. bottle and give injection immediately.

The object of this routine is to avoid transferring P.Z.I. to the bottle of soluble insulin.

By varying the proportions of P.Z.I. and soluble insulin, it is possible to control many diabetics on a single morning dose, the main disadvantage of the régime being the danger of hypoglycæmic reactions at night. It seems likely that in the future a single injection of Insulin Zinc Suspension (Danish "Lente") or of a mixture of Insulin Zinc Suspensions will replace mixtures of P.Z.I. and soluble in most cases.

GLOBIN INSULIN WITH ZINC, prepared from ox globin, insulin and zinc, usually has an action midway between that of soluble and P.Z.I., that is to say, the action comes on in about 2 hours and lasts from 12 to 18. Hypoglycæmic reactions after a dose given before breakfast usually come on at midday or in the afternoon. The carbohydrate should, therefore, be distributed with rather more than one-third at lunch-time, one-fifth each at tea and supper, and one-fifth or rather less at breakfast, with small snacks at mid-morning and last thing at night. Globin insulin is useful for controlling some middle-aged and elderly diabetics, who do not need more than 40 units a day. If attempts are made to control more severe diabetics with a single daily dose of this insulin, they are often found to be hypoglycæmic at midday or in the early afternoon and at the same time to have diabetic symptoms (thirst, etc.) during the night.

INSULIN ZINC SUSPENSIONS (Danish "Semilente", "Lente" and "Ultralente").—It has recently been found that the phosphate previously used as a buffer inhibited the delaying action of zinc. The new Danish preparations consist of insulin precipitated with very small quantities of zinc and resuspended in an acetate buffer without the addition of any protein or protamine. The length of action was found to vary with the size and form of the insulin particles. Insulin Zinc Suspension Amorphous (Danish "Semilente", available in strength of 40 units per ml.) has an action lasting up to about 16 hours. Insulin Zinc Suspension Crystalline (Danish "Ultralente", available in strength of 40 units per ml.) has an action lasting up to 30 hours or more. A mixture of the two, consisting of 3 parts of amorphous to 7 of crystalline, Insulin Zinc Suspension (Danish "Lente", available in strengths of 40 and 80 units per ml.) has an action of approximately 24 hours, and has been introduced as the preparation likely to control most diabetics when used in a single dose. Mixtures in any proportions desired can, however, be made up from the amorphous and crystalline preparations, and will remain stable at ordinary temperatures.

I.Z.S. (Danish "Lente") is the variety which has been most used in this country at the time of writing. It appears that the effect is much like that of a mixture of P.Z.I. and soluble, except that hypoglycæmic reactions appear to be less common. With a single morning dose, these may occur during the morning or afternoon but rarely, if ever, at night. Local reactions to the injection are much rarer than with the older insulins. The carbohydrate in the diet should be distributed in three main meals, a quarter each at breakfast, lunch and tea, with a snack during the morning and a small supper in the evening.

Insulin Zinc Suspension Crystalline (Danish "Ultralente") appears to have much the same length of action as P.Z.I. or an even longer one. Insulin Zinc Suspension Crystalline (Danish "Semilente") is said to act for 12 to 16 hours, which would be somewhere between soluble insulin and globin zinc insulin. The action of I.Z.S. "Lente" can be lengthened by adding I.Z.S. crystalline "Ultralente" or shortened by adding I.Z.S. amorphous "Semilente"; or a mixture of any proportions of I.Z.S. crystalline and I.Z.S. amorphous can be made up to suit an individual patient. Insulin zinc suspensions cannot be mixed with P.Z.I. or globin insulin.

*Choice of insulin.*—There is no indication to change the régime of patients who are happy and doing well on two doses of soluble or on one dose of either P.Z.I. or globin insulin. I.Z.S. (Lente) should be tried on patients who are poorly controlled

on their present régime; on patients who dislike two injections a day, or on patients who are subject to frequent hypoglycæmia on their present régime and on patients who show allergic reactions to other types of insulin. When the transfer is made the distribution of carbohydrate in the diet must be altered to that already stated. The total dose of the previous régime should be given as I.Z.S. (Lente) before breakfast. Regular urine tests should then be made. The dose of insulin or the distribution of the carbohydrate in the diet may have to be adjusted, and if significant glycosuria is still found at bedtime or on rising, I.Z.S. Crystalline (Ultralente) may have to be added to the I.Z.S. (Lente).

*Control of insulin dosage.*—Good control means first a state in which the patient feels well, leads a normal life and is free from symptoms, and this is more important than normal biochemical findings. Further, the correct dose of insulin can only be determined when the patient is at home and leading a normal life. Patients with a normal renal threshold can usually be controlled satisfactorily by urine tests. Few, if any, such patients can maintain a sugar-free urine throughout the day without periods of hypoglycæmia, and a very few can never be got sugar free for any time without becoming hypoglycæmic. One should, however, aim to get the urine sugar free at some times during the day, even if temporary glycosuria occurs after the main meals. In determining how far this has been achieved, a record of a patient's own urine testing over a day or two of normal activities is of more value than is a single urine test or even a blood sugar under the abnormal circumstances of a visit to the doctor or the diabetic clinic. Reasonably intelligent and co-operative patients can all be taught to use the "Clinitest" apparatus.

If a patient, particularly an elderly one, is too easily controlled and shows constantly sugar-free urine without hypoglycæmia, one should suspect a high renal threshold. If a patient has frequent hypoglycæmic attacks, but is rarely or never sugar free, one should suspect a low renal threshold. In such cases the approximate level of the threshold can be determined by performing a series of simultaneous blood and urinary sugar estimations. Patients with low and high renal thresholds should have this information clearly marked on their records. The main indications for blood sugars in the control of treatment occur in dealing with such patients.

Some patients remain well controlled on a given dose of insulin for long periods. Others need more or less frequent adjustment of their doses. Sudden loss of control with heavy glycosuria or ketosis may be due to:

1. Infections such as colds, influenza, urinary infections, boils, injection abscesses or pulmonary tuberculosis.
2. Mistakes in measuring insulin, a leaking syringe or failure to take insulin.
3. Worry or "aggravation".
4. Serious dietary indiscretions.

Hypoglycæmia may be due to

1. Too large a prescribed dose or a mistake in measuring dose of insulin.
2. Missing a meal.
3. Unusual exertion.

*Hypoglycæmia.*—The usual symptoms are a sense of apprehension, hunger, sweating, trembling, palpitation and unsteadiness, which may progress to stupor, coma and convulsions. Some patients become emotionally unstable, or aggressive or behave as if they were drunk. With protamine zinc insulin headaches and lassitude may be complained of, particularly in the early morning; and nocturnal reactions may occur in which the patient may have night sweats or may pass into a convulsion without waking up. A few patients become unconscious almost without warning and old people may develop prolonged confusion. It is wise to think of hypoglycæmia whenever a patient receiving insulin complains of an unusual sensation or behaves in an unusual manner.

All diabetics on insulin should carry sugar (or glucose tablets) and take 2 to 4 lumps (10 to 20 g.) as soon as they recognise the symptoms. Many semi-comatose and uncooperative patients can be brought around if their heads are held firmly under the arm and spoonfuls of syrupy sugar solution are forced into their mouths. If the patient is comatose, glucose should be given intravenously in doses of 10 to 20 g. This is most conveniently administered as 33½ per cent. or even 50 per cent. glucose in a 20 ml. syringe.

*Local reactions to insulin.*—A few patients suffer from painful, red, itching bumps, which appear at the site of each insulin injection, and last about 36 hours. They appear to be due to a form of sensitisation. Sometimes they can be avoided by changing to a different brand of the same type of insulin. In rare intractable cases desensitisation may be attempted, but if the claim that they rarely occur with the new Insulin Zinc Suspensions is substantiated, change to one of these will usually be the simplest solution.

*Insulin fat atrophy.*—Curious hollows at the sites of injection due to disappearance of subcutaneous fat are sometimes seen in children and adult females, rarely in adult males. They can occasionally be disfiguring. No treatment is constantly effective, though it has been claimed that persistence in injecting the insulin into the tissue at the base of the hollow will cause it to fill up. The simplest course is to advise the patient to use 80 strength insulin and to make injections into the lower abdomen, the buttocks and the tops of the thighs, where loss of subcutaneous fat is unlikely to be noticed and may be welcome.

*Management of intercurrent illness.*—Many cases of ketosis and coma would be prevented if it were generally realised by both patients and doctors that diabetics with intercurrent illnesses, particularly infections, often need an increase in their insulin dosage. On no account should insulin be discontinued or the dose seriously reduced because the patient is unable to eat his ordinary diet, as this leads to ketosis and coma. If a patient is unable to eat his usual diet on account of an intercurrent illness, he should take his usual dose of insulin (or a larger one) and take the carbohydrate of the diet either in the form of sugar in water or lemonade, or as some kind of carbohydrate in fluid form. This can easily be arranged if it is remembered that 10 g. of carbohydrate can be taken as:

Sugar .. ..	2 large lumps or 2 teaspoonfuls.
Glucose .. ..	½ oz. or 2 teaspoonfuls.
Orange juice ..	4 oz.
Milk .. ..	7 oz.
Horlicks } ..	2 heaped teaspoonfuls.
Ovaltine }	

*Diets for patients on insulin.*—The argument between the protagonists of "fixed" and "free" diets is to some extent a matter of words. No one seriously suggests that a diabetic on insulin should be free to gorge on sweets one day and eat almost nothing the next; and no one now attempts to make patients weigh all food eaten. Both accept the need for some degree of control, but differ as to how the control should be exercised. A reasonable compromise is to ask patients to learn to measure their carbohydrate foods by weighing them until they can guess standard 15 or 5 g. portions of carbohydrate foods fairly accurately, and thereafter to weigh them occasionally as a check on their ability to guess. They can thus limit themselves to a prescribed amount of carbohydrate and a prescribed distribution of carbohydrate among the meals for the day without undue hardship. Protein foods and fat are allowed in "average" amounts, though patients should be warned to avoid an excess of fat in view of the probable association between a high fat intake and atherosclerosis.

In arranging a diet for an intelligent and knowledgeable patient, it is usually

enough, therefore, to prescribe the total amount of carbohydrate and how it should be distributed throughout the three or four main meals of the day. Such patients can then select such 15 or 5 g. portions of whatever carbohydrate foods they prefer. Less intelligent patients may need to have the exact foods they should take written out for them, as in the following example:

BREAKFAST		CH in grammes	
Tea or coffee with milk from allowance.			
Breakfast cereal, $\frac{2}{3}$ oz., or porridge made from oats, $\frac{2}{3}$ oz.	..	15	
Bacon, egg, fish, etc., an average portion.			
Bread, 2 oz. (two $\frac{1}{2}$ -in. slices off a large loaf)	..	30	
Butter or margarine from allowance.			
		<hr/>	
		45	
		<hr/>	
MID-MORNING			
Tea or coffee with milk from allowance.			
1 plain biscuit .. .. .	..	5	
		<hr/>	
DINNER			
Meat, fish, rabbit, liver, cheese, etc., an average portion.			
Unthickened gravy.			
Potato, 6 oz., or bread, 2 oz.	..	30	
Vegetable from Group II, as desired.			
Fruit from Group I, 2 portions .. .. .	..	10	
		<hr/>	
		40	
		<hr/>	
TEA			
Tea, with milk from allowance.			
Bread, 2 oz. .. .. .	..	30	
Butter or margarine from allowance.			
Tomato, watercress, cucumber, Marmite (to make sandwiches).			
		<hr/>	
		30	
		<hr/>	
SUPPER			
Fish, cheese, meat, egg, bacon, etc.			
Salad or vegetable from Group II.			
Bread, 2 oz., or potato, 6 oz. .. .. .	..	30	
Butter or margarine from allowance.			
Fruit, 3 portions or equivalent .. .. .	..	15	
Tea or coffee, with milk from allowance.			
		<hr/>	
		45	
		<hr/>	
BEDTIME			
Tea or coffee, with milk from allowance.			
1 plain biscuit or equivalent .. .. .	..	5	
		<hr/>	
Daily allowance of milk = 1 pint .. .. .	..	30	
Daily allowance of butter or margarine = $1\frac{1}{2}$ oz.			
		<hr/>	
Total carbohydrate .. .. .		200 g.	

This diet has the carbohydrate divided more or less equally throughout the day, as is generally suitable for a patient on a mixture of P.Z.I. and soluble. For other régimes, rearrangement of the carbohydrate would be necessary as indicated in the table. Substitutions can be made *ad lib.* A few examples follow :

#### SUBSTITUTES FOR 1 OZ. BREAD (15 G. CARBOHYDRATE)

Or 3 portions of any fruit or vegetable from Group I.

Milk .. .. .	10½ oz.	Rice, sago, etc. .. .. .	} 3 oz.
Orange juice .. .. .	6 oz.	Cornflakes .. .. .	
Potato .. .. .	3 oz.	Oatmeal .. .. .	
Jam .. .. .	} ½ oz.	Quaker oats .. .. .	
Marmalade, etc. .. .. .		Vita-Weat biscuits .. .. .	
Ovaltine .. .. .		Ryvita biscuits .. .. .	
Plain biscuits .. .. .			

The following weighed amounts of these fruits and vegetables may be exchanged for either 1 oz. potato or ½ oz. bread or 3½ oz. milk.

*Each portion contains 5 g. CARBOHYDRATE*

#### FRUITS

##### Group I.

Banana, without skin .. .. .	} 1 oz.	Apple, raw .. .. .	} 2 oz.
Grapes .. .. .		Cherries, raw .. .. .	
Prunes, stewed .. .. .		Damsons, raw .. .. .	
Raspberries, raw .. .. .	} 3 oz.	Pears, raw .. .. .	
Strawberries, raw .. .. .		Plums, raw .. .. .	
		Orange, without skin .. .. .	

#### VEGETABLES

##### Group I.

Baked beans .. .. .	} 1 oz.	Peas, fresh .. .. .	2 oz.
Butter beans, boiled .. .. .		Carrots, boiled .. .. .	4 oz.
Peas, tinned .. .. .			
Potatoes, boiled .. .. .			

#### FRUIT AND VEGETABLES

##### Group II.

An average helping of any of the following fruits or vegetables may be taken in addition to the other foods given on the diet sheet :

ARTICHOKES	CELLERY	MARROW
ASPARAGUS	CUCUMBER	GOOSEBERRIES, stewed without sugar
BROCCOLI	FRENCH BEANS	MUSHROOMS
BRUSSELS SPROUTS	GRAPEFRUIT	RHUBARB
CABBAGE	LETTUCE	OLIVES
CAULIFLOWER	LEMON JUICE	RADISHES
		TOMATOES
		RUNNER BEANS
		WATERCRESS

No exact rules can be laid down for the total amount of carbohydrate. This will depend on the age, weight, appetite and habits of the particular patient, and may

vary for an adult by anything from 120 to 350 g. or more, which with average amounts of protein and fat will correspond roughly to 1,200 to 3,500 calories. Growing children and adolescents should be given larger amounts of carbohydrate in proportion to their weights than adults. The aim should be to provide a diet which satisfies patients' appetites but keeps them from getting fat.

The distribution of carbohydrate foods in the day varies with different insulin régimes, and may have to be adjusted by a process of trial and error for individual patients. The following table shows some of the properties of different insulins and the kind of distribution of carbohydrate generally found most suitable for the commonly used régimes:

Type of insulin	Strengths available in units per ml.	Length of action	Time of maximum effect (when hypoglycæmic attacks are most likely)	When given	Suggested distribution of CH in diet (for total of 200 g. per day)					
Soluble	20, 40, 80	Small doses $\frac{1}{2}$ to 6 hours  Large doses $\frac{1}{2}$ to 10 or 12 hours	2 to 5 hours after injection  2 to 8 hours after injection	About 20 minutes before breakfast and evening meal	Breakfast	Mid-morning	Lunch	Tea	Evening Meal	Last thing
					65	10	30	20	65	10
P.Z.I.	40, 80	4 to 24 hours or more	Afternoon, evening, night or early morning	About 20 minutes before breakfast	40	10	45	45	50	10
Globin	40, 80	2 to 18 hours	Midday or early afternoon	About 20 minutes before breakfast	30	10	70	40	40	10
I.Z.S. Lente	40, 80	2-24 hours	Morning or afternoon	About 20 minutes before breakfast	50	10	50	50	30	10
					60	20	50 or 30	30	30	10

Patients with severe diabetes are best admitted to hospital for rapid control. Others can start treatment successfully at home, preferably with the help of a district nurse.

In either case, a patient who is not in ketosis can be placed immediately on the diet considered likely to be suitable for his age and occupation. In hospital rapid control of more severe cases can usually be obtained by starting soluble insulin in doses of from 16 to 24 units three times a day, 20 minutes before the three main meals; and by increasing or decreasing the dose according to the results of urine tests. When satisfactory control has been attained, two doses of soluble insulin or an equivalent single dose of a long-acting insulin may be substituted for three doses of soluble.

In milder cases starting treatment at home, it is usually satisfactory to begin

with a single small dose of a long-acting insulin, and to increase this gradually according to the results of urine tests. It will usually be found satisfactory to start with a dose of 12 or 20 units and to increase this by 4 or 8 units at each visit.

*c. Treatment of patients with ketosis.*—The treatment of coma is considered under complications. Patients with mild ketosis (positive nitroprusside test, negative ferric chloride test) should have their dose of insulin increased by one-quarter or one-third, and should be seen again within a few days. Patients with severe ketosis (positive nitroprusside and ferric chloride tests), whether new or known diabetics, should be treated vigorously, preferably in hospital.

The ketosis is abolished most rapidly by giving soluble insulin and either glucose or carbohydrate feeds at frequent intervals. In some cases it may be enough to continue with the patient's usual diet and give a dose of soluble insulin before each of the three main meals. In more severe cases the following régime will be found useful:

#### STAGE I (4-hourly insulin and glucose)

Forty g. of glucose in water or lemonade, with 20 units of soluble insulin subcutaneously every 4 hours. The urine is tested 4-hourly and the insulin dosage increased or decreased as necessary. This is continued until the urine is free from ketone bodies, and vomiting has ceased.

#### STAGE II (thrice daily insulin and fluid or semi-solid carbohydrate feeds)

Insulin			CH in grammes
	7.30 a.m.		
	8 a.m.	Tea made with milk from allowance.	
		Porridge made from $\frac{2}{3}$ oz. oats or breakfast cereal, $\frac{2}{3}$ oz.	
		Glucose or sugar, 15 g. . . . .	30
		Milk from allowance.	
		Orange juice, 6 oz., with glucose, 10 g. . . . .	25
			55
			—
	10 a.m.	Lemonade (fresh lemon juice and water), glucose, 10 g.	10
		Cream crackers, $\frac{1}{2}$ oz. . . . .	10
			20
			—
	12 noon.	Clear soup, meat or yeast extract.	
	1.30 p.m.		
	2 p.m.	Milk pudding made from:	
		Semolina, rice, sago, tapioca, $\frac{2}{3}$ oz. . . . .	15
		Milk from allowance.	
		Glucose or sugar, 15 g. . . . .	15
		Orange juice, 6 oz., with glucose, 10 g. . . . .	25
			55
			—
	6 p.m.	Tea, with milk from allowance.	
		Cream crackers or water biscuits, 1 oz. . . . .	20
		Butter from allowance.	
			20
			—

CH in grammes

	8 p.m.	Clear soup, meat or yeast extract.				
Insulin	9.30 p.m.					
	10 p.m.	Remainder of milk from allowance.				
		Horlicks or Ovaltine, $\frac{1}{2}$ oz.	..	..	..	10
		Cream crackers, 1 oz.	..	..	..	20
		Orange juice, 6 oz., with glucose, 15 g.	..	..	..	30
						<hr/> 60
						<hr/>
		Daily allowance of milk, 1 pint				30
		Daily allowance of butter or margarine $\frac{1}{2}$ oz. }			..	
						<hr/>
		Total carbohydrates	..	..	..	240 g.

## STAGE III (thrice daily insulin and light diet)

Insulin	7.30 a.m.						
Breakfast	8 a.m.	Tea or coffee, with milk from allowance.					
		Boiled or poached egg.					
		Bread or toast, 2 oz.	..	..	..	..	30
		Butter from allowance.					
		Marmalade or jam, $\frac{1}{2}$ oz.	..	..	..	..	15
		Orange juice, 4 oz.	..	..	..	..	10
							<hr/> 55
							<hr/>
Mid-morning.		Meat or yeast extract.					
		Water biscuits, $\frac{1}{2}$ oz.	..	..	..	..	10
							<hr/>
Insulin	11.30 a.m.						
Lunch	12 noon.	Steamed fish or rabbit or chicken, a small portion.					
		Boiled potatoes, 3 oz.	..	..	..	..	15
		Cabbage, spinach, cauliflower, as desired.					
		Grapes, 3 oz., or bananas, 3 oz.	..	..	..	..	15
		Orange juice, 6 oz., with glucose, 10 g.	..	..	..	..	25
							<hr/> 55
							<hr/>
Tea		Tea, with milk from allowance.					
		Digestive biscuits, 1 oz.	..	..	..	..	20
							<hr/> 20
							<hr/>
Insulin	6 p.m.						
Supper	6.30 p.m.	Clear soup or meat or yeast extract.					
		Cream crackers, 1 oz.	..	..	..	..	20
		Rice, semolina, sago, $\frac{2}{3}$ oz.	..	..	..	..	25
		Milk from allowance	..	..	..	..	
		Glucose or sugar, 10 g. (as milk pudding)	..	..	..	..	5
		Stewed apple, 4 oz.	..	..	..	..	10
		Glucose or sugar, 10 g.	..	..	..	..	<hr/> 60
							<hr/>



	CH in grammes
Bedtime.	
Remainder of milk from allowance.	
Ovaltine or Horlicks, $\frac{1}{2}$ oz. . . . .	10
or 1 plain biscuit, $\frac{1}{4}$ oz.	
	<hr/> 10
Daily allowance of milk, 1 pint. . . . .	} 30
Daily allowance of butter or margarine 1 oz.	
	<hr/> 30
Total carbohydrates . . . . .	240 g.
	<hr/>

From Stage III the patient can be changed back to his usual diet and insulin régime.

**SURGICAL OPERATIONS ON DIABETICS.**—*Emergency operations.*—In an emergency a diabetic patient with glycosuria, but without ketosis, can safely be operated on without preliminary treatment. If the patient is found to have a ketosis of any severity (nitroprusside and ferric chloride tests positive), the operation should, if at all possible, be postponed for a few hours while the ketosis is treated vigorously with frequent doses of soluble insulin. The dose must depend on the patient's previous dose, the severity of the ketosis, the degree of urgency and the experience of the physician, but 20 to 40 units of soluble insulin hourly would be safe and suitable for most patients. As such a patient is likely to be severely dehydrated, he should also be given several litres of either half normal saline by mouth or normal saline intravenously. If he has been vomiting, the stomach should be washed out before the operation. One of the main difficulties is the diabetic patient who presents in ketosis with symptoms suggesting an abdominal emergency. Patients with ketosis alone may have vomiting, abdominal pain, tenderness, rigidity and a leucocytosis, which improve rapidly when the ketosis is corrected. In doubtful cases the history is of more value than the physical signs. If thirst and polyuria preceded the abdominal symptoms, it is likely that the whole picture is due to diabetic ketosis. If the abdominal symptoms preceded the thirst and polyuria, it is more likely that the ketosis is the result of acute abdominal disease.

*Planned operations.*—Diabetic patients should be in hospital for a few days before operation for regulation of the diabetes. Those on a small dose (*i.e.* under 20 units) of a long-acting insulin can remain on this régime. Those on a larger dose should be changed temporarily on to two or three doses of soluble insulin. On the day of the operation, the patient should be given a dose of soluble insulin and a carbohydrate feed 3 to 4 hours before the operation. No rule can be given as to the exact amounts. The dose of soluble insulin may be  $\frac{1}{2}$  to  $\frac{2}{3}$  the patient's usual morning dose of soluble insulin, reckoned on the basis of control by two daily doses of this type of insulin; 32 units of soluble insulin and 64 g. of glucose in water flavoured with orange juice would be average amounts. Hypoglycæmia is a greater danger than hyperglycæmia under the anæsthetic, and this will be avoided if 2 g. of glucose are given for every 1 unit of insulin.

With good pre-operative treatment of the diabetes, the choice of anæsthetic is not particularly important. Ether and chloroform are best avoided. Regional and spinal anæsthetics when practicable are satisfactory, but not by any means essential. Gas and oxygen or intravenous thiopentone followed by cyclopropane and oxygen have given excellent results.

The object in the post-operative period is to give carbohydrate either as intravenous 5 per cent. glucose or as fluid carbohydrate feeds, covered by adequate amounts of soluble insulin, until the patient can return to his normal diet or régime. A ratio

of 1 unit of insulin to 2 g. of glucose will usually be found satisfactory. A minimum of 160 g. of glucose a day, i.e. 40 g. and 20 units soluble insulin 6-hourly should be maintained, the amount of insulin being varied according to the results of urine tests. The stage I, II and III diets for the treatment of severe ketosis (p. 435) can be used satisfactorily with or without minor modifications for most such patients.

*Pregnancy in diabetics.*—Insulin therapy has made pregnancy practically as safe for the diabetic as for the non-diabetic mother, provided she has the benefit of strict and skilled diabetic supervision. It has not, however, done the same for the fetus, and in general the foetal loss rate from intra-uterine death, obstetric complications and neonatal death has remained in the region of 40 per cent.

It is known that women who subsequently develop diabetes tend to have large babies, as well as diabetic women; and also that the high foetal loss rate is evident before the onset of the diabetes, particularly in the last 2 years before this onset. It is also known that diabetic women show an undue incidence of hydramnios and toxæmia of pregnancy. Diabetic babies, apart from their size, usually have a tough leathery skin with coarse features. There is œdema of the skin and subcutaneous tissues. The heart, liver and spleen may be pathologically enlarged, and there is a high incidence of congenital abnormalities. The babies are usually slow and lethargic and subject to cyanotic attacks in the first few days of life. It seems likely that such babies may be hypoglycæmic shortly after birth, but it is unlikely that this accounts for the high early neonatal death rate. In practice, oxygen seems more important than glucose. Babies that survive this period are often difficult to feed and rear at first, but then develop normally.

It seems likely that the abnormal features of diabetic pregnancies are associated with a complicated hormonal disturbance, in which, amongst other things, the placenta fails to utilise chorionic gonadotrophin in the production of œstrogen and progesterone, particularly in those women who develop toxæmia. It is uncertain, however, whether the hormonal upset is the result or the cause of the abnormal pregnancy states. The whole subject is still under investigation, and substitution therapy with synthetic œstrogens and progesterone must be regarded as experimental.

There is no doubt that strict control of the diabetes is essential. The insulin requirements of pregnant diabetic women undergo variations, and usually increase considerably as the pregnancy proceeds. Further, the renal threshold commonly falls between the third and fifth month, which makes good control more difficult. Such women should be under close supervision and should be seen at short intervals. Those on large single doses of a long-acting insulin should be changed to two or three doses of soluble insulin a day. When control is difficult, such patients may have to be admitted to hospital once or twice during the pregnancy, and should all be admitted by the thirty-second or thirty-third week. Most authorities now favour Cæsarean section at or about the thirty-sixth week. This reduces the incidence of toxæmias and foetal deaths, which are commonest in the last week or two of pregnancy, and avoids prolonged labour and obstetrical difficulties, but is open to the objection that it may increase the neonatal death rate by adding prematurity to the babies' difficulties. There is often a rapid fall in the mother's insulin requirements early in the puerperium.

*Complications.*—Diabetics appear more liable than normal persons to suffer from infections (particularly staphylococcal skin infections) pulmonary tuberculosis and urinary infections (commoner in women), from cataracts and from various forms of arterial degeneration. Diabetic ketosis and coma, nephropathy, neuropathy, retinopathy and a rare form of "true diabetic cataract" may be regarded as true complications of diabetes.

*Diabetes and pulmonary tuberculosis.*—Diabetics should have their chests radiographed as a yearly routine, and pulmonary tuberculosis should always be remembered as a possible cause of unexplained loss of weight or deterioration in diabetic

control. Patients with diabetes and active pulmonary tuberculosis should be treated with a liberal high carbohydrate diet and enough insulin to ensure good control. It is often necessary to give such patients two or three injections of soluble insulin a day, and to vary the dose frequently to obtain good control. It has been claimed also that isoniazid impairs carbohydrate tolerance and may increase insulin requirements. There is unfortunately a shortage of suitable accommodation where patients may get the most expert control of both their tuberculosis and their diabetes.

*Arteriosclerosis and obliterative arterial disease in the legs.*—It is probable that diabetics are more liable than non-diabetics to all forms of arterial degeneration, including coronary and cerebral artery disease and obliterative arterial disease in the legs. The reason is unknown, as is the pathogenesis of arteriosclerosis in general. It has been suggested that arteriosclerosis is an integral and inevitable part of certain forms of diabetes, but some physicians with great experience believe that its onset is delayed by strict treatment. Obesity appears to be a factor, and this is an additional reason for encouraging obese diabetics to reduce their weight.

Obliterative arterial disease in the legs presents in diabetics more often as gangrene than as intermittent claudication. The reverse is the case in non-diabetics. Arteriography shows that this is due to the fact that the obstruction in the arteries of diabetics is usually in peripheral vessels, rather than in the femorals and popliteals. The incidence is related to age rather than to the severity or duration of the diabetes.

Many of the complications of poor circulation in the feet, infected corns, calluses and ulcers—all of which may lead to gangrene—can be prevented by foot precautions. Older diabetics should be taught to wash, dry and powder their feet daily. Drying and powdering between the toes is particularly important to prevent fungus infestations, which may be the start of septic infection and gangrene. Toe-nails should be cut carefully straight across by someone with good eyesight, and corns should be treated cautiously by experienced chiropodists.

The treatment of intermittent claudication does not differ from that in non-diabetics, and drugs are equally ineffective. Good control of the diabetes and the use of antibiotics has robbed diabetic gangrene of its worst terrors. Patients with localised areas of gangrene, usually of a toe, should be in bed with a cradle over the foot, which should be only lightly covered. The diabetes should be well controlled and antibiotics should be used *secundum artem* to control infection. The gangrenous area can be kept clean and dry with spirit or covered with tulle gras. If a radiograph shows there is no necrosis of bone, the most conservative surgery, merely "nibbling" at the gangrenous area, will produce excellent results. If necrosis of bone is present, the affected digit or portion of the foot should be amputated. Mid-thigh amputation is only necessary in a small minority of patients, when all more conservative measures have failed.

*Diabetic coma.*—Diabetic coma is one of the most serious of medical emergencies and one with a considerable mortality, unless it receives skilled and speedy treatment and constant attention. It cannot be emphasised too often, therefore, that most cases of diabetic coma are preventable. The exceptions are occasional patients with undiagnosed diabetes, who present in coma without ever having consulted a doctor, and a few patients who are either too stupid, too unco-operative or too ill-disciplined to learn to avoid it, however much effort is expended on their education. Coma can occur if a patient has an infection or if he stops taking insulin, but it occurs most commonly from a combination of these causes. A patient with an infection cannot eat his normal diet, and therefore stops taking his insulin. Many cases of coma would be prevented if both doctors and patients understood how to deal with infections and intercurrent illnesses as outlined on p. 431.

The main clinical features of diabetic coma are listed in the following table and contrasted with those of hypoglycaemic coma, though the big difficulty in practice

is usually not in diagnosing between these conditions, but between diabetic coma and other varieties of coma occurring in a diabetic.

	<i>Diabetic.</i>	<i>Hypoglycæmic.</i>
History.	Missed insulin. Infection, etc.	Missed meal. Unusual exertion, etc.
Onset	Slow.	Rapid.
Skin.	Dry.	Sweating.
Tongue.	Dry.	Moist.
Pulse.	Small volume.	Bounding.
B.P.	Reduced.	Normal or raised.
Breath.	May be acetone.	No acetone.
Eye-ball tension.	Reduced.	Normal.
Respiration.	Deep and slow "air hunger".	Rapid and shallow.
Urine.	Sugar. Ketosis ++.	May be sugar. No ketones.
Blood sugar.	Usually 400 mg. per cent. or over.	Less than 60 mg. per cent.
Plasma CO <sub>2</sub> .	Diminished.	Normal.

Diabetic coma is a major emergency and should, if at all possible, be treated in a hospital with facilities for urgent biochemical investigations, but treatment should be begun without waiting for the results of such investigations. If the practitioner is certain of the diagnosis of severe diabetic coma, he should give 100 units of soluble insulin before sending the patient to hospital.

Wherever the patient is to be treated, he should be placed in a warmed bed and a specimen of urine should be obtained immediately by catheter. If blood sugar estimations are not available, the catheter should be left in position, so that regular specimens can be obtained.

Treatment consists in:

1. Adequate doses of insulin. Give 100 units (80 i.m. and 20 i.v.) as soon as diagnosis is made. Take blood for blood sugar. If this is over 600 mg. per cent., give further 100 units by same routes. Repeat blood sugar at 1½-hour intervals and adjust further insulin dosage accordingly. If no facilities for blood sugars, give 100 units and then 40 units hourly. Amount of sugar in urine gives no indication of blood sugar until this falls below 300 mg. per cent.

2. Replace water and salt deficiency. Set up intravenous drip and give normal saline, or better, "saline-lactate" solution (Nabarro) consisting of:

Sodium chloride	.. 5.85 g.
Sodium lactate	.. 3.36 g.
Distilled water to	1 litre

Give 1 litre in 15 minutes, a second in the first hour and then continue more slowly; 6 or 8 litres of parenteral fluid in the first 12 hours or so is not an excessive amount. The blood pressure should be taken half-hourly, and if this falls or if other signs of circulatory collapse appear, blood (or dextran or plasma) should be given in place of the saline or saline lactate solution.

3. Wash out stomach and evacuate colon.

Patients in diabetic coma often have dilated stomachs containing quantities of fluid, which may be regurgitated and inhaled. The stomach should therefore be evacuated by stomach tube and washed out with warm water, and the tube may be left in position to allow of repeated gastric suction. Patients are also sometimes extremely constipated, with palpable scybala in the colon. As soon as the patient is out of danger from ketosis and dehydration, olive oil should be given per rectum and followed by plain water enema.

4. Look for and treat any infections (boils, injection abscesses, pulmonary tuberculosis, etc.) which may be present. Penicillin 500,000 units b.d. should be given prophylactically even if no infection is found.

5. When the blood sugar begins to fall, or if blood sugars are not available, when the sugar in the urine diminishes, substitute 5 per cent. glucose for the saline or saline lactate solution, and give at the rate of 1 litre every 4 to 6 hours. Once the patient is conscious and the blood sugar is normal, give sips of water, followed by milk and fluid carbohydrate feeds. Transition to a normal diet can be conveniently planned by using the diets provided for the treatment of severe ketosis (p. 435).

It is now known that once ketosis is controlled, the greatest danger is deficiency of potassium. Under ideal conditions, intravenous 5 per cent. glucose should be replaced by a solution containing glucose, potassium and other electrolytes, provided always the urinary output is normal. When such a solution is not available, 5 per cent. glucose should be used and potassium should be given by mouth as soon as possible. This can be given as potassium citrate 4 g. = 60 grains t.d.s. or a drink containing glucose 50 g., dibasic potassium phosphate 2 g. in 500 ml. water flavoured with orange juice. Up to 2 litres of this mixture should be given daily for 2 or more days or until the patient is taking a full diet. Patients who have been in deep coma should not be allowed to sit up or otherwise exert themselves for several days.

*Eye complications.*—Impairment of vision in diabetics may be due to temporary changes in refraction, associated with change in water balance; to lenticular opacities or to retinopathy. Slowly progressive impairment of vision is more often due to cataracts than to retinopathy. Rapid loss of vision, fortunately rare but sometimes leading to complete blindness, is usually due to advanced retinal disease.

*Transient changes in refraction.*—Blurring of distant vision from myopia may occur in untreated diabetics, and the sudden onset of myopia in any patient should raise a suspicion of diabetes and lead to testing of the urine. But visual symptoms of this kind are commonly encountered shortly after starting treatment with insulin due to changes in hydration of the lens. The patient should be dissuaded from seeking glasses or new glasses until it is seen whether the blurring disappears after the diabetes has been satisfactorily controlled for 4 weeks.

*Lenticular opacities.*—Two kinds of cataract occur in diabetics. It is usually stated that ordinary senile cataract is commoner in diabetics than in the general population, though this has been denied by one or two observers of large series, who claim that if sufficiently careful examination is made, the incidence is about equal. The treatment is the same as in non-diabetics. "True diabetic" cataract or "snow-flake" cataract is very much rarer, and occurs in adolescence or early adult life. It is said that it is reversible and may improve or even disappear with strict treatment of the diabetes.

*Retinopathy.*—Diabetic retinopathy is commoner in younger patients than is generally realised. In older patients there is often a mixture of diabetic and hypertensive changes.

The earliest and only specifically diabetic change is the appearance of capillary micro-aneurysms, tiny sharply defined rounded spots, venous in colour and much smaller than most hæmorrhages. These are aneurysms of communicating branches between the capillaries of different layers of the retina. If carefully looked for, they can sometimes be seen as the only change in the retina of quite young patients who have had diabetes for a number of years. The later changes are round "deep" hæmorrhages and small, irregularly shaped, yellowish-white, "hard" or "waxy" exudates. "Fluffy" or "cotton wool" exudates are occasionally also seen, even in the absence of hypertension.

Some diabetics also show changes in the veins which may be proliferative or non-proliferative. In the latter, the veins in some areas may be "beaded", or overfilled and tortuous, or may be thrown into loops and coils. In the proliferative form,

"retinitis proliferans", new vessels are formed, which may in time grow into the vitreous. If vitreous hæmorrhages then occur, organisation of the clot may lead to retinal detachment; retinitis proliferans with hæmorrhages and retinal detachment being the usual cause of sudden and rapid deterioration of vision in diabetics. Such patients are also liable to glaucoma.

In older patients, the picture of diabetic retinopathy is often complicated by the addition of hypertensive changes, narrowing of the arterioles, superficial flame-shaped hæmorrhages and "cotton wool" exudates. It is likely that good control of diabetes delays the onset of retinopathy, and it has been claimed that the earliest changes in young diabetics are reversible by strict treatment. Once retinopathy has become established, stricter treatment of the diabetes makes disappointingly little difference.

Retinopathy is probably part of a generalised vascular process, since capillary fragility as measured in the arms is increased in diabetics with retinopathy. There is no evidence that drugs which may reduce capillary fragility, such as ascorbic acid, vitamin P and rutin, have any effect on the course of diabetic retinopathy.

*Nephropathy.*—If the urine of diabetics is tested for albumin as a routine at every visit, a surprising number are found to have intermittent or continuous albuminuria. This may be due to cystitis, acute or chronic, pyelonephritis, nephritis, arteriosclerotic kidney, heart failure and so on. Symptomless urinary infections are common, particularly in elderly females.

In 1934 Kimmelstiel and Wilson described an histological picture in the kidneys characterised by the presence of discrete islands or nodules of hyaline material in the glomeruli. It is probable that this picture of "intercapillary glomerulosclerosis", at least in its severe forms, is confined to the kidneys of diabetics, and is associated with a recognisable clinical picture. This has come to be known as diabetic nephropathy and is one of the diabetic's most serious long-term risks. Patients are usually middle-aged or over, more often female than male, with a history of diabetes for many years. Intermittent or continuous albuminuria which may last several years without other signs, is followed by slight or massive œdema of the dependent parts, severe hypertension and retinopathy, which may be severe and lead to failing vision. Characteristically, the insulin requirements fall as the renal disease advances. When the œdema is gross, it is associated with low plasma protein, and can sometimes be controlled to some extent by a high protein, low sodium diet. Otherwise treatment has no effect, and death from renal failure, cardiac failure or cerebral hæmorrhage occurs up to about 10 years from the first manifestation of a renal complication. It seems likely that intercapillary glomerulosclerosis and retinopathy are both manifestations of a single vascular degenerative process. It is probable that really good control of the diabetes delays or prevents the onset of these complications, but once they are established, control of the diabetes does not prevent their progressive course.

*Neuropathy.*—The manifestations are protean. Absence of the ankle jerks with diminution or absence of the knee jerks, sometimes associated with some loss of vibration and deep pressure sensation in the legs, but without subjective complaints, is common in those who have had diabetes for some years. In addition, various pains and paræsthesiæ, usually in the legs, may occur with or without objective sensory changes. Occasionally severe burning pain in the feet, worse or almost intolerable at night, may be complained of. In rare instances the neuropathy takes the form of an acute neurological illness with gross weakness of the legs, particularly of the quadriceps, so that patients may have to go upstairs on all fours. The legs show weakness, wasting, flaccidity, loss of tendon jerks and various degrees of sensory loss. In some of these patients the pupils are irregular and react poorly to light; a neuropathic bladder may occur, and the cerebrospinal fluid protein is raised, a syndrome which has been called "diabetic pseudo-tabes". Another curious feature is nocturnal diarrhœa, which may be controlled by injections of liver extract. Isolated cranial nerve palsies which recover spontaneously are also seen. Impotence

can occur, but in general, impotence in diabetics is due more often to anxiety than to neuropathy.

Diabetic neuropathies usually supervene in patients whose diabetes is badly controlled and are the one form of complication in which strict treatment will bring about a remarkable improvement.

## SPONTANEOUS HYPOGLYCÆMIA

Mild hypoglycæmia some time after meals or in association with emotional upsets is fairly common in unstable asthenic individuals. Such people discover that carbohydrate relieves their symptoms. Ingestion of carbohydrate then leads to a rise in blood sugar followed by a compensatory overproduction of insulin, a fall in blood sugar and return of hypoglycæmic symptoms, further ingestion of carbohydrate and so on. A similar mechanism is thought to operate in the post-gastrectomy dumping syndrome (p. 587) in which hypoglycæmic symptoms may occur shortly after meals. Both these conditions can often be relieved by a high protein, low carbohydrate diet, avoiding particularly sugar and easily assimilable forms of carbohydrate.

By comparison other causes of spontaneous hypoglycæmia are excessively rare. It is found as a curiosity in hypopituitarism and hypocortico-adrenalism (failure of pituitary-adrenal blood sugar raising mechanism) in advanced liver disease (failure to store glycogen), von Gierke's disease (abnormal fixation of liver glycogen), possibly in cases of very severe renal glycosuria, and finally in hyperinsulinism. It is important that hyperinsulinism should be diagnosed since a progressive and fatal condition can then sometimes be completely relieved by surgery.

## HYPERINSULINISM

**Ætiology and Pathology.**—Hyperinsulinism is usually due to a small islet-celled adenoma (1 to 2 cm. diam.), which probably has no predilection for any part of the pancreas, but is more likely to be found when it is in the body or tail. Occasionally two or three such adenomata are present. More rarely the tumour is a carcinoma and metastasises to the adjacent lymph glands and the liver. Occasional cases have been attributed to generalised hyperplasia of islet-cell tissue.

**Symptoms.**—The main difficulty in diagnosis is that patients with attacks of the kind of symptoms usually associated with hypoglycæmia (apprehension, tachycardia, shakiness, sweating, weakness and fainting) nearly always turn out to have the functional hypoglycæmia mentioned above, whereas patients with islet-cell tumours are apt to present with bizarre attacks or peculiar neuro-psychiatric manifestations, which are easily misdiagnosed as hysteria, epilepsy, alcoholism, cerebral tumour (particularly hypothalamic tumour) or psychosis. It is, therefore, in neurological, neuro-surgical and psychiatric departments and in the observation wards of mental hospitals that such patients are likely to be found. This diagnosis should be considered in any peculiar neuro-psychiatric illness, particularly if associated in the earlier stages with episodes of change of mood or loss of consciousness, in which sweating is noticed. Later convulsions and irreversible neurological changes or psychosis may be added.

**Diagnosis.**—The diagnosis of hyperinsulinism is confirmed by the finding of a blood sugar of less than 50 mg. per 100 ml. in an attack, and by prompt recovery, at least in the early stages, on administration of large quantities of glucose intravenously. It is, however, important to remember that when a patient has been comatose from this cause for some time, intravenous glucose may not cause rapid improvement, and a random blood sugar may not always be at a hypoglycæmic level.

probably have little effect, but sweetbreads, liver, kidneys, fish roes, tripe may be actively harmful. Spirits have little effect, and gout was almost unknown in Scotland when it was common in England. Beer is much more potent and is probably partly responsible for the prevalence of gout in England and Germany. The strong wines like port and sherry, and the red wines such as Burgundy and claret, are also probably responsible for evoking some gout among the well-to-do classes, and champagne has a bad reputation. The light white wines like Graves and hock and cider are less evil. Gout was formerly very common among lead workers in England, and the cessation of serious poisoning may be another cause for the decrease in gout. Trauma plays a great part in the causation of the acute attack. The big toe may be affected so frequently because of the pressure of the boot. An injured joint may be the seat of the first attack of gout. Syringing the ear of a gouty patient for cerumen was followed by an acute attack in the external auditory meatus (A. E. Garrod). Local sources of infection are very common among gouty patients, *e.g.* septic gums and tonsils.

**Physiology and Pathology.**—The fact that sodium biurate was deposited in and around the joints suggested that uric acid played an essential part in the causation of gout. After A. B. Garrod (1848) had demonstrated by means of his thread test that the blood of gouty patients contained uric acid in abnormal qualities, the hypothesis seemed to be proved. The problem is, however, not so simple as was thought at first.

The uric acid which is excreted in the urine of healthy people on an ordinary mixed diet comes from two sources, exogenous and endogenous. When all the exogenous sources of uric acid, *e.g.* meat, fish, sweetbread, tea and coffee, etc., are removed from the diet the output sinks to a level of 0.5 to 0.7 g. per day. The amount is fairly constant for each individual. If all proteins are removed from the diet, the endogenous uric acid output falls to a lower level than before (Folin). The removal of carbohydrates and a reduction of the caloric value of the diet also cause a decrease in the endogenous uric acid output to the lower level (Graham and Poulton). The endogenous uric acid output is believed to come from the breakdown of the cell nuclei of the body, *i.e.* wear-and-tear, but it can also be synthesised from histidine and arginine (Hopkins and Ackroyd). When the exogenous purines are eaten, or when uric acid is injected, there is an increase in the uric acid output, but the whole of the uric acid is not excreted in one day. If cinchophen is given at the same time, the excretion-rate of the uric acid is increased.

The blood always contains uric acid, and the limits of normal variation in health are 1 to 3 mg. per 100 ml. The total uric acid in the blood of a man weighing 10 st. 3 lb. or 65 kg. would be 50 to 150 mg., assuming that the blood constitutes  $\frac{1}{15}$  of the body weight, *i.e.* 5000 ml.

In cases of gout there is usually a considerable increase in the amount of uric acid in the blood. Before an attack the blood may contain 4 to 6 mg. of uric acid per cent., though occasionally between the attacks there may be no increase. The uric acid may also be increased in some people who have never had gout; as, in leukaemia, where there is a great destruction of leucocytes, and in cases of renal failure. The increase in the uric acid in the blood is, therefore, not pathognomonic of gout, although it is extremely suggestive of it.

In gout the output of uric acid varies widely. It may be quite small in amount, less than 0.2 g. per day, or it may be equal to that excreted by healthy people. Before the attack of gout it is usually very small in amount, but the paroxysm always causes a great increase in the output for a few days only. When purine bodies are eaten by a gouty patient, or if uric acid is injected, there is great delay in the excretion of uric acid. If cinchophen is given at the same time, the uric acid is excreted much more quickly. The diminution in the uric acid output may be due to an increased destruction in the body or to its retention by the kidneys. There is no evidence of increased destruction in the body, as the blood of a patient before an attack may contain 4 to



6 mg. of uric acid per 100 ml. This suggests that the uric acid is retained by the kidneys. When cinchophen is given to a patient whose blood contains 4 to 5 mg. per 100 ml. uric acid there is a great increase in the uric acid output and a decrease in the uric acid in the blood (Folin and Lyman). The "extra" uric acid excreted in 6 days was 1.9 g., while the blood uric acid decreased from 4.5 mg. to 2.9 mg. per cent. The "extra" uric acid must come from the uric acid "pool" in the body, as the blood does not contain enough uric acid (Graham).

The evidence points to the view that although gout cannot exist in the absence of excess of uric acid in the blood yet uric acid is not the cause of gout.

The essential change is the deposition of uric acid as sodium biurate in the joints. The sodium biurate appears to be plastered over the surface of the cartilage, but on microscopical examination it is seen that there is a layer of cartilage over the deposit, which is always interstitial. The deposits may be quite small or enormous. In severe cases the structure of the bones is destroyed and replaced by sodium biurate. The ligaments, tendon sheaths and bursæ are also infiltrated. The big toe joints may contain sodium biurate, although the patient has never had an acute attack of gout (Norman Moore). The skin covering a tophaceous deposit may ulcerate and break down, and small masses of sodium biurate may be discharged (chalky gout).

*Tophi.*—Sodium biurate is also deposited in the cartilage of the ear, especially in the outer margin of the pinna. The tophi appear as white nodules from which uric acid crystals can be recovered. They also give the murexide test and a blue colour with Folin's phospho-tungstic reagent.

*The kidneys.*—An uratic deposit may occur in the pyramids. Norman Moore found it in 12 out of 80 cases. Well-marked changes of chronic interstitial nephritis are often found.

*Symptoms.*—The earliest sign of gout is sometimes the deposition of sodium biurate in the cartilage of the ear (tophus). This stage usually passes unnoticed, but is sometimes accompanied by an intolerable itching or tenderness.

*Acute gout.*—The first attack of "classical" gout usually occurs at night. There may have been a few preliminary symptoms, such as dyspepsia, slight pain in the hands, and irritability of temper, but the patient goes to bed feeling well. "The patient suddenly wakes with pain, more or less intense, generally in the ball of one great toe, frequently accompanied with a slight shivering; the pain in the toe gradually increases and is attended with a sensation of burning, throbbing, together with great tension and stiffness; heat of skin and other symptoms of febrile disturbance usually follow the shivering, accompanied with a considerable degree of restlessness" (A. B. Garrod). The temperature is raised to 101° or 102° F., but after a few hours the patient begins to sweat and finally falls asleep. "In the morning the toe is swollen, the skin shiny, tense and dark red, and the whole joint is extremely painful" (A. B. Garrod). Usually the acute pain lessens in the daytime, but returns with great violence in the night hours. The temperature remains high and the temper of the patient is irascible in the extreme. The attack may last many days or pass away in 2 days. When the attack is ceasing "the inflamed joint becomes less intense and swollen, and pitting is readily produced on pressure" (A. B. Garrod). The attack may spread from the great toe to the other joints of the tarsus or to other joints of the body. The first joint of the big toe is most commonly affected. The ankles, knees and small joints of the hands and wrists are next in the order of frequency.

During the attack there may be a considerable degree of leucocytosis, 20,000 to 25,000, and all but 2000 to 3000 are polymorphonuclear cells as the lymphocytes and other cells are unaltered by gout. The uric acid output, which was low before, is greatly increased for a few days. Sodium biurate is deposited in the cartilage of the joint and head of the bone and in the tendon sheaths, but the swelling and stiffness may eventually disappear completely. The acute attack may be complicated by a severe gastro-intestinal disturbance, and there may be other symptoms, such as

dyspnoea, delirium and coma, but these are probably due to a coincident uræmia. Phlebitis of the veins of the limb may be a complication of an acute attack.

After the attack, whether as the result of illness or as a consequence of the simple living which the patient has endured, the general health of the patient is much improved. The attack usually occurs in the spring and autumn. The second attack may follow at once, or may be delayed for many years.

*Chronic gout.*—After several attacks, especially if badly treated, the joint may not recover completely. The deposits of urates occur in the ligament and capsule, as well as in the articular cartilages and bones. The joint, therefore, becomes swollen and irregular in its shape. The urate is especially deposited in the bursæ about the joints. In the advanced stages the skin over the uratic deposits breaks down and masses of chalky material are extruded, and the wounds heal with difficulty. The general health of the patient suffers after several attacks and does not recover completely. Dyspepsia is complained of, and the patient may show signs of high blood pressure and arterial disease. The urine is increased in amount, and may contain albumin and casts.

*Irregular gout.*—Almost any symptom or physical sign which occurred in a person who was of a gouty disposition was formerly ascribed to gout. Cutaneous eruptions, such as eczema, gastro-intestinal disorders, cardio-vascular symptoms and pericarditis, headache, migraine and neuralgia, were all thought to be gouty. A gouty patient may develop any of these diseases, but the belief that there is a general type due to gout is now regarded as unfounded. The urine is usually acid, and on cooling often deposits uric acid crystals. This does not mean that there is an excess of uric acid in the urine, but that the urine is too acid to keep it in solution. On heating the urine the urates are re-dissolved. Gouty persons may suffer from calculi. Glycosuria occurs in some cases, but usually responds readily to treatment. Albuminuria and casts are present when the kidneys are also affected. Elderly persons often suffer from chronic bronchitis. Gout has been accused of rendering patients more disposed to iritis, retinitis and glaucoma. It is possible that iritis and retinitis can have a gouty basis though they may arise independently.

*Diagnosis.*—The diagnosis in a case of classical gout, with recurring attacks of arthritis in the toe or tarsus, is easy, especially if the patient comes of a gouty stock or indulges in good living. The joints of the hands affected are usually asymmetrical in shape and in distribution unlike those of rheumatoid arthritis. The presence of tophi is proof positive that the patient is a subject of gout. Tophi must be distinguished from Woolner's tip, fibroid nodules and sebaceous cysts, and in cases of doubt an examination should be made for the crystals of sodium biurate with the microscope, and for uric acid with the murexide test or Folin's phosphotungstic reagent. The blood uric acid should be estimated in all cases of doubt, and if more than 3 mg. per cent. is found the case is probably one of gout; it may be normal in amount just after an acute attack. It must be remembered, however, that the uric acid in the blood is increased in cases of chronic interstitial nephritis. While it is certain that gout does not occur in the absence of an increase of uric acid in the blood, the presence of excess of uric acid in the blood does not exclude the presence of other diseases.

Classical gout is much less common than it was, and the modern tendency is to overlook the disease. In the severe cases, in which the joints are severely damaged, the radiographic appearances are very striking. There are dark "punched-out" areas, where the sodium biurate is deposited in large amounts, replacing bone or cartilage, since sodium biurate is not opaque, like the calcium ion. In the less severe cases there may be—(1) lipping at the articular margins; (2) a localised atrophy of the bone; (3) a narrowing of the joint space.

*Prognosis.*—If a patient has once had an attack of gout he will always be liable to another attack, unless he alters his way of life. The frequency and severity of the

rate from cardio-vascular diseases is some 60 to 70 per cent. greater in the obese than in the normal.

*Symptoms of obesity.*—General lassitude and weariness, dyspnoea on exertion, aches and pains, particularly in the knees and lumbar spine, maceration and infection of the skin, and sometimes œdema of the ankles, are the main complaints of the obese. In addition, however, there may be symptoms associated with hypertension or diabetes mellitus, conditions closely associated with the obesity itself.

The pain in the knees and back is not surprising when one considers the extra weight which has to be carried, 4 or 5 stones (56 to 70 lb.) being not at all uncommon. This alone will tend to produce dyspnoea, but the position is aggravated by the extra blood flow required through the adipose tissue—it has been estimated that there are about 25 miles of blood vessels in every 30 lb. of adipose tissue. This extra strain on the cardio-vascular system is probably one of the reasons why obese people are relatively poor operative risks, and why they do not stand infections such as pneumonia at all well.

*Treatment.*—There are two main factors to be considered, (1) to correct any obvious underlying cause and (2) to restrict the daily calorie intake below the daily caloric requirements.

When there is any obvious endocrine disturbance the main line of treatment must be to correct it. Psychological disturbances may exist, but they do not usually require prolonged psychiatric treatment. In the vast majority of cases, however, the main line of treatment will consist in a considerable restriction of the calorie intake. Many diets have been devised for this, but it is often very difficult to ensure that the patient will adhere to them satisfactorily—mainly because of the rigidity or, failing this, the complicated nature of the instructions. For this reason a considerable contribution was made by Marriott when he introduced the diet shown below. This is suitable both for simple obesity and for obese patients with diabetes mellitus who do not require insulin. A patient will generally lose at least 2 lb. per week when on this diet.

#### REDUCING DIET

(Devised by H. L. Marriott (1949), *B.M.J.*, ii. 18)

1. Eat or drink as much as you like (or can get) of :

Lean meat, poultry, game, rabbit, hare, liver, kidney, heart, sweetbread—cooked in any way, but *without addition of flour, breadcrumbs or thick sauces.*

Fish (not tinned), boiled or steamed only; *no thick sauce.*

Eggs, boiled or poached *only.*

Potatoes, boiled, steamed or baked in skins, but *not fried, roast, sauté or "chips"*; *not potato powder.*

Other vegetables of all kinds (fresh, tinned or dried), cooked in any way *not involving the use of fat.*

Salad and tomatoes *without oil or mayonnaise.*

Beetroot, radishes, watercress, parsley.

Fresh fruit of any kind, including bananas. Also bottled fruit if bottled *without sugar. Not tinned or dried fruits (including dates, figs and raisins).*

Sour pickles, *not sweet pickles or chutneys.*

Clear soup, broth, "Bovril", "Oxo", "Marmite".

Salt, pepper, mustard, vinegar, Worcester Sauce (*no other sauces*).

Saccharin for sweetening.

Water, soda-water and non-sweetened mineral waters.

Tea and coffee (milk only as allowed below).

2. You may have milk (not condensed) up to half a pint daily. *No cream.*

3. You may have three very small pieces of bread per day, and take them either

one at each main meal or all three at one meal as desired ("very small" means *not exceeding 1 oz.*).

4. You may have *nothing else whatever*: particularly note that this means:

No butter, margarine, fat or oil (except for cooking meat, *not fish*).

No sugar, jam, marmalade, honey, sweets, chocolate, cocoa.

No puddings, ices, dried or tinned fruits, nuts.

No bread (except as above), cake, biscuits, toast, patent reducing breads, cereals, oatmeal, "Allbran", "Ryvita", "Vita Wheat".

No barley, rice, macaroni, spaghetti, semolina, sausages, cheese.

No cocktail savouries, alcohol (beer, cider, wines and spirits).

Weigh before you begin, and thereafter weekly, on the *same scales* in the *same clothes*, and at the same time of day.

It may be necessary to help the patient by diminishing the appetite and this can be achieved by giving 5 to 10 mg. of dextroamphetamine sulphate about 30 minutes before each of the main meals of the day. It should not be given too late in the day, however, to those patients in whom it prevents sleep. It must also be emphasised to the patient, who usually wants an easy way to slim, that this drug is no substitute for cutting down the food intake, that it is, in fact, given in order to help the patient to cut down the food intake. *To instil a real desire to lose weight is an absolutely essential beginning to successful treatment.*

Restriction of fluids is sometimes advocated, but there is little point in this. Fluid retention does *not* cause obesity. The main virtue of restricting fluids with meals is that dry food, which cannot be washed down, is not quite so attractive and thus less will probably be eaten. It is quite often observed that an obese person will maintain weight for anything up to 2 weeks even though the calorie intake is considerably less than the energy expended. This is due to fluid retention, and if the patient is followed for long enough it will be found that the retained fluid is always ultimately eliminated.

*Results of treatment.*—Some obese patients feel lightheaded at times while they are losing weight and most of them feel the cold. At first it requires much effort of will to restrict the food intake, but the ability to do this improves with training. The improvement in general well-being is often quite remarkable and quite enough to illustrate to the patient how important it is to be rid of the excessive weight. When diabetes mellitus is present the symptoms usually recede and sometimes even the glucose tolerance test will become normal. Where a patient is hypertensive the blood pressure nearly always falls and symptoms such as headache frequently disappear.

## LIPODYSTROPHIA PROGRESSIVA (BARRAQUER—SIMMONS' DISEASE)

**Definition.**—This is a condition in which there is loss of subcutaneous fat, the loss usually being confined to the upper part of the body.

**Ætiology.**—About 80 per cent. of the reported cases are females. The onset tends to occur in early life, in about half of all cases being before the age of 10 years, and in about three-quarters before the age of 20 years. In the relatively few males who have been reported with the condition, the onset was before the age of 10 years in nearly 90 per cent.

A history of infection preceding the onset has been frequently noted, but in view of the frequency of infections in childhood there seems to be no convincing evidence that these infections were causal.

Two endocrine abnormalities have been noted to occur in a significant proportion of cases, namely, hyperthyroidism and either frank diabetes mellitus or a high blood sugar curve, which is sometimes of the "lag" type. *Insulin resistance is sometimes found in those cases which have diabetes mellitus.*

**Symptoms and Signs.**—Apart from the psychological disturbances resulting from the abnormal appearance, there are no real symptoms associated with the disease, the patients being in good health; patients in whom there is either associated hyperthyroidism or diabetes mellitus may, of course, have symptoms and signs associated with those conditions.

Characteristically, there is a great loss of subcutaneous fat from the face, neck, upper limbs and trunk, whereas the buttocks and legs may be normal or even have some excess of fat. The loss of fat gives a superficial appearance of emaciation, but closer inspection reveals the muscles to be normal in size and the outlines of the more superficial ones can readily be seen through the skin.

Occasionally cases are seen where the fat has left the lower limbs and is normal on the upper part of the body. It has also been suggested that the relatively common condition in females of obesity of the lower limbs associated with a normal amount of fat on the upper part of the body may be an allied condition.

There is no treatment, the condition, once established, remains more or less stationary, and the expectation of life is unaffected by the lipodystrophy.

### THE LIPOMATOSES

Lipomata, simple encysted fatty tumours, may occur in the subcutaneous tissue or in the fatty tissues associated with the internal organs; they may be single or multiple. Usually they are painless, but occasionally a dull ache may be experienced, and sometimes the tumour may be quite painful when palpated; when present in an internal organ pressure symptoms may be produced.

Fatty tumour formation sometimes occurs symmetrically round the neck at times descending on to the trunk. This occurs more frequently in males than in females and the main complaint is of the disfigurement produced by the tumour.

GEORGE A. SMART.

### GLYCOGEN DISEASE

**Synonym.**—Von Gierke's Syndrome.

A rare disease of metabolism due to a congenital abnormality of the enzyme system concerned with the break-down of glycogen which therefore accumulates in the tissues or organs affected. It was first recognised by Von Gierke and is sometimes called by his name. There are probably several clinical or clinico-pathological varieties of the disorder. It occurs in both sexes, may be familial and is thought to be inherited as a Mendelian recessive.

**Pathology.**—Abnormal deposits of glycogen are found in the affected organs—liver, kidney, heart—which are therefore enlarged.

**Clinical Features.**—The child is smaller, and the affected organ is larger, than normal. Sudden death may reveal the so-called "idiopathic hypertrophy of the heart" as one type of the disorder. The commonest, however, is when the liver is mainly involved. A large abdomen is found to contain a large, smooth painless liver. The child is stunted in growth but well covered with subcutaneous fat. The fasting blood sugar will be found to be low and the normal rise after the injection of adrenaline is absent or diminished. Acetone is frequently present in the urine and the breath, heavily increased by infection, from which the child eventually succumbs. Undue fatigue is often noted: hypoglycæmic convulsions have been described. There is no treatment which affects the course of the disease.

ALAN MONCRIEFF.

### DISORDERS OF PORPHYRIN METABOLISM

Porphyryns are tetrapyrrolic pigments which are formed mostly during the synthesis of the hæmoproteins—hæmoglobin, the cytochromes and other enzymes. Four

stereoisomers of the basic porphyrin nucleus are theoretically possible, but only types I and III are known to occur naturally and only porphyrin III is utilised for hæm synthesis. It is believed that uroporphyrin III is the first recognisable porphyrin produced in the bone marrow. It is decarboxylated to coproporphyrin III and the latter transformed to protoporphyrin and then hæm. Uroporphyrin I, formed as a by-product, may be the precursor of coproporphyrin I which is normally excreted in the urine. The pigment hæmatoporphyrin, which was formerly confused with protoporphyrin, does not occur in nature and the term "hæmatoporphyrinuria" is therefore a misnomer.

*Porphyria* implies an excess of porphyrins, mainly coproporphyrin, in the urine. It is usually symptomatic of anæmia, liver disease, infectious diseases and various intoxications. Thus in lead poisoning an abnormal amount of coproporphyrin III is excreted, and its estimation in the urine is as sensitive for diagnostic purposes as the finding of punctate basophilia in the blood (see p. 368).

*Porphyria* is an inborn error of metabolism in which there is abnormal production or failure of utilisation of certain porphyrins and in which large amounts of uroporphyrin appear in the urine. Waldenstrom (1937) recognises three main varieties, *Porphyria congenita*, *Porphyria cutanea tarda* and *Porphyria acuta*.

1. *Porphyria congenita* is a very rare hereditary disease which manifests itself early in life. Porphyrins, predominantly uroporphyrin I, are found in the bones, the teeth and the urine, which are in consequence red or chocolate brown in colour. There is marked photosensitivity with cicatrisation of the skin, loss of digits and hypertrichosis.

2. *Porphyria cutanea tarda* usually appears in early adult life. Photosensitivity recurs intermittently and may be accompanied by abdominal colic and jaundice. During the attacks, porphyrins are diverted from the fæces to the urine, due possibly to episodes of hepatic insufficiency. Many complex porphyrins have been isolated from the urine including uroporphyrins I and III, and in some cases porphobilinogen (see below).

3. *Porphyria acuta* is the commonest and most important of the porphyrias, acute attacks usually occurring in patients between the ages of 20 and 30 years. The disorder is familial and in some cases symptomless, although there is evidence that, in these, attacks may be precipitated by certain drugs such as the barbiturates. Latent, abdominal, nervous, classical and comatose forms have been described. In classical attacks of acute porphyria there is severe burning or colicky abdominal pain, vomiting and constipation with, as the disease progresses, involvement of the nervous system giving rise to paralysis of the limbs and trunk and later of the cranial nerves. Psychological disturbances, tachycardia, hypertension and signs of angiospasm are not unusual. Remissions in the progress of the disease are sometimes dramatic, but the ultimate prognosis is poor, death in respiratory failure being the usual outcome. The urine is reddish brown or purple in colour, either when passed or after standing for some hours. It invariably contains porphobilinogen, which is colourless, but which becomes converted into uroporphyrin III either in the bladder or after the urine has been voided. The finding of porphobilinogen in the urine is specific for acute porphyria and some cases of porphyria cutanea tarda. It gives a red Ehrlich's aldehyde reaction but differs from urobilinogen in being inextractable by chloroform.

## OTHER DISORDERS OF METABOLISM

The following disorders of metabolism are discussed elsewhere: hæmochromatosis (see p. 680), congenital methæmoglobinæmia (see p. 751), the Fanconi syndrome (see p. 1179), cystinosis (see pp. 1107 and 1179), cystinuria (see p. 1140), alkaptonuric ochronosis (see p. 1105), albinism (see p. 1203), phenylketonuria (see p. 1686), amyloidosis (see p. 1131) and disorders of lipid metabolism (see p. 783).

DONALD HUNTER.

## SECTION VI

### DEFICIENCY DISEASES

#### THE VITAMINS

**Definition.**—Vitamins are organic substances, distinct from proteins and carbohydrate, which are present in small quantities in food and which are necessary for the normal nutrition of the body. A substance which by this definition is a vitamin for one species of animal, is not necessarily so for another. For example, ascorbic acid or vitamin C is a vitamin for man and for guinea pigs, but not for dogs or cats.

The vitamins can be divided into those which are water soluble and those which are fat soluble. Since their nature was at first quite unknown, they were labelled with the letters of the alphabet—A, B, C, D, more or less in the order of their discovery. It was soon clear, however, that these were not all pure substances, and with further discovery and labelling in different centres, the nomenclature became chaotic. It is therefore preferable to refer, where possible, to the established chemical name of the vitamin. This is especially important for members of the B complex, but not for the fat soluble vitamins, since here the various members of a given group have a qualitatively similar physiological action.

**Vitamin deficiency diseases.**—If the diet contains less than the requisite minimum of a vitamin for long enough, symptoms and signs develop. Although disease entities are ascribed to various vitamin deficiencies, such pure deficiencies rarely occur except under experimental conditions.

Such dietetic deficiencies are rare in the British Isles where vitamin deficiencies are most commonly associated with conditions interfering with absorption, such as steatorrhœa. Where dietetic deficiencies do exist they are usually associated with some social or psychological abnormality, such as chronic alcoholism or dietary fadism.

#### THE FAT SOLUBLE VITAMINS

##### VITAMIN A

This substance is contained in liver (the richest source in the normal diet), butter, cheese, eggs and fish liver oils. It can be formed in the body, however, from the carotenes, and good sources of these are green vegetables, apricots and red palm oil. The international unit of vitamin A is the equivalent of 0.6 micrograms of  $\beta$ -carotene. There are two very similar compounds, both having a similar physiological action. One, vitamin A<sub>1</sub>, is found in mammals and salt-water fish, whereas the other, vitamin A<sub>2</sub>, is found in fresh-water fish.

Vitamin A can be estimated in the plasma, and the curve obtained by frequent plasma estimations after an oral test dose is frequently used as an index of the efficiency of fat absorption. The minimal daily dose required to protect against deficiency has been shown by human experiments to be about 20 I.U. per kg., or 1300 I.U. for an adult man. In order to allow for storage and to supply a safe margin, however, about 2500 to 5000 I.U. per day of vitamin A should be ingested. If the carotenes are the sole dietary source then the intake should be about 7500 to 10,000 I.U.

Vitamin A forms part of the molecule of rhodopsin or visual purple, and hence one of the first signs of deficiency is a high dark-adapted rod threshold. This is not

the same as poor night vision, although naturally night vision is inevitably poor when the dark-adapted rod threshold is very high. Psychological factors, however, are very important in determining how well a person can manage in the dark, and may well result in complaints of defective night vision in the absence of vitamin A deficiency.

Other manifestations in man of vitamin A deficiency are xerophthalmia, follicular hyperkeratosis of the skin and keratinising metaplasia, particularly of the respiratory epithelium, the urinary tract and the pancreas. Xerophthalmia is the most serious of these lesions. Keratinisation of the cornea and conjunctiva occurs, and also Bitot's spots, which are thickened, opaque, triangular lesions of the conjunctiva. Infection may supervene to cause a panophthalmitis and resultant total destruction of the eye.

Hyperkeratosis of the hair follicles, particularly on the extensor surface of the limbs, producing the so-called goose skin or phrynoderma also occurs, but it is not absolutely certain that this is entirely due to vitamin A deficiency. It was not produced in experimental vitamin A deficiency when this was studied at Sheffield.

Changes in the respiratory epithelium have been described in children, and it has been suggested that vitamin A deficiency, resulting from malabsorption of fat, may be a factor in producing the lung infections associated with congenital cystic disease of the pancreas.

Vitamin A deficiency resulting from faulty diet, is practically never seen in European communities. It is, however, prevalent in parts of Asia, notably in China and India, and in Africa.

#### VITAMIN D

Vitamin D is found in large quantities in cod liver oil, and it is present in small quantities in certain foodstuffs such as milk, cheese, butter and eggs.

Furthermore, it is synthesised from various sterols by the action of ultra-violet light, and this reaction occurs both when suitable foodstuffs are irradiated and in the skin when sunlight falls upon it.

When cholesterol is irradiated, a compound called calciferol or vitamin D<sub>2</sub> is obtained, which is active in man but not in chickens. Irradiation of 7-dehydrocholesterol produces another compound, vitamin D<sub>3</sub>, which is effective in man, animals and chicks; this is the compound found in fish-liver oils.

Vitamin D is expressed in International Units, one of which is equivalent to 0.025 micrograms of calciferol. The minimal daily intake is difficult to define, partly because of the variable amount synthesised in the skin and partly because the requirements vary to some extent according to the composition of the rest of the diet; 400 I.U. per day from birth to the age of 20 years is recommended by the Food and Nutrition Board of the National Research Council of the United States of America.

The exact mode of action of vitamin D is not known, but it is necessary for the correct absorption of calcium from the gut and it may also increase the reabsorption of phosphate by the renal tubules. Deficiency results in rickets in the growing child and in osteomalacia in the adult.

As would be expected, deficiency of this vitamin is seen most frequently in countries with relatively small amounts of sunshine. The soot and grime of industrial areas also tend to intensify the situation, since, when these are present, most of the ultra-violet is absorbed from sunshine. This deficiency of sunshine is largely counteracted by children taking vitamin D concentrates, particularly during the winter.

Overdosage with vitamin D can give rise to serious intoxication. Nausea and vomiting, together with muscular weakness are usually the first symptoms. The serum calcium is raised and widespread metastatic calcification occurs, particularly in the blood vessels and in the kidneys, where there may be a serious decrease in function.



## VITAMIN E

Vitamin E is found in the germ of cereals, and in green vegetables. There are several compounds which have vitamin E activity. They are all tocopherols, and of these, alphatocopherol is probably the most potent.

Vitamin E acts as an antioxidant, preserving vitamin A and delaying the onset of rancidity in fats. As might be expected, the vitamin is itself rapidly destroyed by rancid fats. There have been no convincing reports of vitamin E deficiency in man, but the tocopherols have been extensively used as therapeutic agents in arterial disease and in muscular dystrophy. Most objective investigations have failed to show any significant effect in these conditions.

## VITAMIN K

Vitamin K is present in a large variety of foods and notably in green vegetables. In addition, however, bacteria normally present in the intestine can synthesise the vitamin, and for this reason the daily requirement is unknown.

Two naturally occurring compounds with vitamin K activity are known,  $K_1$ , or 2-methyl-3-phytyl-1, 4-naphthaquinone, and  $K_2$ , or 2-methyl-3-difarneryl-1, 4-naphthaquinone. The former is the compound present in green plants and the latter is produced by bacteria. It has been found that the removal of the side-chains does not result in a loss of vitamin activity, and the simple synthetic compound 2-methyl-1, 4-naphthaquinone (Menadione) is frequently used therapeutically. Many other compounds now are known which possess vitamin K activity, some of them being water soluble.

Vitamin K is necessary for the liver to form prothrombin and deficiency results in a fall in the prothrombin content of the blood. When the level is less than about 15 per cent. of normal, spontaneous hæmorrhage occurs. The first manifestation of this is usually hæmaturia, but spontaneous hæmorrhage, which may prove fatal, may occur in any organ in the body.

Bile must be present in the alimentary tract for vitamin K to be absorbed, and deficiency is therefore almost inevitable in any long-standing jaundice of the hepatic or obstructive type. To give the compound by mouth is quite useless under these circumstances, but intramuscular injection is fully effective if liver function is not unduly diminished.

Vitamin K deficiency is also seen in the infant for the first few days after birth. It is presumed that this period occurs after the vitamin K acquired *in utero* is exhausted and before intestinal bacterial synthesis has started. The condition can be prevented by giving the mother about 2 mg. per day of vitamin K during the last week or so of pregnancy.

Steatorrhœa, whether idiopathic or resulting from pancreatic or other disease, is also at times associated with vitamin K deficiency, and this can be corrected by giving large doses such as 3 to 5 mg. daily by mouth, though injections may have to be given in severe cases. It is possible that the water soluble compounds may be the most effective when steatorrhœa is present.

The plasma prothrombin level is used as an index of vitamin K nutrition. It is only valid, however, when there is no liver disease (since liver cells produce prothrombin, vitamin K being necessary in the process) and when no drugs of the dicoumarin group have been given. This group of drugs, which are used as anti-coagulants in conditions such as coronary occlusion, in some way antagonise the action of vitamin K. Overdosage, resulting in very low prothrombin levels and spontaneous hæmorrhage, is not rapidly counteracted by vitamin K compounds; the most effective, vitamin  $K_1$ , takes 4 to 12 hours to raise the prothrombin level.

Doses of vitamin K far in excess of the therapeutic amounts do not produce any toxic symptoms.

## THE WATER SOLUBLE VITAMINS

VITAMIN B<sub>1</sub>—ANEURINE OR THIAMINE

Foods rich in aneurine are cereals (where it is mainly found in the germ and the pericarp), legumes, pulses and nuts, pork, ham and bacon, liver, kidney and eggs.

The vitamin has been isolated, identified chemically and synthesised. It is usually measured in milligrammes but 1 international unit is defined as 3 micrograms of aneurine hydrochloride.

Like all vitamins, aneurine was originally estimated biologically, but it is now usual to convert it to thiochrome and to estimate this substance fluorimetrically.

The requirements of aneurine vary with the energy value and carbohydrate content of the diet, but approximately 0.3 mg. per 1000 calories is the minimum intake. Thus, an adult will require something like 1 mg. per day.

Aneurine forms an essential part of two coenzymes which are important in the decarboxylation of the alpha-ketoacids. In aneurine deficiency, pyruvic acid accumulates in the blood and this finding can be used as an estimate of the deficiency, particularly if the production of pyruvic acid in response to a test dose of glucose is measured. It is probably the toxic effects of the accumulating alpha-ketoacids which play a large part in the production of beriberi, the condition resulting from aneurine deficiency. Estimations of aneurine deficiency can also be made by measuring the output of the vitamin in the urine by the thiochrome method.

Deficiency of aneurine gives rise to beriberi (see p. 468), and to pathological changes in the brain which have been described by Wernicke and which are associated with the clinical manifestations of clouded consciousness and ophthalmoplegias of various types.

In western countries deficiency is usually associated with chronic alcoholism where a high carbohydrate intake is associated with a low intake of vitamin B<sub>1</sub>. Under these circumstances the manifestations are usually those of peripheral neuritis or of mental changes rather than of wet beriberi.

In the world as a whole aneurine deficiency is most frequently seen among populations whose main cereal is rice. When the pericarp is removed from this cereal, practically no aneurine is left unless the rice has first been partly cooked.

Reactions to large doses of aneurine have occurred which have occasionally been fatal. These have probably been hypersensitivity reactions, however, since they followed injections of the vitamin. Two types of reaction have been described, one resembles anaphylactic shock and occurs after numerous previous injections, and the other presents symptoms somewhat like hyperthyroidism with tremors, palpitation, excitement, giddiness and insomnia.

## RIBOFLAVIN

Riboflavin is a bright yellow substance with a yellow-green fluorescence. It is widely distributed in natural foodstuffs but milk, cheese, eggs, liver, green vegetables and yeast are particularly good sources. It is rapidly destroyed when exposed to light, so that considerable loss occurs in substances like milk. Riboflavin is also synthesised by intestinal bacteria, and some of this is absorbed and utilised—a process known as refection, which is common to most of the vitamin B complex. Riboflavin has been isolated and is synthesised on a large scale. It is measured in mg. of pure substance. The quantity present in natural products can be determined biologically by its effect on the growth of rats or chicks, or microbiologically by its stimulating effect on *Lactobacillus casei* (the usual method).

The minimal requirement of riboflavin is about 0.6 to 0.7 mg. per day, but,

since animal experiments indicate that the optimum is about twice this, a daily intake of 1.5 to 1.8 mg. for an adult woman and man, has been recommended.

This vitamin forms part of the coenzyme flavin mononucleotide, concerned in the oxidation of carbohydrate, and the coenzyme adenine dinucleotide, which forms part of xanthine oxidase. It is also associated with the retinal pigments.

Riboflavin deficiency in man manifests itself by a dermatitis of seborrhœic type affecting the skin of the nose and round the mouth and of the scrotum or vulva, and by a superficial glossitis which starts with loss of fur in patches from the dorsum and later the tongue is smooth and occasionally fissured and painful; some observers describe the colour as magenta. It is possible that corneal vascularisation and degeneration of the corneal epithelium also occurs. Riboflavin deficiency often occurs in pellagra and signs of the deficiency have been observed to be precipitated when nicotinic acid (*q.v.*) has been given. During the War of 1939-1945 neurological abnormalities, particularly optic atrophy with blindness and also deafness, were observed in prisoners of war, and it has been suggested that riboflavin deficiency played a part in these conditions.

None of the signs described above occur specifically as a result of ariboflavinosis. Thus, although the presence of any of them might suggest that the patient is deficient in riboflavin, the proof must lie in recovery when the pure vitamin is given. The excretion of riboflavin in the urine can be measured, but it is not a reliable index of the nutritional state. The riboflavin content of the plasma or of white blood corpuscles can also be measured microbiologically, and these probably are reasonable indices of possible deficiency. In well-nourished individuals the mean plasma level is 0.8 µg. per 100 ml. for free and 3.2 µg. per 100 ml. for total riboflavin. In white blood corpuscles the mean total riboflavin content is 252 µg. per 100 ml.

Manifestations of riboflavin deficiency tend to occur in communities who develop pellagra and where milk is not consumed; it is seen most commonly in Africa, China and India. It is sometimes seen in patients with steatorrhœa, and riboflavin should always be given with ancurin and nicotinamide to patients who have long periods of intravenous glucose as their sole source of nourishment, or who have to receive long courses of wide spectrum antibiotics which prevent the occurrence of refection.

### NICOTINAMIDE (VITAMIN B<sub>3</sub>)

Nicotinamide and nicotinic acid are equally effective as vitamin B<sub>3</sub>, but in bodily tissues the vitamin is present practically exclusively as nicotinamide. Moreover, whereas nicotinamide produces no untoward reactions, even when taken in large quantities, nicotinic acid in amounts of 25 mg. or more causes intense flushing of the skin, and headaches. In vegetable tissues, however, the vitamin is nearly all present as nicotinic acid. The amino-acid tryptophane can be converted by the tissues to nicotinamide and thus can also fulfil the role of vitamin B<sub>3</sub>. The vitamin is present in cereals, though in maize it is probably present in a bound form, from which it does not become available for human nutrition. The vitamin is also present in good quantities in meat, liver and yeast. It is synthesised by bacterial flora and part of this is available to the body.

The vitamin B<sub>3</sub> content of foodstuffs is usually estimated by a chick-growth method, but for samples of biological fluids it is more usual to measure the growth stimulation of *Lactobacillus arabinosus*.

The requirements of nicotinamide are not easy to estimate, partly because of the role of tryptophane, partly because of the process of refection, and partly because of the occurrence of the vitamin in forms unavailable to the body. It is probable that 10 to 20 mg. per day should be entirely adequate.

Nicotinamide forms part of Coenzyme I and Coenzyme II, which are dehydro-

genases and are concerned in a variety of metabolic reactions such as the conversion of lactate to pyruvate and glutamic acid to  $\alpha$ -ketoglutaric acid.

Nicotinamide is excreted in the urine partly as  $N^1$ -methyl nicotinamide, a substance which has a blue fluorescence. This substance can readily be measured and it falls to very low levels in patients suffering from nicotinamide deficiency.

Deficiency of vitamin  $B_3$  is the major factor in the production of pellagra. It seems to be most common in maize-eating communities. In European communities, apart from the poor of maize-eating areas, it is seen mostly in conjunction with chronic alcoholism in steatorrhœa and in mental hospitals. Deficiency can also occur after prolonged treatment with wide spectrum antibiotics.

### PYRIDOXINE (VITAMIN $B_6$ )

Three compounds occurring in foodstuffs have vitamin  $B_6$  activity, pyridoxine, pyridoxal and pyridoxamine. Although the last two compounds are the ones found in the tissues as part of decarboxylating and transaminating enzymes, the first is the more effective when given by mouth. This is probably because it is not so readily utilised by intestinal organisms as the others, so that a greater proportion is absorbed. Pyridoxine is also concerned in the oxidation of unsaturated fatty acids and seems to be necessary for normal adrenal cortical function. Further, it appears to be necessary for the normal metabolism of tryptophan and when supplies are deficient, an abnormal tryptophan derivative, xanthurenic acid, appears in the urine. This forms the basis of suggested tests for vitamin  $B_6$  deficiency. Vitamin  $B_6$  is widely distributed in foodstuffs, the richest sources being yeast, wheat germ, liver, pulses and cereals. The exact daily requirement is not known, but on the basis of animal experiments it is probably about 1.5 mg. per day.

Experiments on man have shown that  $B_6$  is essential for human nutrition. The symptoms which arise are many and varied; mental depressions and confusion, seborrhœic skin lesions round the nose, eyes and mouth, cheilosis and glossitis, albuminuria, hypochromic anæmia and granulopenia have all been induced by deficiency and have been subsequently cured by giving pyridoxine. Some cases of pellagra appear to require pyridoxine in addition to nicotinamide and riboflavin.

There are several compounds similar to pyridoxine, which antagonise its action and act as anti-vitamin  $B_6$  substances. The most potent of these is desoxy-pyridoxine. The substance is useful experimentally, but so far does not seem to have therapeutic applications.

### PANTOTHENIC ACID

Pantothenic acid is very widely distributed and this may account for the fact that certain evidence of deficiency in man has not yet been produced. It forms part of the prosthetic group of coenzyme A, an important enzyme concerned in acetylation. It seems also to be concerned with the function of the adrenal cortex, since animals deficient in the substance show evidence of cortical deficiency together with definite histological lesions in the adrenal cortex. Also pantothenic acid-deficient pregnant rats give rise to young with absence of eyes and abnormalities of the central nervous system. It has been suggested that deficiency of this nutrient was responsible for a syndrome characterised by a subjective feeling of burning in the feet and legs and seen in prisoners of war in the Far East in the War of 1939-1945.

*Biotin.*—This substance is excreted in the faeces and urine in greater quantities than it is ingested; it is probably synthesised in very adequate quantities by intestinal organisms. Avidin, a protein in egg-white, combines with biotin and renders it unavailable. In man deficiency of biotin has been produced by feeding large quantities of egg-white and the chief manifestations were a scaly dermatitis, anæmia and muscle pains.

It is very unlikely that spontaneous biotin deficiency occurs in man.

**Choline.**—Choline is probably necessary in human nutrition in amounts of about 500 mg. per day. The requirement, however, is almost certainly related to the intake of other substances such as methionine. Animals deficient in choline develop fatty livers and hæmorrhagic lesions in the kidney.

Choline is one source of labile methyl groups, it is also concerned as a lipotropic factor in preventing the undue deposition of fat in the liver, it is concerned in the formation of phospholipids and it is necessary for the formation of acetylcholine.

Choline is frequently used in the therapy of liver disease, but it seems possible that a large part of choline given by mouth is broken down in the intestine to trimethylamine, so that it is more likely to be effective when given parenterally than by mouth.

**Inositol.**—The function of inositol in nutrition is not known and there is no evidence to suggest that deficiency of this substance occurs in man.

**Para-aminobenzoic acid.**—There is no evidence for man that this substance must be present in the diet; it is part of the molecule of folic acid. It is necessary for the metabolism of many pathogenic organisms and metabolic pathways involving this substance are blocked when sulphonamides are present in sufficient quantities. The molecules are very similar and this was the first known example of the antimetabolic action of compounds structurally related to substances occupying key places in metabolic processes.

**Folic acid and citrovorum factor or folinic acid.**—Folic acid (pteroylglutamic acid) occurs widely in foodstuffs, mostly in the form of the conjugates, pteroyltriglutamic acid and pteroylheptaglutamic acid. It is converted in the body in the presence of vitamin C to folinic acid (citrovorum factor) which is active and which is itself effective when given in appropriate cases of anæmia. Folic acid is also synthesised by the intestinal flora and this probably forms an important part of the total intake.

Megaloblastic anæmias of various types respond to folic acid. This includes true pernicious anæmia, but here such treatment is dangerous, since subacute combined degeneration of the cord may be precipitated; it seems probable that what little vitamin B<sub>12</sub> (*q.v.*) there may be available is utilised for hæmopoiesis when folic acid is given, thus precipitating evidence of B<sub>12</sub> deficiency in the central nervous system. Some cases of macrocytic anæmia, usually associated with steatorrhœa or pregnancy, do not respond to vitamin B<sub>12</sub> but are responsive to folic acid or citrovorum factor. When folic acid is given to patients with steatorrhœa the megaloblastic anæmia usually responds, the stools become less watery and the glossitis may heal.

#### VITAMIN B<sub>12</sub> (CYANOCOBALAMIN)

This vitamin, which contains cobalt, and which exists as three closely related compounds, is Castle's extrinsic factor. Deficiency leads to megaloblastic anæmia, to superficial glossitis, to the neurological lesions of subacute combined degeneration of the spinal cord and to a general lack of well-being. Such deficiency does not occur in man as a result of deficient intake, but usually secondary to degenerative changes in the stomach resulting in an absence of Castle's intrinsic factor. It seems that this substance may either protect B<sub>12</sub> from destruction in the alimentary tract or aid in its absorption, because the vitamin is ineffective by mouth unless accompanied by sources of intrinsic factor or unless it is given in doses about one hundred times greater than is necessary parenterally.

Single parenteral doses of the order of 5 to 10 µg. will cause a considerable response in cases of pernicious anæmia, but for maintenance the requirement is about 4 µg. per day, administered parenterally twice a month.

Vitamin B<sub>12</sub> has also been found to stimulate the growth of children and of animals; it is certainly closely related to animal protein factor. Very large doses (1000 µg.

per day) have been claimed to relieve the pain of trigeminal neuralgia and of herpes zoster. It is also possibly concerned in preventing some of the complications of diabetes mellitus.

### VITAMIN C

Vitamin C or l-ascorbic acid is widely distributed, green vegetables, citrus fruits and potatoes, being particularly good sources of the substance. It is, however, easily destroyed in cooking, because it is rapidly oxidised when heated in air, and because in many foodstuffs in which it occurs, ascorbic acid oxidase is also present. This rapidly destroys the vitamin whilst the foodstuff is being warmed up in the initial stages of cooking. In general, vegetables cooked for large numbers of people contain very small amounts of ascorbic acid, whereas home-prepared vegetables are much more satisfactory. This is because it is not easy, on a large scale, to raise the temperature of vegetables rapidly to boiling point and so destroy the ascorbic acid oxidase before it has oxidised much of the ascorbic acid. In the home, vegetables can be "blanched" in boiling water, and this rapidly destroys the ascorbic acid oxidase.

Ascorbic acid can readily be estimated chemically, since it will reduce methylene blue or the dye, 2, 6-dichlorophenolindophenol.

The requirements of ascorbic acid are not exactly known, but human experiments have shown that a daily dose of 10 mg. will cure clinical scurvy and is sufficient to prevent the onset of scurvy at least for over a year. Ascorbic acid is utilised, however, more rapidly than usual during stress and when infections are present, so that the League of Nations Technical Commission's recommendation of 30 mg. per day is probably about right. The National Research Council (U.S.A.) recommends 75 mg. per day, and this would seem to allow a considerable margin of safety.

In spite of the ease with which ascorbic acid can be estimated and of the fact that its position in tissues can be demonstrated by histochemical methods, little detail is known of the actual action of the substance. It is concerned in tyrosine metabolism and it seems to be essential for the production of collagen; it is necessary for the conversion of folic to folinic acid. It is also present in very large quantities in the adrenal cortex and depletion occurs when corticotrophin (A.C.T.H.) is given.

Ascorbic acid deficiency can be estimated by a saturation test devised by Harris, in which the vitamin is given in a dose of 5 mg. per 1 lb. body weight each morning. The ascorbic acid content of the urine secreted between 4 and 7 hours after the test dose is estimated each day, and this shows a sharp rise after the procedure has been repeated a sufficient number of days to saturate the subject. Normally only 1 or 2 days are required for saturation.

Deficiency can also be estimated by a determination of the ascorbic acid content of leucocytes and platelets. A concentration below 2 mg. per 100 g. indicates severe depletion. Estimation of the ascorbic acid concentration in plasma is not so useful.

### SCURVY

Scurvy is a disease characterised by subcutaneous ecchymoses, ulceration and hæmorrhage of the gums, anæmia, debility and failure of wounds to heal.

**Ætiology.**—Until about 150 years ago scurvy was the scourge of sea voyages and was a factor of paramount importance in naval warfare. Owing to this disease, sea-going fleets had to be relieved every 10 weeks so that the men could be rehabilitated ashore. It was asserted that, when Lind's recommendation of a daily ration of 1 oz. of lemon juice was implemented, it was equivalent to doubling the fighting strength of the British Navy. A further example of the effects of the disease on sea

voyages is furnished by Anson's journey round the world; during 3 months of the voyage more than half the men on two of the ships died from scurvy.

Scurvy also was seen until comparatively recently in infants fed on dried milk powders (see Infantile Scurvy) but, owing to prophylactic measures, this, too, is rarely seen among European communities.

At the present time in western society, scurvy is most usually seen among old people (particularly men) of meagre means, who are living by themselves—so-called "Bachelor's Scurvy". In them it appears because of a deficient intake of foods containing vitamin C and tends to occur in the late spring.

**Pathology.**—It is generally agreed that the fundamental defect in scurvy is a failure to deposit adequate amounts of intercellular material, of collagen, osteoid material or of dentine. Hæmorrhages occur into the skin, subcutaneous tissues, under the periosteum and into the joints, pleura and pericardium. Furthermore, bones are not adequately calcified, the structure of growing bone is disorganised and wounds do not heal properly. Ascorbic acid is also necessary for the proper maturation of erythrocytes and anæmia of variable type also occurs in scurvy.

**Symptoms and Signs.**—Scurvy usually has an insidious onset and it is difficult in patients who present all features to assess the earliest manifestations. However, in experiments on human volunteers who had been saturated with the vitamin it was noted that after some 17 to 20 weeks of ascorbic acid deprivation hyperkeratosis of the hair follicles began to appear. This was usually first seen on the outer aspect of the upper arms and was also seen on the back, buttocks, backs of the thighs, calves and shins. Affected follicles became plugged with keratinous material and the hair became coiled up inside. Following this, the capillaries round the follicle became dilated and filled with blood and, finally, hæmorrhage occurred. After about 30 weeks, hæmorrhages occurred in the tips of the interdental papillæ of the gums and later swelling and more gross degrees of hæmorrhage appeared. Bacterial examination of the gums of patients with scurvy reveals that they are infected with large numbers of Vincent's spirochætes and anaerobic fusiform organisms. Also, after about 30 weeks, scars which had been made before deprivation of ascorbic acid became livid and red, and at about this time freshly made wounds failed to heal properly. Subcutaneous ecchymoses also occurred at about this time in one subject, but in the experimental disease large subcutaneous ecchymoses did not appear to feature so prominently as they do in the spontaneously occurring condition. Two experimental subjects experienced sudden cardiac pain, electrocardiographic changes being found. It seems probable that these symptoms might have resulted from hæmorrhage into the heart muscle and a similar occurrence or hæmorrhage into the pericardium might well account for the sudden deaths which were a feature of florid scurvy before measures of preventing and curing the disease were known. During the experiments carried out at Sheffield, it was also noted that subjects, who already had acne before ascorbic acid deprivation, experienced an exacerbation of this condition at a time when manifestations of scurvy were developing.

Although anæmia is a feature of naturally occurring scurvy it did not occur in the experimental subjects. This may well underline the fact that under natural conditions man rarely suffers from deficiency of one nutrient, and scurvy, as seen in clinical practice, is almost certainly associated with deficiencies of other nutrients as well as of ascorbic acid.

**Diagnosis.**—The concurrence of subcutaneous ecchymoses, hyperkeratosis of the hair follicles with perifollicular hæmorrhages, and swollen hæmorrhagic gums, should suggest the diagnosis at once, and a total and differential white blood count should exclude leukaemia, a condition which can resemble scurvy very closely. In mild cases, however, where the skin lesions are the only clinical manifestation, it is not possible to make a diagnosis without laboratory aids, the lesions themselves not being pathognomonic of scurvy. Either the saturation test or the level of ascorbic acid in the

white cell and platelet layer (see Vitamin C) should help to establish the diagnosis. The diagnosis can also be established by the response to ascorbic acid, since healing and retrogression of the lesions occur rapidly when adequate treatment is given.

**Prognosis.**—Untreated, and with a continuation of a scorbutic diet, death will occur. With all but the most serious cases in which sudden death can occur, however, the response to treatment is entirely satisfactory.

**Treatment.**—**PROPHYLAXIS.**—The diet should contain at least 10 mg. of ascorbic acid per day and preferably more than 30 mg. (see Vitamin C).

The established disease is best treated (a) by giving 1000 mg. of ascorbic acid daily for 5 to 10 days followed by a daily intake of 30 mg. or more, (b) by accompanying this by a good nutritious diet of high vitamin content (since other nutrients than vitamin C will almost certainly have been in poor supply).

It should be noted that healing occurred in subjects with experimentally produced scurvy when they were given as little as 10 mg. of ascorbic acid per day. It would seem, however, that, since it is quite harmless to give saturating doses of ascorbic acid, it would be better to do this and thus ensure that a maximum therapeutic effect is obtained.

GEORGE A. SMART.

## INFANTILE SCURVY

Infantile scurvy—known on the Continent as Barlow's disease—is identical in its pathology with the adult form of the disease, its special clinical features being due to the anatomical and physiological peculiarities of early life.

**Ætiology.**—The disease usually appears between the eighth and twelfth months—both sexes being equally affected. As in adult scurvy, the essential cause is the absence from the dietary of a sufficiency of anti-scorbutic vitamin. Any heating of milk reduces the amount of vitamin C present. Certain commercial processes in condensing or drying milk may completely destroy the vitamin. Pasteurisation is the least harmful process. In any case the addition of vitamin C to the diet is so easy that it is better to make milk a safe food by some heating process rather than to rely on it as a source of anti-scorbutic vitamin. A few cases have been recorded in which the child had been fed on the breast only; it is probable that in these the mother's diet had been deficient in fresh constituents. The normal *prophylactic* dose of vitamin C for the infant is about 25 mg. daily.

**Pathology.**—The chief changes are in the neighbourhood of the bones. A section made across a limb at the site of a swelling shows that the periosteum is hyper-vascular, thickened and separated from the subjacent bone by a layer of partially organised blood clot. There is no sign of inflammation, and no hard bone is formed in the periosteum, except in very long-standing cases; in which circumstances the muscles surrounding the bone may be infiltrated with blood or serum, and look sodden. The bone exhibits rarefaction, and may be fractured. There may be hæmorrhagic effusions into the joints or serous cavities. The organs exhibit no characteristic change.

**Symptoms.**—The onset is gradual, the first symptoms noticed being often a refusal of food, along with fretfulness and restlessness. There is a tendency for the child to resent being handled. Meanwhile the general nutrition is usually unimpaired, and the child's colour is often fresh and healthy looking. After a variable period the more prominent symptoms appear. The most striking of these is extreme tenderness of the legs, which causes the child to scream loudly when touched or even when approached. In a well-marked case some swelling will be found, usually of the lower end of the femur or upper end of the tibia. Involvement of the arm bones is much rarer. The skin over the swelling is often tense and glossy, and may be slightly œdematous; but there is no local heat. Soft crepitus may be elicited on handling the



limb, indicating a fracture or a separation of the epiphysis. In some cases hæmorrhage takes place into the orbit, giving rise to proptosis and ecchymosis of the eyelid. Rarer sites of hæmorrhage are around the ribs, clavicles or bones of the skull.

Changes in the gums are not nearly so pronounced as in adult scurvy, and are not usually present, unless some teeth have been cut; in that case the gum around them is usually swollen and of a purplish colour. Petechiæ and subcutaneous ecchymoses are very rare in infantile scurvy, and hæmorrhage from mucous membranes is not common. Hæmaturia, however, is not infrequent, and red blood cells, on microscopical examination, are nearly always present. Fever is not a conspicuous feature, but may be present if extensive hæmorrhages have taken place; it rarely exceeds 102° F. The blood changes are the same as have been described in the adult form of the disease.

**Diagnosis.**—This is easy in a well-marked case, provided the leading features of the disease are known to the observer. The screaming of the child on examination, the swelling and tenderness of the legs and the condition of the gums leave no doubt as to the nature of the affection with which one has to deal. All cases, however, are not so pronounced in type. Not infrequently, mild or incipient forms are encountered which it is easy to overlook. In these, tenderness when the child is handled, or when it is put in the bath, may be the only symptom. In other cases again, slight sponginess around the incisor teeth may also be present, or one may have to deal with an apparently causeless hæmaturia. In any case in which there is doubt two points will help. One is the nature of the feeding. If this has been of such a kind as is known to favour the development of the disease the diagnosis will be greatly strengthened. The other point is the application of the therapeutic test. If the symptoms present are really due to incipient scurvy then they will certainly disappear rapidly so soon as appropriate treatment is begun; if they fail to do this, then some other condition must be thought of.

Infantile scurvy may be mistaken for rheumatism, although the mistake should not occur if it be remembered that acute rheumatism is hardly ever seen below the age of 2 years. The distinction between scurvy and suppurative periostitis or epiphysitis is much more difficult, especially if the gum changes are absent. A very high temperature and much constitutional disturbance are against scurvy. The nature of the diet will also be of weight in the diagnosis. A radiogram will be of great assistance in coming to a conclusion. In scurvy the shadow due to subperiosteal hæmorrhage, and a sharp dark epiphyseal line, are characteristic.

The absence of swelling in the affected limb and of the other symptoms of scurvy should distinguish those cases of infantile paralysis in which there is much tenderness of the paralysed leg, and the blood examination should eliminate acute leukæmia or chloroma.

**Prognosis.**—This is quite favourable, provided the disease is recognised in time and proper treatment adopted. Nothing in therapeutics is more striking than the rapidity with which such patients improve on a change of diet, although some degree of thickening of the bones may persist for a long time. Death, when it occurs in the more severe cases, is usually the result of intercurrent disease, such as bronchopneumonia and chronic diarrhœa, although sudden hæmorrhage, cardiac failure or exhaustion may occasionally lead to a fatal issue.

**Treatment.**—The first step is to bring the disease under control by administering vitamin C in concentrated form as ascorbic acid. This can be given in tablets by mouth, crushed just before use, in a dose of 50 to 100 mg. daily for 2 or 3 days for an infant of 9 to 10 months. Some advocate a much larger loading dose—say 300 to 400 mg. Indeed there is almost no upper limit as when the tissues are saturated excessive vitamin C is excreted in the urine. While the disease is being brought under control dietetic changes can be made, such as the introduction of orange juice or tomato juice, the institution of mixed feeding (baked potato is particularly valuable)

and a change from any overheated milk or milk product to plain milk just brought to the boil for safety. In very severe cases ascorbic acid can be given intravenously. Iron is useful if there is anæmia present.

*Scorbutic infants should be handled carefully, and the clothing so made that it can be easily taken off and on. If it is necessary to move the child about it should be carried on a pillow. The affected limb should be supported by light splints or wrapped in wet towels, which, if allowed to dry in position, afford considerable support. In mild cases a covering of cotton-wool secured by a light bandage is sufficient protection.*

## RICKETS

**Definition.**—Rickets is a disease of nutrition occurring in early childhood. It mainly affects the growth of the bones, but may be accompanied by tetany in some cases. Associated nutritional disorders produce anæmia and a tendency to catarrh of the mucous membranes in many instances.

**Ætiology.**—Various theories have been held in the past as to the cause of rickets, but it is now clear that it is essentially due to absence of vitamin D in sufficient amounts to promote adequate calcification of growing bones. The fault is usually dietetic and not only because of deficiency of vitamin D-containing foods but also because excess of carbohydrate promotes more rapid growth than calcification can cope with. The ultra-violet rays of sunshine can manufacture vitamin D in the skin. Hence all those conditions which prevent the free access of unfiltered sunshine to the skin of the growing infant may be regarded as predisposing to rickets.

**Pathology.**—The chief changes are in the bones. Section through the end of a long bone shows that ossification, instead of proceeding in an orderly way, is greatly disorganised. In the zone of proliferation of the cartilage the cells show excessive multiplication, and are arranged irregularly instead of in columns. A broad bluish area results, which is the cause of the thickening of the epiphysis. In addition to this, calcification between the cells is defective, the affected area shows excessive vascularity, and the new bone formed is soft and deficient in lime. The whole process has been summed up in the statement that "there is an excessive preparation for ossification and a defective accomplishment of it". In addition, the vascular layer of the periosteum is thickened and the marrow congested.

Chemical analysis shows that the bones contain only from 30 per cent. to 50 per cent. of calcium, instead of the normal 60 per cent. or more. They may show signs of old or recent fracture. Other organs show no characteristic change.

**Symptoms.**—The disease can rarely be recognised before the sixth month. Amongst the earliest indications to attract attention are restlessness and irritability, sweating about the head, especially when asleep, and a tendency on the part of the child to kick off the bedclothes at night. There is no wasting, indeed the infant may be abnormally fat, though usually flabby and pale. The appetite is capricious. An early sign, found sometimes as early as 3 months, is cranio-tabes: this is a curious softening of the bones of the occipital region.

As the disease progresses, it will be found that dentition is delayed, and that changes in the bones become manifest. They first show themselves in the epiphyses of the ribs, which enlarge and form a row of knobs down the sides of the chest (the rickety rosary). Enlargement of the epiphyses of the bones of the limbs then takes place, being most conspicuous at the lower end of the radius.

The softening of the bones leads to various deformities. The chest sinks in at the line of junction of the ribs and cartilages, so that a broad groove forms, running downwards and outwards towards the axilla (Harrison's sulcus). The bones of the limbs bend, the femur curving forwards and outwards, and the tibia bending sharply forwards and often also outwards at its lower third; there may also be a curving of

the upper part, leading to "bow-leg". The humerus and bones of the forearm may become bent in an outward direction, as the child sits supporting itself on the hands, and the clavicle may show a sharp kink at the junction of the inner and middle third. The pelvis becomes flattened. Greenstick fractures of the limb bones are not uncommon.

The skull shows striking changes. It is usually somewhat enlarged, elongated and flattened on the vertex (box head), the anterior fontanelle remaining widely open long after the normal period of closure at the eighteenth month. There may be pronounced thickening of the frontal and parietal eminences, leading to the so-called "hot-cross bun" or bossed head, especially in cases complicated by anæmia with enlarged spleen.

The muscles are often so weak and flabby that paralysis is simulated, and the ligaments may be so lax that the limbs can be bent into almost any position ("acrobat rickets"). In consequence also of the laxity of ligaments, kyphosis often develops in the lower lumbar region (rickety spine).

The blood usually shows a varying degree of anæmia of the hypochromic type, and in a few cases the changes are so profound as to resemble those met with in chlorosis. Biochemical studies show a raised blood phosphatase, a lowered blood phosphorus and in severe cases a lowered blood calcium.

The digestive system is usually deranged. Chronic diarrhœa with pale, offensive stools is not uncommon. The abdomen is distended so that the child has a pot-bellied appearance. In the production of the distension, muscular weakness, intestinal fermentation and the pushing down of the diaphragm by the sinking in of the chest all play a part. The edge of the liver can often be felt at a lower level than normal, partly from displacement and in part from enlargement through fatty change. The spleen is also palpable in a considerable number of cases, although this is due more to its being pushed down than to actual enlargement.

In the respiratory system bronchial catarrh is very often present, and not uncommonly results in broncho-pneumonia. In the nervous system the disease shows itself by general nervousness and irritability, and in some cases by the development of laryngismus stridulus, tetany or even convulsions, of all of which rickets is a strong predisposing cause.

The clinical picture here outlined refers to fully developed rickets, which has become a rare disease in Britain. Radiographic examination confirms the clinical findings in the established case, but also it reveals changes in the growing ends of the long bones at a stage when clinical examination is essentially negative. This mild type of rickets is relatively common, and indeed some observers regard it as almost "physiological" in the sense that for calcification to be optimum in the rapidly growing bones of the small child a high degree of "saturation" with vitamin D and calcium seems to be necessary. Radiographic studies have also drawn attention to the fact that the clinical diagnosis of rickets based upon enlarged epiphyses and bow-legs, for example, is often unreliable.

**Diagnosis.**—In a fully developed case the diagnosis is easy. Early cases, and those in which the rickety element is overshadowed by some complication, such as broncho-pneumonia or diarrhœa, are more apt to be overlooked. The suggestive points will be delayed dentition, an open fontanelle and the presence of the rickety rosary. A radiograph will show some cupping of the diaphysis; the epiphyseal line will be irregular and ill-defined, and the epiphysis itself poorly ossified. There will also be a tendency to osteoporosis throughout the whole bone. The appearance of the epiphyses of the carpus and tarsus may be retarded.

The rickety head is apt to simulate hydrocephalus, but in the latter condition the skull is more globular, and bulges above the ears, the fontanelle is tense and the eyeballs, in marked cases at least, pushed downwards. The kyphosis of rickets may be mistaken for spinal caries; but in the former the bend straightens out as a rule

when the child is held up by the armpits. In severe cases this may not happen, and a radiograph may be required to settle the diagnosis. Bowing of the legs in the toddler is often more due to muscular development than to bent bones. If the muscular weakness is pronounced infantile paralysis may be imitated; but the history, the retention of the reflexes and the presence of other signs of rickets should prevent mistakes.

**Prognosis.**—Rickets is not fatal *per se*, and usually passes off spontaneously after the second year, although the deformities of the bone may persist for a long time. Even these, however, have a wonderful way of righting themselves without any special treatment. On the other hand, rickets is a very serious complication of other diseases, especially of broncho-pneumonia and diarrhœa, and adds greatly to their fatality if present.

**Treatment.**—Rickets can be prevented if the child is properly fed and cared for. Breast feeding for the first 9 months is the best safeguard, provided that the mother's diet is satisfactory; but it must always be remembered that the disease is apt to develop in children who are kept *too long* on the breast. The increasing use of dried milk fortified with vitamin D is undoubtedly an important factor in the decrease of rickets in its serious forms. After weaning, the premature and excessive use of starchy foods must be avoided. Care should be taken that the diet contains an adequate amount of animal fat. Plenty of fresh air, sunlight and exercise are also important factors in prophylaxis. It is probable that all infants in temperate and cold climates require a daily supplement of cod-liver oil or the official "cod-liver oil compound" to give 800 international units of vitamin D daily for the first 2 years of life. The same dose should be used throughout to give a relatively larger amount to the small infant.

If the disease has already developed, the diet should be altered in accordance with the requirements indicated above, the most important point usually being to increase the allowance of cow's milk, which should not fall below  $1\frac{1}{2}$  pints *per diem* during the second year of life. Cod-liver oil and halibut oil (or one of the artificial substitutes containing vitamin D) are most useful, having a specific influence on the disease; but iron may also be given with advantage if there is anæmia. It is wise to start with a pure vitamin D concentrate in adequate dosage for about a month to bring the disease under control. Sun baths or exposure to the rays of the mercury-vapour lamp have a definitely curative effect but act more slowly than vitamin D concentrates.

To prevent bending of the legs, long splints may be applied, projecting beyond the feet, so as to make standing impossible. Orthopædic treatment may be required for the more permanent deformities. Alimentary and respiratory complications should be treated by the measures appropriate to them.

#### LATE OR ADOLESCENT RICKETS

After growth has ceased certain deficiency and metabolic disorders may produce osteomalacia. Between this adult manifestation and the usual infantile type of rickets there is a series of rare and rather bewildering conditions in young and older children in which the radiogram changes at the ends of the still-growing bones resemble those of rickets. In some cases the cause is found in a missed case of cœliac disease where failure of fat absorption means also failure of vitamin D and calcium absorption. Another group, termed *renal rickets*, is found when a child, say of school age, has knock-knee, some stunting of growth and albuminuria. Investigation of the renal system may reveal other signs of a chronic nephritis and at post-mortem examination small contracted kidneys may be found. The blood usually shows a high blood urea and raised blood phosphates. Modern biochemical investigations indicate that the term renal rickets may cover various disorders, in some of which the renal tubules

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are allowing the loss of amino-acids or of calcium or of other metabolites leading to metabolic disorders such as a chronic state of acidosis with reduced plasma bicarbonate and increased chlorides. The "Fanconi syndrome" is the name given to one variety with amino-aciduria, glycosuria and acidosis. In Lignac's disease cystine storage occurs and bone changes have been noted. Some of these conditions have been described as vitamin-resistant rickets. It still seems possible that certain rare cases of what appears to be an ordinary deficiency rickets with no other metabolic disorder require very large doses of vitamin D to prevent or cure the condition. This is a genuine vitamin-resistant rickets and may be familial. Treatment of the various metabolic disorders mentioned is unsatisfactory. Usually it is advisable to give alkali in the form of citrates and citric acid. Orthopædic help may be needed to deal with the bony deformities.

"Fætal" and "congenital" rickets are ambiguous terms which have been loosely used to cover several distinct pathological conditions, amongst which are achondroplasia, mollities ossium and osteogenesis imperfecta. They are best avoided. So-called "scurvy rickets" and "acute rickets" are identical with infantile scurvy, although rickets often co-exists with the latter, seeing that both are due to faulty feeding.

ALAN MONCRIEFF.

## BERIBERI

**Synonyms.**—Polyncuritis Endemica; Hydrops Asthmaticus; Kakke; Barbiers.

**Definition.**—A nutritional disease due to deficiency in vitamin B<sub>1</sub>, and occurring most frequently in tropical regions where polished rice constitutes the main article of dietary. It is characterised typically by congestive heart failure and œdema (wet beriberi), and, or, multiple symmetrical polyneuritis especially involving the lower limbs, progressing to atrophic paralysis, sensory loss and ataxic gait (dry beriberi). The acute and subacute forms with congestive heart failure respond well to crystalline vitamin B<sub>1</sub> when given parenterally in adequate amounts early in the disease: treatment of the chronic "dry" beriberi is less satisfactory.

**Ætiology.**—The rice-eating populations of India, Japan, Malaya, the Dutch East Indies and Philippine Islands are mainly affected, but the disease is also endemic in Newfoundland and Labrador, where the population eat chiefly white wheaten flour. Though the disease is specially rife amongst people eating polished rice, rice *per se* is not essential, any dietary deficient in the antineuritic vitamin B<sub>1</sub> being a potential source of danger. Parboiled and undermilled or husked rice are not deficient in vitamin B<sub>1</sub>. During milling the husk, pericarp and germ, which are rich in protein, fat, phosphorus and vitamin B<sub>1</sub> (see p. 457) are removed, leaving the white polished rice poor in these constituents. Milled rice, white flour, breakfast cereals, macaroni, spaghetti and cane sugar contain practically no vitamin B<sub>1</sub>. This vitamin, known also as "aneurine hydrochloride" or "thiamine hydrochloride" was synthesised in 1937 in crystalline form (1 mg. = 333 international units), and is available for therapeutic purposes. It is mainly found in yeast, Marmite, whole seeds, the germ of cereals, pulses and nuts. Aneurine is a precursor of co-carboxylase, which removes, by oxidation, an important intermediary product of carbohydrate metabolism—pyruvic acid—from the tissues and blood. Excess of pyruvate can be demonstrated in the blood in beriberi, the value rising from a normal of 0.4–0.6 mg. to 1–7 mg. per 100 ml. The quantity normally present in the cerebrospinal fluid is also increased. When no complicating factor is present, 5 mg. of vitamin B<sub>1</sub> will restore the blood to a normal value in 10 to 15 hours. B<sub>1</sub> is readily absorbed and is stored in the liver, kidneys and heart, but the storage capacity is limited and clinical experi-

ence indicates that symptoms may appear in man in a few weeks with a  $B_1$  deficient diet.

**Pathology.**—In “wet beriberi” there is an acute congestion of the mucosa of the duodenum and lower end of the stomach, sometimes associated with pin-point hæmorrhages. The peripheral nerves show a Wallerian degeneration, with possibly an axonal degeneration of the neuron involved. The sheath of Schwann may exhibit multiplication of its nuclei and invasion by leucocytes. The vagi, phrenic nerves and sympathetic system may present stigmata of degeneration, and sometimes the anterior horn cells of the spinal cord and the nuclear connections of the vagus in the floor of the fourth ventricle are said to be implicated. Scattered foci of degeneration also may occur in the posterior columns of the spinal cord. The cardiac muscle may show degenerative changes, while the naked eye appearances are those of fatty degeneration associated with dilatation and hypertrophy, especially involving the right side. Nutmeg-liver, œdema of the soft tissues and effusions into the serous cavities are common. Wenckebach regarded œdema of the heart muscle with resulting loss of contractility, and not involvement of the vagi, as responsible for the cardiac condition. Weiss and Wilkins point out that the myocardium shows an unaltered water content, with “hydropic” degeneration of the muscle and conductive fibres, and increase in intercellular substances. In acute beriberi the essential condition appears to be an acute metabolic breakdown affecting both the cardiac and nervous system which responds therapeutically to vitamin  $B_1$ . In experimental animals the process underlying the nervous manifestations is a dysfunction associated with degenerative non-inflammatory changes. It has been suggested that the term “neuropathy” is more accurate than “polyneuritis”. In long-term deficiencies, however, damage to tissue may ensue which cannot be repaired merely by correcting the vitamin deficiency. Cases of so-called “dry” beriberi rarely come to necropsy unless suffering from intercurrent disease.

**Symptoms.**—There is generally a latent period of some 2 to 3 months before deficiency symptoms become manifest. Typically the onset is gradual, being characterised in the initial stages by epigastric discomfort, nausea and perhaps vomiting and diarrhœa. Later, polyneuritis, with palpitation, shortness of breath and weakness develop, the subsequent clinical picture varying according to involvement of the peripheral nerves, the vagus or the sympathetics. The disease runs an afebrile course, except possibly in its early stages. Recurrences are common. Several different types are described:

(1) **LARVAL OR AMBULATORY CASES.**—There is numbness of the legs with patchy anæsthesia and diminution of knee-jerks, all of which quickly disappear if the condition is recognised and a more varied diet containing vitamin  $B_1$  be given.

(2) **ACUTE FULMINATING BERIBERI.**—The onset is sudden, often with anorexia, epigastric discomfort, nausea and perhaps vomiting, while paræsthesia and loss of sensation especially over the front of the legs and dorsum of the feet are common. Congestive heart failure rapidly follows (see p. 903), and, or, widespread paralysis of the limbs and trunk. Alteration of the voice or aphonia due to laryngeal paresis, diaphragmatic paralysis secondary to phrenic nerve involvement, bilateral facial paralysis and paralysis of the muscles of mastication may supervene. Death may follow in a few hours to a few days. Acute cardiac failure may also suddenly develop in either the wet or dry forms.

(3) **SUBACUTE BERIBERI (Wet form).**—*Prodromata include paræsthesiæ and heaviness of the limbs.* The knee-jerks are at first exaggerated and then decreased and lost. Tenderness of the calf muscles, blunting of sensation and patches of hyperæsthesia and anæsthesia appear. The patient becomes weak, and cannot rise from the squatting position. Varying grades of œdema, at first involving the subcutaneous tissues over the tibiæ, appear and later effusions into the serous cavities with water-logging may develop. Shortness of breath, dyspnœa and tachycardia indicate cardiac



involvement. There are manifestations of dilatation of the heart, especially the right side (see p. 810). Several factors may contribute to the œdema; (1) intracellular œdema associated with failure of cell nutrition; (2) cardiac failure; (3) decreased plasma proteins and (4) secondary renal insufficiency. When the nervous manifestations are slight and the patient can still do muscular work, œdema is more likely to develop. Sudden death may occur without clinical evidence of cardiac involvement.

(4) **CHRONIC BERIBERI (Dry form).**—This is similar to the above except that œdema is absent and the disease runs a more chronic course. The onset is insidious, gastro-intestinal disturbances may be absent, the dominant features being wasting and weakness of the muscles, associated perhaps with cardiac irritability. Numbness of the limbs or face, cramps in the calf muscles and coldness of the feet may be troublesome. In rising from the squatting position the patient levers himself up by placing his hands successively on his knees and thighs. Foot drop, high-steppage gait, muscular tenderness and anæsthesia, sometimes of glove and stocking distribution, are frequently present. Generally leg symptoms are advanced before the arms are seriously affected but wrist drop and the high-steppage gait may co-exist. Clinically, the disease closely resembles alcoholic neuritis and the neuritis in pellagra, both of which are now regarded as being due to a deficiency in  $B_1$ . Wet beriberi may develop at any time, but this is less likely if the neuropathy is sufficiently severe to keep the patient resting. Lesions of the cranial nerves other than the vagi are very rare.

(5) **INFANTILE BERIBERI.**—This disease occurs especially in the Philippine Islands and Japan, where it is responsible for many deaths in breast-fed infants whose mothers are affected with latent or clinical beriberi. More than 50 per cent. of cases show symptoms between the third and fourth weeks of life. The disease occurs in both acute and chronic forms. In the latter gastro-intestinal features like anorexia, vomiting, diarrhœa or constipation occur, associated with wasting, pallor, œdema, mainly involving the face and extremities, dyspnœa and other evidences of cardiac insufficiency. Aphonia or an altered cry is often striking, and loss of knee jerks is present in 75 per cent. of cases. In the acute form death may occur with great rapidity, the infant developing convulsive attacks, suffering severe colicky pain and presenting cyanosis, dyspnœa and muscular rigidity.

(6) **SECONDARY BERIBERI** may be associated with (1) gastro-intestinal diseases leading to defective absorption of vitamin  $B_1$ , (2) chronic alcoholism, or (3) pregnancy, diabetes, febrile states or diseases increasing metabolism which lead to a relative deficiency by increasing the demand for  $B_1$ .

(7) **ASSOCIATED DEFICIENCY DISEASES.**—Visual disturbances are probably very rare in uncomplicated beriberi, but in prisoners of war nutritional polyneuritis was frequently associated with failing vision, photophobia and pallor of the temporal halves of the optic discs. Though undoubtedly nutritional in origin, there is no satisfactory evidence that retrobulbar neuritis or optic atrophy is due to deficiency in  $B_1$ . It is seen apart from beriberi in lactating women in Japan, and in advanced cases there is not infrequently deafness and ataxia as well. This fully developed syndrome was not uncommon in prisoners of war in the Far East associated with beriberi. Other deficiency conditions which may occur in beriberi patients include scrotal dermatitis (ariboflavinosis), night blindness (vitamin-A deficiency), skin and mucous membrane lesions due to nicotinic acid deficiency (pellagrous beriberi), and scurvy due to lack of vitamin C (ship's beriberi).

**Diagnosis.**—Wet beriberi has to be diagnosed from cardiac failure, nephritis, famine œdema and severe ankylostomiasis, while the dry form has to be differentiated from other causes of peripheral neuritis, post-diphtheritic paralysis, tabes dorsalis and progressive muscular atrophy. The dietetic history is important and multiple cases of neuritis, especially if associated with œdema, should always suggest beriberi: so

should oliguria and œdema in a breast-fed baby. Vitamin B<sub>1</sub> is greatly decreased or practically absent from the urine in cases of beriberi, and this test (p. 457) may determine the diagnosis in doubtful cases. Volhard's diuresis test may also be helpful, since there is water retention in beriberi.

**Prognosis.**—In acute beriberi with cardiac involvement, whether in adults or infants, the prognosis largely depends on the administration of large doses of crystalline vitamin B<sub>1</sub> parenterally; this improves the cardio-vascular condition in "wet" beriberi, and is often a life-saving measure in acute fulminating beriberi with cardiac failure, provided it be given intravenously or intramuscularly in adequate dosage. If the patient survives the first 2 weeks and an adequate maintenance dosage of B<sub>1</sub> be continued, recovery ensues. In infants the disease tends to run a rapid course and shows a high mortality unless promptly treated. Tachycardia, œdema and congestive heart failure not infrequently precede death. Chronic "dry" beriberi with neurological manifestations follows much the same course as multiple peripheral neuritis from any cause, despite intensive B<sub>1</sub> therapy. Recovery is slow and the condition persists for many months. In some cases muscular weakness is permanent or there may be persistent flaccid paralysis due to nerve cell degeneration. After improvement or recovery patients who return to their polished rice diet are liable to relapse and sooner or later die of the disease.

**Treatment.**—**PROPHYLACTIC.**—Prophylactic measures consist in providing a balanced dietary adequate in B<sub>1</sub>, i.e. 1 to 2 mg. daily. An allowance of 10 to 15 I.U. (international units) or 3.3 to 5.0 micrograms per 100 calories of food intake suffices for most purposes. Any condition which increases the metabolic rate requires an increase in vitamin B<sub>1</sub>. These include (1) a diet high in starch, sugar or alcohol, (2) fever and (3) hyperthyroidism. In institutions where polished rice or white bread is the main article of dietary, under-milled or parboiled rice and whole-wheat flour should be substituted. The addition of cooking soda to vegetables should be avoided, since boiling in the presence of alkali destroys B<sub>1</sub>, though heat alone does not. The importation of milled rice to communities with beriberi should cease.

**CURATIVE.**—Rest and dietary are all-important factors in recovery, and the introduction of crystalline vitamin B<sub>1</sub> (aneurine hydrochloride: thiamine hydrochloride) has revolutionised treatment in acute beriberi with cardiac involvement.

**Crystalline vitamin B<sub>1</sub>.**—In ordinary cases this drug is administered orally, but the intravenous route is indicated (1) in severe and fulminating cardiac cases, (2) when there is reason to believe absorption is defective and (3) in liver disease. The optimum oral dosage remains to be determined, but 5 to 10 mg. daily for mild cases and 20 mg. daily for moderately severe cases should prove adequate. In severe cases, especially those with cardiac features, 20 to 50 mg. should be given each day by the intravenous route for the first 2 weeks, followed by a similar dosage daily taken by the mouth. In fulminating cardiac cases 100 mg. may be immediately injected and this should be repeated until relief is obtained, after which the dose may be reduced.

Careful nursing and absolute rest in bed are essential, and when there is right-sided cardiac failure venesection is of definite value. Small feeds containing Marmite should be given 2-hourly. Subsequently a low carbohydrate diet rich in B complex and adequate in other vitamins is advisable. Yeast, Marmite, wheat germ, rice polishings, wholemeal flour, barley, oatmeal, liver, kidneys and other glandular organs serve as a satisfactory source of B<sub>1</sub>. Orange and tomato juice and, where possible, milk, butter, eggs and cream should also be included in the dietary of such cases.

In infantile beriberi the mother should receive vitamin B<sub>1</sub> treatment, and artificial feeding substituted for natural feeding or a healthy wet-nurse employed. Vitamin B<sub>1</sub> should be administered intramuscularly in adequate dosage, and the 2-hourly feeds reinforced with Marmite.

The efficacy of B<sub>1</sub> in acute fulminating beriberi and its relative inefficacy

the chronic polyneuritic form suggests its main therapeutic effect is on the cardiovascular system and not the peripheral nervous system. Where there is polynecrosis rest is essential until the pulse is normal in all respects. Crystalline vitamin B<sub>1</sub> may be given orally in addition to a well-balanced diet reinforced with Marmite, brewer's yeast, etc. Where the lower limbs are involved a cradle should be put over the feet, while splinting may be necessary to prevent muscular contracture. After the more acute symptoms have subsided massage and electrical treatment may help to restore the circulation and muscle tonus. If the patient has lost postural sensation in the lower limbs re-education may be necessary during convalescence; sometimes in chronic "dry" beriberi ataxia persists after recovery of muscular power.

In all types of beriberi it is most important to treat intercurrent disease which is not infrequent.

## PELLAGRA

**Synonyms.**—Mal de la Rosa; Mal del Sole; Maidismus; Psilosis pigmentosa; Malattia della Miseria; Asturian Leprosy; Alpine Scurvy.

**Definition.**—Pellagra is a chronic relapsing disease occurring especially in maize eaters, probably due to a deficiency in certain factors, especially those contained in the vitamin B<sub>2</sub> complex, i.e. riboflavin (B<sub>2</sub>), pyridoxin (B<sub>6</sub> or adermin) and nicotinic acid (B<sub>3</sub>). Clinically, it is characterised by buccal and gastro-intestinal disturbances, psychological and nervous features, and a symmetrical eruption especially affecting areas of skin exposed to the sun's rays or to friction.

**Ætiology.**—Pellagra (*pelle*, the skin; *agra*, rough) prevails endemically in the southern states of the U.S.A., lower Egypt, Turkey, Roumania, the Balkans, Spain and Italy, and has been reported from India, China, Japan, parts of Africa, Mexico, West Indian Islands and elsewhere. People of any race, age or sex are susceptible, and the malady is more common amongst the poorer classes. The incidence of the disease is greater in the spring. It occurs particularly amongst maize eaters, and in poorer communities living on cereals containing a low protein content or protein of low biological value. Following the work of Elvehjem on canine black tongue, nicotinic acid (B<sub>3</sub>) and its amide have been found to clear up the early dermal changes and mucous membrane lesions in pellagra and to relieve many symptoms referable to the central nervous system. Certain coenzymes contain nicotinic acid amide (Warburg and von Euler), and severely ill pellagrins usually have a low coenzyme content in the blood (Vilter and Spies). It has been suggested that an interference with general cellular metabolism may result from a deficiency of available respiratory enzymes. When infection or hyperthyroidism increase the oxidative activity of the body and when the enzymes which facilitate such activity are wanting owing to a deficiency of their precursors, a deficiency syndrome follows. Other factors in the B<sub>2</sub> complex, i.e. riboflavin (B<sub>2</sub>) and pyridoxin (B<sub>6</sub>), as well as proteins, are also essential in preventing pellagra and probably have a closely interrelated function (see pp. 457, 459). Sydenstricker suggests that vitamin deficiency leads to changes in the gastric mucosa, liver and central nervous system and that some unidentified factor present in normal gastric and liver preparations may play an ætiological rôle; he reports that the administration of normal gastric juice often relieves the pellagrous syndrome, and that though gastric juice from pellagrous patients contains Castle's intrinsic factor, it is often lacking in this other factor, as well as HCl. Sporadic cases of true pellagra occur in alcoholics or are secondary to disease of the alimentary tract. They arise from malabsorption of pellagra-preventing factors or from deficiencies in the dietary prescribed. Irrespective of whether the development of pellagra follows poverty, erroneous dietary habits, dietary idiosyncrasies, organic disease, chronic alcoholic addiction, or some combination of these factors, the lesions, symptoms and methods of treatment are essentially the same (Spies).

**Pathology.**—Emaciation is marked and the internal organs, including the heart and spleen, are small and atrophic. Skin lesions consist of an initial erythema involving the superficial layers, terminating later in a true exfoliative or exudative dermatitis, associated with pigmentation. Stomatitis and glossitis with ulceration of the tongue, denudation of its epithelium and ultimate atrophy may ensue. The jejunum is congested and atrophic, and small superficial ulcers involving the jejuno-ileum, colon and rectum are described. The mesenteric glands may be enlarged. Demonstrable pathological changes in the nervous system are generally slight, but there may be a subacute combined degeneration of the cord involving the posterior and lateral tracts, and especially Clarke's column (Wilson). Degeneration of the anterior-horn cells in the lumbar region, and subacute inflammation of the ganglion cells in the posterior roots are described, while Briauchi recorded meningeal thickening and adhesions, atrophy of the cerebrum, and hydrops of the ventricles and sub-arachnoid space. More than 50 per cent. of pellagrins show achlorhydria which is histamine-fast, but Castle's intrinsic factor appears to be secreted normally by the pyloric glands and megalocytic anæmia is rare. The total white count is generally normal in uncomplicated cases, there is often a lymphocytosis, and some degree of secondary anæmia is common. The cerebrospinal fluid exhibits no abnormality.

**Symptoms.**—The exact incubation period is unknown, and it should be realised that prodromal symptoms may recur over long periods before the classical oral or dermal features develop. In this stage a definite history is most important in making a correct diagnosis. Generally there is a history of having lived for a long period on (1) maize or other cereals poor in protein of high biological value, or (2) a diet high in fat and carbohydrate, and poor in proteins and vitamins, such articles as red meat, eggs, milk, fish, fresh vegetables and fruit being lacking.

**Prodromal symptoms.**—These include anorexia, loss of weight and strength, dyspepsia, flatulence, vomiting, sensations of burning or discomfort in the epigastrium, constipation or diarrhœa, insomnia, headache, palpitation, vertigo, numbness, forgetfulness, nervousness, mental irritability and mental confusion. Later, characteristic involvement of skin, alimentary tract and nervous system may supervene, but all three systems are not necessarily affected in any one pellagrin, while the sequence and the severity of the symptoms show considerable variation in individual cases.

**Alimentary features.**—The glossitis and stomatitis which usually appear early in the disease are diagnostic. In the early stages the tip and sides of the tongue are red and swollen; later the whole organ becomes fiery red (beet tongue) and inflamed, with lateral indentations from the teeth. Deep ulcers may develop on the sides and tip, while the dorsum becomes covered with a thick grey membrane, perhaps containing Vincent's organisms. A similar condition may involve the buccal mucous membrane, palate, gums and the muco-cutaneous surface of the lips. Hot, spiced and acid foods increase the ptyalism and the burning sensations felt in the tongue, pharynx, œsophagus and stomach. Other symptoms include nausea, vomiting and abdominal discomfort, flatulence and distension, especially after food. The bowels may act normally or be even constipated in the early stages, persistent diarrhœa being characteristic only of the advanced cases. In the latter the stools are non-fatty in type, diarrhœa occurs at all hours, and is often associated with colicky pain and tenderness. Sigmoidoscopy may reveal a proctitis. Associated vaginitis and urethritis are not uncommon.

**Skin lesions.**—Their distribution is on the back of the hands, wrists and forearms, the dorsum of the feet, the face, neck, upper part of the chest, under the breasts and in the perineal region—in short, over those areas directly exposed to the sun's rays or friction. Commencing as an erythema resembling a severe sunburn, there is redness, swelling and tension of the skin, followed by itching, burning and possibly bleb formation, while later, a deeper dermatitis develops with desquamation and exfoliation. Pigmentation and thickening of the dermis result, but finally atrophy

supervenes, the skin becoming wrinkled, inelastic and thinned. Pathognomonic features of pellagrous eruptions are their absolute symmetry and their sharply demarcated pigmented borders—the hyperkeratotic border of Merk. Angular stomatitis, cheilosis and scrotal dermatitis are not infrequent and are manifestations of riboflavin deficiency.

**Nervous system.**—The early mental symptoms, which are often regarded as functional, include depression, apprehension, irritability, headache, insomnia and bilateral burning sensations involving the extremities or other parts of the body. Later these mental symptoms are accompanied by rigidity, tremor of the tongue, coarse tremors of the limbs and head, athetoid movements and cramp; while numbness and paralysis of the extremities are common. The reflexes which at first are generally increased, later become decreased, and finally are often entirely absent. The gait may be spastic or ataxic, and cord involvement or peripheral neuritis due to associated  $B_1$  deficiency may be factors in the production of the neurological picture. If improperly treated, insanity often results. Retardation of growth occurs in children, but fortunately neurological complications are not common in them.

The course of the disease is generally afebrile and characterised by definite attacks alternating with remissions extending over many years unless a proper diet be maintained.

**Diagnosis.**—In classical pellagra the glossitis, stomatitis and the characteristic skin lesions make the diagnosis easy, but these features occur only in the well-established disease and it is the subclinical cases or those presenting vague prodromal manifestations which are so important to recognise early. A reliable history of dietary deficiency is important, and the rapid amelioration of gastro-intestinal and mental symptoms following nicotinic acid therapy will confirm the diagnosis. The urinary test for nicotinic acid excretion devised by Harris and Raymond may clinch the diagnosis in doubtful cases. Atypical pellagra may be confused with sprue or ergotism, while erythema multiforme and dermatitis venenata may cause difficulty.

**Prognosis.**—In endemic pellagra if patients receive modern treatment and a maintenance diet adequate in vitamin  $B_2$  complex and good biological protein, the mortality should be low. In the past, about 40 per cent. have been estimated to develop mental trouble, and many of these died in asylums. Fever is an unfavourable sign, and in the absence of intercurrent disease occurs either as a terminal event or in the fulminating form known as typhoid pellagra, which is characterised by intense prostration, tremor, muscular rigidity, convulsions and death. In secondary pellagra, the prognosis depends on rectification of a faulty diet and treatment of the underlying alimentary trouble.

**Treatment.**—**PROPHYLACTIC.**—The addition to a pellagrin's diet of red meat, milk, eggs and substances rich in vitamin  $B_2$  complex, e.g. brewer's yeast and Marmite, will prevent the disease.

**CURATIVE.**—Rest in bed, a high calorie, nutritious diet low in carbohydrate but rich in protein, and foodstuffs containing vitamin  $B_2$  complex are desirable. The diet should include fresh milk, lean scraped red meat, liver, canned salmon, tomato juice, fresh fruit and vegetables. Articles which have been found to possess curative value when given in large dosage include brewer's yeast (75 to 100 g. daily), Marmite (30 to 60 g. daily), wheat germ (250 to 300 g. daily), ventriculin (200 g. daily) and liver extract (75 to 100 g. daily). The discovery of the curative effects of adequate doses of nicotinic acid on many of the manifestations of pellagra has revolutionised the treatment of the disease. The drug is administered by the mouth, in tablet form and in divided doses, the daily dosage ranging from 200 to 1000 mg., 500 mg. being generally effective. After 10 days the dosage may be decreased. Flushing, burning and itching, nausea, vomiting and colic may follow, especially if the drug is given in large dosage on an empty stomach. Nicotinic acid also stimulates gastric activity and acid secretion, and is liable to elicit a mild histamine-like type of reaction. The

mucous membrane lesions, including pellagrous glossitis, stomatitis, vaginitis, urethritis and proctitis, are healed and bowel function restored to normal, the early erythematous lesions are blanched, while the early and late mental relapse symptoms are greatly benefited. The chronic skin lesions, however, are not cured by nicotinic acid therapy. Associated symptoms of peripheral neuritis are not relieved by nicotinic acid, but both pain and numbness disappear after daily injections of 50 to 100 mg. of crystalline vitamin B<sub>1</sub> (Spies).

Riboflavin is indicated if there is scrotal dermatitis, angular stomatitis or cheilosis; the oral dosage is 5 to 15 mg. daily. No toxic effects have been described following oral administration.

## NUTRITIONAL MACROCYTIC ANÆMIA

**Synonyms.**—Tropical Megalocytic Anæmia. Pernicious anæmia of Pregnancy.

**Definition.**—A severe nutritional anæmia, megalocytic in type, especially affecting pregnant women in hot climates and responding specifically to liver extract, Marmite or folic acid therapy. Non-hæmolytic and hæmolytic types are encountered.

**Ætiology.**—It is an unconditioned deficiency disease affecting both sexes, though it is specially common in women during the child-bearing period owing to the super-added nutritional demands of pregnancy and lactation. It occurs mainly in the tropics and subtropics and is associated with poverty and a low calorie diet which is predominantly vegetarian and poor in good biologic protein. It has been reported from India, China, Africa, Macedonia, British Guiana and Puerto Rico. In Macedonia it is prevalent in the refugee population whose diet is poor in animal protein while in South India it occurs in rice eaters. A similar nutritional macrocytic anæmia can be produced experimentally in monkeys fed on the same sort of diet as human sufferers from the disease. It is now known that nutritional macrocytic anæmia is not due to lack of extrinsic factor as was suggested originally by Castle. Probably it arises from deficiency of some other factor (Wills' factor) associated with good biological protein and contained in autolysed yeast and crude liver but not in highly purified liver extract; it has not been identified with any known constituent of B<sub>2</sub> complex. Possibly Wills' factor is an activator or co-enzyme in an enzyme system in which liver principle plays an important part (Wills). Its relationship, if any, to folic acid remains to be determined.

Hæmolytic nutritional macrocytic anæmia arises as a similar condition complicated by chronic malaria; the spleen is greatly enlarged and frequently the liver also. Probably some of the abnormal red cells produced by megaloblastic erythropoiesis undergo hæmolysis in the blood-stream; others are phagocytosed by an irritated and hypertrophied reticulo-endothelial system resulting from repeated malaria infections. In these cases reticulocytosis is almost always present, hyperbilirubinæmia is characteristic and those cases in which intravascular hæmolysis is occurring yield a positive Schumm's test due to the production of methæmalbumin (Fairley).

**Pathology.**—In the uncomplicated non-hæmolytic type the body is generally emaciated, fat is absent and the organs are pale and atrophic, the heart and liver especially being greatly reduced in size. Red marrow due to megaloblastic hyperplasia fills the long bones but as in sprue the tibia may sometimes show both red and aplastic marrow with a curious gelatinous appearance (Wills). The picture is really one of pan-hæmopoietic dystrophy with megaloblastic erythropoiesis with the production of Ehrlich's polychromatic megaloblasts, disturbances of the myeloid series with the production of macromyeloid cells, and abnormalities of the megakaryocytes. This is reflected in the peripheral blood by the presence of megalocytic anæmia, leucopenia and thrombocytopenia. In the hæmolytic type the body is reasonably well nourished and bright-yellow subcutaneous fat is present. The liver and spleen are

enlarged and there may be an enlarged heart with fatty degeneration in the myocardium. There is generalised hypertrophy and hyperactivity of the reticulo-endothelial cells which may contain malaria pigment and phagocytosed red cells, fine hæmosiderin deposits in the parenchymal cells of the liver and spleen and a decrease of lymphoid tissue in the latter organ in which the Malpighian bodies have disappeared. Hæmorrhages may be found in the skin, mucous membranes and serous membranes. Panmyelopathy of the bone marrow is present. Basophilic and polychromatic megaloblasts are common but ripening sufficient to produce a really pink cytoplasm with a finely stippled primitive nucleus is not common. The reticulo-endothelium lining the marrow sinusoids is the ultimate source of erythrocytes, leucocytes and platelets, and it is probable that both defective production of liver principle due to lack of Wills' factor and malaria are exerting a deleterious influence on the reticulo-endothelium in the hæmolytic type of nutritional macrocytic anæmia.

**Symptoms.**—In the uncomplicated *non-hæmolytic* type the symptoms are essentially those associated with a grave anæmia. The patient often first seeks advice for cardiac palpitations, giddiness, shortness of breath, weakness on walking and physical fatigue. Sore tongue, anorexia, vomiting, flatulence, abdominal distension and diarrhœa may be complained of, and fever or cough may or may not be present. Diarrhœa is variable and in some outbreaks is absent altogether. If present it is generally enteric in type, the stools being watery in consistency, brownish in colour and showing no excess of fat. Physical examination generally reveals pale mucous membranes, a low blood pressure, a rapid pulse and perhaps hæmic cardiac murmurs. Later frank congestive cardiac decompensation may ensue. The blood picture resembles that of pernicious anæmia with megalocytes and often nucleated red cells present in the blood smears. Red cell counts as low as 500,000 to 1,000,000 erythrocytes per c.mm. may be found. The colour index generally exceeds unity. The mean corpuscular volume is increased, and the Price-Jones curve shows a shift to the right, and an increased variability in mean corpuscular diameter. Thrombocytes are decreased, leucopenia is common, the reticulocytes are not increased, the serum bilirubin values are normal and the fractional test meals show that, unlike pernicious anæmia, the oxyntic cells retain their power of secreting HCl after the administration of histamine. Petechial hæmorrhages in the skin and mucous membranes and signs of mild neuritis are occasionally found but spinal cord involvement does not occur.

In the *hæmolytic* type of tropical macrocytic anæmia, certain features are superadded. The spleen is enlarged and hard but not tender while associated enlargement of the liver is not uncommon. Petechial eruptions involving the skin, epistaxis, bleeding gums or bleeding from other mucous membranes occur in about 25 per cent. of cases, and are associated with thrombocytopenia. An icteroid tinting of the skin or conjunctivæ is not uncommon, while hyperbilirubinæmia and dark-brown stools are characteristic findings. The blood picture resembles in many respects the megalocytic anæmia already described, but reticulocytosis is the rule, and megalospherocytosis may be found which is not the case in the *non-hæmolytic* type. Leucopenia and thrombocytopenia are frequent findings.

Apart from cardiac decompensation, the more common complications in both types include uterine sepsis in the puerperium, *Bact. coli* infections of the genito-urinary tract and respiratory infections. In the hæmolytic type the increased pressure on the diaphragm exerted from below by the pregnant uterus and greatly enlarged spleen, causes considerable respiratory embarrassment. Typical paroxysms of malarial fever at this late stage are rare, and parasites are not demonstrable between attacks.

**Diagnosis.**—An adequate hæmatological investigation is essential in diagnosis. The *non-hæmolytic* type has to be distinguished from other megalocytic anæmias. It differs from pernicious anæmia in that HCl is secreted in response to histamine injections and spinal cord complications are absent. The atrophic, distended abdominal parietes, the marked loss of weight and the bulky pale fatty stools so characteristic

of tropical sprue are not observed in tropical macrocytic anaemia. The hæmolytic type clinically resembles acholuric family jaundice, but there is no family history, the corpuscular fragility is not increased to hypotonic saline solutions, and the anaemia is of an entirely different type in the two diseases.

**Prognosis.**—Balfour estimated the death rate as 40 per cent. before the introduction of liver therapy. With modern treatment and in the absence of complications patients whose condition is diagnosed at a reasonably early stage should recover completely. The non-hæmolytic type responds more readily to treatment than the hæmolytic type.

**Treatment.**—**PROPHYLACTIC.**—Prevention depends on the adoption of a well-balanced diet containing adequate amounts of protein of good biological value and vitamin B<sub>2</sub> complex.

**CURATIVE.**—Uncomplicated cases of non-hæmolytic type generally respond to Marmite (Wills) in a dosage of 30 grammes daily, to liver extract by the mouth equivalent to 1 lb. of fresh liver daily, or to daily injections of 2 ml. of injection of liver (Campolon type). Excellent results are also reported following the administration of folic acid 10 mg. daily. Maximal reticulocytosis develops about the seventh to ninth day, and provided treatment is maintained satisfactory blood regeneration follows.

In the hæmolytic variety, or where complications exist, the anaemia is frequently very refractory and even much larger daily doses of Marmite (60 grammes) or parenteral liver extract (6 to 8 ml.) are by no means always satisfactory; in severely ill patients, it is often advisable in addition to parenteral liver therapy to give repeated blood transfusions in order to tide the patient over the critical period before specific therapy initiates the hæmopoietic response. More recently it has been reported that the proteolysed liver extract Hepamino (1 oz.) and also folic acid (10 mg.) daily elicit an excellent hæmopoietic response in refractory megaloblastic anæmias associated with pregnancy (Davidson and Davis). Successful termination of labour and the cessation of lactation decrease the nutritional demands on the body and may result in spontaneous cure, but it is important to remember that skilled medical and nursing attention during the puerperium and the daily examination of the patient for the onset of complications such as cardiac failure and pulmonary infections are very necessary. Throughout treatment a nutritious diet containing meat, eggs, milk and foods rich in vitamin B<sub>2</sub> complex is desirable.

N. HAMILTON FAIRLEY.

## PROTEIN DEFICIENCY

Since most cereal foods contain enough protein to supply most of the bodily needs when sufficient calories are ingested, protein deficiency rarely results from dietetic insufficiency without an accompanying deficit of calories. Some of these proteins are deficient in some of the essential amino-acids and have been called second-class proteins, but it has been shown that a small addition of first-class protein supplies adequate amounts of these missing amino-acids, so that the biological value of the mixture is high. In certain areas, where roots such as tapioca supply an appreciable portion of the total calorie intake, protein deficiency without calorie deficiency may occur.

**Ætiology and Pathogenesis.**—In those parts of the world where food is generally available in adequate quantities, protein deficiency occurs mainly as a result of conditions which prevent adequate food intake, such as anorexia nervosa or obstructions of the œsophagus, or which interfere with absorption. Abnormalities of the digestive organs, such as idiopathic steatorrhœa, chronic pancreatitis and the results of a variety of surgical mutilations may all result in protein deficiency, and may



produce a similar picture to that found resulting from a dietetic deficiency. Liver disease may interfere with protein synthesis, and conditions with massive proteinuria such as the nephrotic syndrome may result in protein abnormalities, but produce a different picture from that of true deficiency. During infections and after any form of trauma in well-fed subjects, there is a considerable breakdown of protein and resultant loss of nitrogen; this is very difficult to prevent and may occur even when the protein intake is much above normal. It seems to be part of the bodily reaction which occurs as a result of trauma and is probably mediated by overaction of the adrenal cortex. In extensive burns the situation is greatly intensified, since, in addition to the loss just described, there is a considerable direct loss of protein in seepage from the burned area.

**Symptoms and Signs.**—It is difficult to separate the symptoms and signs of deficient protein intake from that of semi-starvation. Unlike acute starvation, where ketosis is prominent and hunger after a day or two is absent, long-standing undernutrition is not associated with ketosis (provided about 150 g. of carbohydrate per day are ingested), and hunger and thoughts of food are a dominant feature of the mental make-up; for all else there is apathy and depression. Muscle wasting is very evident and this is associated with weakness and, most strikingly, with great lack of endurance.

Bradycardia, hypotension, a small heart and slight anaemia also occur and examination of the serum proteins may reveal them to be low, a finding, however, which is not always present, even in the presence of famine oedema. The basal metabolic rate is also lowered but this is more apparent than real, because in undernutrition there is a high extracellular fluid volume relative to total body weight; nevertheless it does seem that there is a slight reduction in the metabolic rate of the tissues themselves. More striking, however, is the decrease in the overall daily expenditure of energy which may be only about half that of the normally fed individual. A loss of about 30 per cent. of the lean body-weight is the maximum which can occur without loss of life.

**Treatment.**—Where the deficiency is the result of some pathological condition this must, of course, be corrected. Where the deficiency has resulted simply from lack of adequate food it is advisable to increase the amount of food gradually, since cases of congestive heart failure have occurred when large amounts of food have been given to semi-starved individuals. The main necessity is to supply adequate calories, about 3000 to 3500 being the level ultimately to be achieved, with at least 300 of them in the form of protein. There is a rapid return to normal weight, but it may take as long as a year before full functional normality is attained.

GEORGE A. SMART.

## KWASHIORKOR

**Synonyms.**—Malignant Malnutrition; Nutritional Dystrophy; Fatty Liver Disease; Infantile Pellagra.

**Definition.**—Kwashiorkor is the local name given to a malnutrition syndrome first described in indigenous African children. A similar clinical pattern is now known to occur in many parts of the world, especially in the tropics.

The syndrome appears most commonly in infants between the ages of 6 months and 4 years. It is particularly common in late breast-fed, weaning or recently weaned children. It may occur in other age groups, and even in adults.

Distinguishing features are apathy and pectishness, retardation of growth, changes in the pigmentation of the skin and in the pigmentation and texture of the hair, muscular wasting, oedema, anaemia and fatty, necrotic or fibrotic changes in the liver.

Nutritional dermatoses are commonly but not invariably present.

**Ætiology.**—Kwashiorkor is generally considered to be the result of severe protein deficiency, usually arising from the intake of a diet low in protein and high in carbohydrate. Although the pathogenesis of the syndrome is not understood it has been suggested that on the whole the organs and tissues affected first and most severely are those with the highest turnover of protein, *i.e.*, the gut, mucosa, liver and pancreas (Waterlow). Secondary deficiencies of individual vitamins may develop. Many cases are complicated by the effects of malaria, helminth infestations (especially hookworm) and severe bacterial infections. These complications are not considered to be direct ætiological factors, although they may considerably modify the clinical picture. The syndrome occurs in their absence.

**Pathology.**—The œdema is sometimes said to be associated with the low serum albumin content, but there is no obvious direct relationship. There is some evidence of salt retention.

Changes in the skin vary enormously from patient to patient. Patchy change in pigmentation commonly occurs, which is often indistinguishable from that arising from genetic factors. There may be scattered areas of both hyper- and hypo-pigmentation. Where dermatoses are present the histological changes resemble those described in deficiencies of the particular vitamins concerned.

Changes occur in the texture and pigmentation of the hair. In the latter case, the custom has been to refer to "depigmentation" but since there appears to be qualitative as well as quantitative change, the term "dyspigmentation" is used here.

**THE LIVER.**—Post-mortem examination and biopsy commonly reveal fatty degeneration and infiltration, first seen in the periphery of the lobules. The cells of the whole lobule may be involved. During successful treatment the fatty changes have been seen to regress. Various degrees of fibrosis and sometimes gross cirrhosis may be seen, especially in patients who have had the syndrome for some time. These changes are believed to be late developments of the same process which results in the earlier fatty changes, *i.e.*, the essential protein deficiency.

**THE PANCREAS.**—Degenerative changes have been described, varying from atrophy of the acinar cells with diminution in content of granules to hyaline changes, dilated tubules and periacinar, perilobular and sometimes periductal fibrosis. In advanced cases large areas of acinar tissue may be replaced by fibrous tissue. The islets may also be affected.

Considerable attention has been paid recently to these pancreatic changes. It has been suggested that they may be the essential pathological lesions responsible for the development of the syndrome, including the fatty changes in the liver. Examination of the duodenal contents in severe cases has revealed reduction in amounts of amylase, trypsin and lipase, normal quantities being restored after successful treatment.

**OTHER TISSUES.**—Atrophic changes in the salivary glands have been described. Muscular atrophy is often considerable, although it may be masked clinically by œdema. Some workers have reported atrophic changes in the intestinal wall. Lesions of the kidneys occur in some cases, the most striking features of which are glomerular hyalinisation and pericapsular fibrosis.

**Symptoms and Signs.**—The syndrome comprises some combination of the following features: (i) retarded growth, especially evident during late breast feeding and weaning; (ii) muscular wasting and œdema; (iii) alterations in skin and hair pigmentation and in hair texture. Various forms of nutritional dermatoses may occur but are not invariably present. Biopsy or necropsy reveals the liver changes described above; these are presumed to be present in some form in all cases. Mortality is high in untreated cases.

The syndrome is most easily described as it occurs in the infant. Trowell draws a striking picture of the mother "unwrapping a miserable imp who immediately

Anæmia is present in some degree, probably in all cases. Where there are no parasitic infections, the anæmia is mild and orthochromic. Ankylostomiasis, malaria and schistosomiasis all affect the final blood picture. The red cell count commonly lies between 2.5 and 3.5 million cells per c.mm. The cells are usually orthochromic. Where there is iron deficiency, for example, in the presence of heavy ankylostoma infestation, they may be hypochromic. In severe cases there may be some macrocytosis, probably due to the presence of reticulocytes. Megaloblasts are not present. The bone marrow response is normoblastic.

Serum albumin is low. This is regarded as a reflection of liver dysfunction. The globulins may or may not be increased.

The blood chemistry varies with the condition of the patient. Both chloride and fixed base may be reduced.

Liver biopsy will reveal the fatty or fibrotic changes described above depending on the stage of the syndrome and the length of its duration.

**Course.**—The development of the untreated case is steadily retrograde. The child becomes increasingly dull and apathetic; the retardation of growth continues; the gastro-intestinal symptoms, œdema and skin and hair changes progress, and various signs of vitamin and other deficiencies develop. There is a very high mortality in untreated cases. Nevertheless, the response to treatment is good in the vast majority unless the syndrome has progressed too far before treatment is commenced.

**Diagnosis.**—The combination of retarded growth, especially in infants during weaning or post-weaning, alterations in skin and hair pigmentation and œdema, usually with some grade of dermatosis establishes the clinical diagnosis. Biopsy of the liver revealing fatty or fibrotic changes confirms it.

According to some authorities a pre-œdematous stage of the syndrome exists, but the general view seems to be that the diagnosis of kwashiorkor should be confined to the œdematous stage. Some workers are critical of clinical diagnosis in the absence of evidence obtained by liver biopsy. Dermatitis and vitamin deficiency signs are not essential for the diagnosis. Signs of deficiency of a particular vitamin, for example A or B, are often very common complicating factors of the syndrome in a particular area and account for some of the wide variation of clinical patterns described.

Where the diagnosis is being made in groups of children, it is strengthened by heavy mortality amongst untreated cases.

**Prognosis.**—Prognosis is bad in the untreated case. Mortality ranges from 30 to 40 per cent. and occasionally even higher. Many infants will die within a day or two of being first examined and placed on treatment. Once treatment has been successfully started, however, the prognosis rapidly improves. Mortality in properly treated cases should be less than 5 per cent.

Treatment must be continued over a long period and be carefully supervised, otherwise relapses are common.

Milder untreated syndromes in children may progress into adult life as a state of subnutrition in which one or more of the essential features of kwashiorkor may be emphasised.

**Treatment.**—To be effective treatment must be carefully controlled. It consists essentially of restoring the nutrition balance and dealing with concomitant parasitic or other infections.

Advanced cases require intravenous protein hydrolysates or serum. Severely ill infants should be given 100 ml. human plasma daily for the first 10 days. The intravenous route is preferable, but if this is impossible the serum may be given into the bone marrow or subcutaneously.

Patients who can be treated orally should be given frequent small meals throughout the day. The diet should be high in protein and low in fat. Most cases tolerate fat extremely badly. Milk is the most satisfactory diet. Skim milk or lactic acid milk seems to produce the best results. The average case in infants should be given

grizzles and cries and avoids the light". The child is apathetic, rarely resists examination and tends to stay where it is put instead of wandering off like a healthy child. The state of the child is one of "peevish mental apathy".

It is retarded for its age in both weight and stature. It may not, however, look emaciated since the subcutaneous fat is often considerable and the prevailing œdema may give a superficial appearance of good nutrition. The essential muscular wasting may become obvious only as the œdema subsides during treatment. It is prominent in the occasional case in which the œdema is minimal.

Changes in the texture and colour of the hair occur in all races, but are probably best seen in the African, in whom the black curly coarse wool may be replaced by reddish, grey or white straighter silky hair, sometimes over the whole head, sometimes only over the temples and vertex. Dyspigmentation may occur without change in texture.

In the original description of kwashiorkor, dermatosis was present. It is now generally agreed that dermatoses, although extremely common, are not necessarily an essential part of the clinical pattern. The commonest skin change is one of pigmentation, which may occur without apparent change in skin texture. In many cases the development of hypo- or hyper-pigmentation probably represents the initial change in the development of more serious skin lesions. The commonest form of the latter appears on areas exposed to irritation, such as the napkin area, the back, the buttocks, thighs, etc. The areas usually affected in pellagra, such as the hands and face, escape.

Early lesions are described by Trowell as "sharply defined black varnished patches . . . which rapidly enlarge". The affected hyper-pigmented skin becomes dry, cracks, scales and peels off, sometimes in "large enamel-paint" plaques, half an inch or more across. The area beneath is depigmented, and is easily damaged and infected, especially in the "napkin area". The general picture has been called "crackled" or "crazy pavement" skin. Many cases show an almost universal dry scaling dermatosis which is often particularly prominent in the lower legs. Other forms of skin change include the so-called elephant skin, the skin being thickened, fissured and either hyper-pigmented or often unchanged in pigmentation. Bullous changes associated with secondary infection and ulceration in the pelvic region have also been described. The black scaling peeling dermatosis is easily recognised and its association with the kwashiorkor syndrome is generally accepted. On the other hand, the origin of some of the other skin changes mentioned is often difficult to decide and factors such as exposure, and particularly onchocercal and other skin infections must be carefully excluded as far as possible before accepting such lesions as related to the malnutrition syndrome. The skin lesions respond well to treatment.

Most patients are obviously œdematous. The œdema is characteristically soft and easily pitted. It is most obvious in the legs and extends into the genitals and thighs and sometimes the buttocks. The arms, especially the forearms, are often involved. Oedema of the face especially around the eyes and nose is common.

Most infants with kwashiorkor are notably pot-bellied, a feature which is often exaggerated by the way they sit upright, with their legs bent in front of them. There may be some œdema of the belly wall and evidence of free fluid in the peritoneal cavity. The liver is nearly always palpable. The firm edge may be felt an inch or more below the costal margin; there is usually no tenderness.

Gastro-intestinal disorders are common. Most patients suffer from indigestion and diarrhœa is very common, the infant passing numerous semi-liquid or yellowish stools containing undigested food. There may be some steatorrhœa, with the passage of bulky soft offensive stools, also containing undigested food.

Various signs of vitamin deficiencies are common. Cheilosis, angular or general stomatitis, changes in the eyes, including Bitot's spots and xerophthalmia may be present. Photophobia is common.

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at least 1 pint, and if possible 2 pints, of skim milk daily to begin with. If the child refuses milk at the beginning of treatment it should be coaxed to accept it, and, if necessary, food should be withheld for a few hours until it does. Powdered milk (not reconstituted) may be given several times a day by spoon in addition, to increase the protein intake.

A good mixed diet is gradually substituted for milk as the patient improves, and may replace the milk after several weeks.

Vitamins, if introduced, should be given in the form of cod-liver oil or vegetable extracts. Purified vitamins are seldom necessary and may be harmful.

It may be necessary to give iron. Very anæmic cases require immediate transfusion. A small transfusion often helps the progress of even moderately anæmic patients. Where there has been severe loss of fluid and salt from diarrhoea and vomiting, parenteral administration of isotonic saline or glucose saline may be required.

Parasitic infections should be diligently sought out and treated. Bacterial infections, even when they appear trivial, should be treated, if possible, with antibiotics. Malaria should be treated immediately. Quinine and sulphonamides should be used sparingly, however, in the early stages. Synthetic antimalarials are preferred. Some workers advocate small daily doses of proguanil in any case in endemic areas, even when malaria parasites are not seen.

The treatment of helminth infections, which tends to be toxic, should be deferred until the patient is regarded as strong enough.

The usual lipotropic factors such as methionine are not in themselves of any appreciable benefit in dealing with the fatty liver lesion.

BRIAN MAEGRAITH.

## SECTION VII

### DISEASES OF THE ENDOCRINE GLANDS

#### DISEASES OF THE PITUITARY GLAND

APART from its own special functions, the pituitary gland has a stimulating trophic effect on most of the other ductless glands, which latter tend to atrophy after removal of the pituitary gland (hypophysectomy). The influence, however, is reciprocal and hyper- or hyposcretion of the other endocrine glands influences the activity of the pituitary. The hypothalamus, on either side of the third ventricle, contains many nerve nuclei which are connected with the posterior pituitary gland. The anterior pituitary receives hypothalamic chemical stimuli by vascular channels.

The posterior lobe secretes two hormones, pitressin and oxytocin. The former has a vaso-pressor action, is anti-diuretic and produces an increased urinary excretion of chloride. The latter, oxytocin, produces contraction of the pregnant uterus. The pars intermedia secretes the melanophore expanding hormone.

The anterior pituitary gland appears to secrete 10 or more hormones, but it is uncertain whether they are all distinct chemical substances. It has been postulated that one hormone may have different actions under varying physiological circumstances. Description is facilitated by assuming the existence of separate hormones :

1. Growth or somatotrophic hormone.
2. Lactogenic hormone. This initiates and maintains mammary secretion. Experimental evidence also suggests the existence of a mammogenic hormone, which produces development of mammary acini and ducts even in the absence of ovaries.
3. Thyrotrophic hormone (thyrotrophin). This produces (a) hyperplasia of the thyroid gland and hypersecretion of thyroxine; and (b) exophthalmos, even after thyroidectomy.
4. Gonadotrophic hormone (gonadotrophin). This factor has been chemically separated into two components, Prolan A and Prolan B, which under certain conditions produce different gonadotrophic reactions. Thus, Prolan A stimulates development of the Graafian follicles and of the spermatid tubules; whereas Prolan B produces luteinisation of mature follicles, or of the theca of immature follicles, and hyperplasia of the interstitial cells of the testis.
5. Diabetogenic complex. Pituitary extracts produce hyperglycæmia, glycosuria and ketonuria in some species of animals, intact or partially depancreatised. The complex has two definite components—(a) adrenocorticotrophic (see below), and (b) somatotrophic. F. G. Young has shown that pure growth hormone (somatotrophic) is powerfully diabetogenic in animals and that its action is independent of the adrenal glands. There may be a third factor in the diabetogenic complex, not as yet chemically separated.
6. Insulotrophic hormone. The evidence for this is suggestive rather than conclusive. It may be an initial or inherent action of growth hormone in certain species under appropriate conditions.
7. Adrenocorticotrophic hormone (corticotrophin, A.C.T.H.). This is measured by restriction of adrenal cortex size and weight or by decrease of ascorbic

acid content of adrenal cortex, both tests carried out in the hypophysectomised animal. It stimulates increased secretion both of androgens and glucocorticoids by the adrenal cortex and there may be two corresponding types of the hormone. The glucocorticoids or 11-oxysteroids are diabetogenic and ketogenic.

## ACROMEGALY

**Definition.**—Acromegaly is a condition due to a hypersecretion of the growth hormone of the anterior pituitary gland. It is characterised by enlargement of the hands and feet, and of the bones and cutaneous tissues of the face, and of the thoracic and abdominal viscera. It is frequently superimposed on gigantism.

**Ætiology.**—The disease occurs at any age but usually before 40, and in both sexes. There is a mild familial type. The immediate cause is an excessive secretion of the growth hormone.

**Pathology.**—The primary lesion is an adenoma, or hyperplasia, of the eosinophil cells. Secondary enlargement of the adrenal cortex and the thyroid are often present. The testes and ovaries are usually atrophic in the later stages. The islets of the pancreas may be hyperplastic in the initial phases, and later undergo atrophy. Diffuse lymphoid hyperplasia is frequent. All the viscera are enlarged.

**Symptoms.**—The patient may first seek advice because of increasing size of the hands and feet, or of a blunting and distortion of facial features, or visual disturbance due to a pituitary tumour. The latter is associated with optic atrophy, bitemporal hemianopia, progressive loss of vision and severe headaches. Ocular palsies may result from pressure on the third, fourth or sixth nerve.

The enlargement of the extremities is partly due to bony enlargement and thickening, but there is also overgrowth of the soft tissue. The vault of the skull may be somewhat thickened, but considerable bony overgrowth is more common in the base of the skull and in the facial bones. The overgrowth of the lower jaw leads to prognathism and spreading of the teeth. The vertebrae undergo changes, and kyphosis and scoliosis are common. The soft tissues of the face, nose and lips undergo hypertrophy, which together with the bony changes, may transform the facial appearance. The skin and subcutaneous tissue are thickened, and the sebaceous and sudoriferous glands hypertrophied, producing a greasy perspiring skin. The hair too is thick and greasy, and may be abundant over the trunk. Enlargement of the tongue leads to difficulty in articulation, and enlargement of the larynx produces a deep voice. Speech is also sluggish and memory poor. The general behaviour may be characterised by apathy and lack of initiative. Generalised muscular hypertrophy may initially be associated with great strength, but later weakness and atony result. The heart is enlarged, but hypertension or hypotension may occur.

**Complications and Sequelæ.**—(1) Sex Function. Impotence in the male, and amenorrhœa in the female, are common complications, caused by destructive encroachment of the eosinophil cells on the gonadotrophic basophil cells. (2) Thyroid. A non-toxic colloid goitre, sometimes nodular, is found more frequently than a hyperplastic goitre with thyrotoxicosis, and this fact throws doubt on the thyrotrophic origin of thyrotoxicosis. Myxœdema may develop in the later stages. (3) Adrenals. They are frequently enlarged and contain adenomata. This enlargement indicates stimulation by the adrenocorticotrophic hormone. Hirsutism results in both sexes. (4) Diabetes Mellitus. This disorder is present in a small proportion of patients; but some degree of intermittent or chronic hyperglycæmia with glycosuria, in the absence of diabetic symptoms, may be detected in some 50 per cent. It can be attributed both to the somatotrophic and the adrenocorticotrophic hormones. (5) Mental Changes. Depression, irritability, negativism, melancholia, mania and delusional insanity are possible complications.



**Diagnosis.**—The increase in size of hands and feet, and thickening and blunting of the facial features, with prognathism, makes diagnosis easy, especially if gigantism is already present. Osteitis deformans is a bony disorder which distorts the vault of the skull and does not often affect the facial bones. In acromegaly, radiographic examination may reveal an enlargement of the sella turcica, which if associated with optic atrophy or bitemporal hemianopia, indicates a pituitary tumour. A raised serum phosphorus is indicative of active acromegaly. The urine may show raised values for adrenal glucocorticoids and 17-ketosteroids.

**Prognosis.**—The course is gradually progressive, with intermittent phases of apparent arrest of the pituitary hyperfunction. These phases may be prolonged over many years. As myxœdema may follow exophthalmic goitre, so hyperactivity of the pituitary may be succeeded by hypoactivity with secondary hypofunction of the thyroid and adrenal glands.

**Treatment.**—If there is progressive involvement of the optic nerves, with danger of complete blindness, the treatment is surgical removal of the pituitary tumour. Otherwise irradiation of the pituitary region should be tried first, and relief results in some 50 per cent. The initial dose should be on the small side to guard against secondary hypopituitarism. Testosterone and œstradiol in large doses have some influence in depressing pituitary overactivity. Complications such as thyrotoxicosis, myxœdema, impotence and amenorrhœa are treated appropriately. True diabetes mellitus will need dietetic regulation and insulin, but symptomless glycosuria can be ignored.

## GIGANTISM

This is due to excessive secretion of the pituitary growth hormone before the epiphyses have united. It may be followed by acromegaly. Muscles and bones are usually strong in pituitary gigantism, and weak in eunuchoidism, excessive height being due to delayed epiphyseal closure. Adolescent gigantism with mild acromegaly in males, however, may be associated with delayed puberty, gynœcomastia, delayed epiphyseal closure and absence of muscle strength.

The treatment of pathological gigantism is the same as for acromegaly, namely, irradiation of the pituitary gland, or surgical removal of a pituitary neoplasm. Inhibition of pituitary activity by large doses of testosterone, or œstradiol, may be of some benefit.

## INFANTILISM

**Synonym.**—Levi-Lorraine Syndrome.

**Definition.**—Infantilism consists of a retardation of somatic growth and sexual development with failure to attain adult dimensions and sexual characteristics. The term was first used by Lorraine in 1871 in connection with a case of infantilism associated with tuberculosis. It was later applied by Levi (1908) to hypopituitarism beginning in childhood. Brissaud extended the term to include infantilism associated with hypothyroidism (Brissaud's syndrome), but this is a more complicated and less well-defined disorder.

**Ætiology and Pathology.**—Usually in life there is no gross lesion and necropsies are rare, since the uncomplicated condition is not incompatible with good health. Experimental and biological evidence indicates a deficiency of pituitary eosinophil cells (growth hormone), and of basophil cells (gonadotrophic). Occasionally a third ventricle tumour, or pituitary craniopharyngioma, or chromophobe adenoma may be the cause. Tuberculosis, congenital or rheumatic heart disease, cœliac disease or any chronic childhood illness may be the cause of infantilism.

**Symptoms.**—In childhood, the patient is perfectly formed but somatic growth is much below the usual rate. Development of the primary and secondary sexual characteristics at puberty does not occur, and the genital organs remain infantile

throughout adult life. The condition, however, is not absolute, and varying degrees of sexual development are met with. Although the epiphyses tend to remain open long after the normal time of closure, the ultimate height is well below normal, as the secretion of growth hormone is deficient. Intellectual development is usually normal and sometimes above normal standards, but emotional development and the behaviour pattern tend to remain immature. The patients are usually slender and have graceful limbs, ankles, wrists and fingers. The skin and hair are of smooth silky texture, and the general appearance is becoming.

**Diagnosis.**—The condition should be differentiated from other forms of dwarfism.

**Prognosis.**—This depends upon the time at which treatment is commenced, but in general hormone therapy can only produce a trend towards normality. Health and normal function, other than sexual, is maintained even in the absence of any treatment.

**Treatment.**—In contrast with the dramatic effect in the experimental animal, pituitary growth hormone is not effective in most cases of infantilism and does not even cause nitrogen retention. This is a paradox, as yet unsolved. Methyl testosterone, 25 mg. daily by mouth, produces nitrogen retention with skeletal and muscular growth. In the female or in young children methyl androstenediol is preferable, since its androgenic effect is far less than that of methyl testosterone. Insulin is now known to be chondrotrophic in the hypophysectomised rat, although to a less degree than growth hormone, but this may justify its therapeutic application in selected cases. Gonadotrophins and oestrogens will stimulate sexual development.

## DWARFISM

**Definition.**—A condition of subnormal height well below the normal range. It is the opposite of gigantism. Although no other abnormality may be present, the use of the term is also extended to include a variety of conditions, of which deficient height is only one feature.

**Ætiology and Pathology.**—The essential feature is a deficiency of pituitary eosinophil cells and of their growth-promoting hormone. The condition is quite comparable to that found in a strain of congenital dwarfed mice, in which the dwarfism and deficiency of eosinophil cells follows a Mendelian recessive genetic distribution in successive families. Occasionally in man a pituitary or other intracranial destructive neoplasm may be the cause. Cushing's syndrome in children is associated with dwarfism since cortisone inhibits cartilage proliferation. In sexual precocity there is initial acceleration of growth, but the ultimate height is usually subnormal because of premature union of the epiphyses.

**Symptoms.**—In uncomplicated cases there are no features other than retardation of growth. In some patients, especially girls, there is premature union of epiphyses at puberty, e.g. 12 years of age. If, on the other hand, sexual development is infantile, the condition is that of infantilism (see above). In Fröhlich's syndrome, adiposity is an essential feature. Dwarfism may also be a feature of Simmonds's cachexia, if the condition is due to a pituitary craniopharyngioma commencing in childhood. Progeria (meaning prematurely old) is a name given by Hastings Gilford, in 1904, to a rare condition comparable to Simmonds's cachexia in childhood, and associated with an old, wizened countenance, infantile sex organs, dwarfism, alopecia, absence of breasts and a parchment-like skin. The condition is probably of pituitary origin, but its exact pathology is uncertain. Ovarian agenesis (Turner's syndrome) is due to a congenital absence, or failure of maturation, of rudimentary ovaries, but the associated dwarfism is due to a pituitary defect. Webbed neck, cubitus valgus and other congenital stigmata may also be found in this condition. Urinary gonadotrophins are present in excess.

**Diagnosis.**—With simple failure of growth, or in infantilism, the relative proportion of arms, legs and trunk may be normal. Non-endocrine causes of dwarfism are rickets, renal rickets, fragilitas ossium, coeliac disease, pancreatic disease, von Gierke's glycogen disorder, vitamin deficiency, cardiac disease and achondroplasia. In achondroplasia, a familial condition of defective endochondral ossification, the arms and legs are short compared with the body (human dachshund).

**Prognosis.**—Where the epiphyses are ununited, and treatment is started early with a potent growth hormone preparation, the prognosis is fair, but the response is sometimes poor.

**Treatment.**—As in infantilism, *vide supra*.

## SIMMONDS'S DISEASE

**Synonyms.**—Pituitary Cachexia; Hypopituitarism; Panhypopituitarism; Sheehan-Simmonds's Disease.

**Definition.**—A disorder due to destruction or atrophy of the anterior pituitary gland, and manifested by cachexia, anorexia, subnormal metabolism and hypogonadism.

**Ætiology.**—The disease is more common in women since the commonest cause is atrophy of the anterior pituitary resulting from a local vascular lesion during the puerperium. Multiparæ are especially prone. It may, however, occur at any age and in either sex associated with a pituitary or parapituitary tumour.

**Pathology.**—Simmonds's original case showed atrophy and fibrosis of the anterior pituitary gland as a result of an embolus in the main artery in a fatal case of puerperal fever. The vascular lesion is, however, more commonly thrombosis of the pituitary veins, following severe uterine hæmorrhage at parturition. Suprasellar cystic tumours and chromophobe adenoma are other important causes, and rarely malignant metastases, tuberculosis, syphilis and exanthemas. An unusual ætiological occurrence is simply diminution in the relative number of eosinophil cells. As in the case of hypophysectomy, the gonads, thyroid and adrenal cortex are hypoplastic or atrophic. The viscera are diminished in size in contrast to the splanchnomegaly of acromegaly.

**Symptoms.**—Weakness, amenorrhœa, anorexia and loss of pubic hair are cardinal features. Cachexia is by no means constant and occasionally patients do not even lose weight. Impotence occurs in the male. In both sexes the secondary sexual characteristics, *e.g.* pubic, facial and axillary hair, are lost, and the eyebrows and hair of the scalp also become thin and lustreless, or disappear. The skin is pale and dry, and may become wrinkled, giving a senile facies, known as progeria. The lower jaw may become atrophic (opposite of prognathism), and the teeth decay and fall out. The low metabolism, *e.g.* —40 per cent., is manifested by a subnormal temperature and hypersensitivity to cold. Bradycardia and hypotension are usual features. The blood sugar is low and insulin sensitivity increased. Spontaneous hypoglycæmic attacks occur and may be fatal. Anæmia, relative lymphocytosis, eosinophilia and a raised sedimentation rate are not uncommon.

If the disorder begins in childhood, the lack of growth hormone results in failure to grow, although the epiphyses remain ununited in adult life. There is also failure of sexual development. Panhypopituitarism in childhood, however, is more appropriately called infantilism than Simmonds's disease.

**Complications.**—Pulmonary tuberculosis may follow prolonged inanition. Apathy, inertia and somnolence are characteristic and may progress to melancholia, with disorientation in time and place. Optic atrophy results from tumours. The Snapper-Witts syndrome consists of hypopituitarism, achlorhydria, hypochromic or hyperchromic anæmia, subacute combined degeneration and alopecia.

**Diagnosis.**—The well-developed syndrome cannot escape recognition if the disorder is kept in mind. Cachexia is not always a feature. Minor and incomplete

manifestations are more easily missed, but not if the possibility of the disorder following a puerperium in which there is severe hæmorrhage and (or) infection is remembered. Migrainous headaches can occur even in the absence of a pituitary or parapituitary tumour, but radiographic examination of the sella turcica and examination of the fundi for optic atrophy should not be omitted. The condition is often mistaken for myxædema, but without justification, and the response to thyroid alone is never adequate, as it is in myxædema.

There are many features in common with Addison's disease, but pigmentation in Simmonds's cachexia is either absent, or slight, and is never present in the mucous membranes. Anorexia nervosa in the later stages may show many of the features of Simmonds's cachexia, suggesting perhaps an inhibition of pituitary activity via the hypothalamus. A similar mechanism may explain examples of incomplete Simmonds's disease following shock or psychic trauma. Inanition may itself, however, result in hypotension, hypothermia, hypoglycæmia, hypometabolism and bradycardia. The initial and fundamental cause of anorexia nervosa is psychogenic, and there are essential differences in the clinical history and manifestation of anorexia nervosa and Simmonds's disease. Thus anorexia nervosa usually occurs in young adults, more often in females, and it is possible to elicit a history of psychic trauma, shock, disappointment or emotional upset. In contrast to the apathy of Simmonds's cachexia, these patients are restless and perform feats of activity far beyond their apparent strength; loss of sexual hair, if any, is rarely extreme; in contrast, the trunk and perhaps the face is covered by diffuse downy hair. The 24-hourly output of 17-ketosteroids is low in Simmonds's cachexia, e.g. 0.5 mg. (normal 5 to 12 mg.); and the insulin sensitivity test (intravenous injection of insulin 0.05 units per kg. body weight) shows a rapid fall of blood sugar to low levels, e.g. 30 mg. per 100 ml., and a delayed recovery curve (hypoglycæmic refractoriness). In myxædema, the output of ketosteroids is very low, but the fall in blood sugar after intravenous insulin is somewhat retarded, although the subsequent elevation may also be retarded. The Kepler test for adrenal function (see p. 509), often shows as low an index in Simmonds's disease as in Addison's disease.

**Prognosis.**—There is usually progressive deterioration, but patients with minor manifestations following pregnancy may recover spontaneously. Treatment is beneficial, but it is not easy to provide complete substitution therapy, and the cessation of therapy is often followed by relapse. Patients are usually sterile, but should pregnancy supervene and parturition be normal, clinical recovery may result from hyperplasia of the pituitary remnant.

**Treatment.**—Administration of adrenocorticotrophic hormone is effective in the form of long-acting corticotrophin (A.C.T.H. Gel), 40 units intramuscularly daily. Injections are troublesome and allergic reactions may occur. Cortisone by mouth, 25 to 50 mg. daily, is more convenient, given with methyl testosterone by mouth, e.g. 25 mg. daily and thyroideum siccum gr. 1 or more daily. Methyl testosterone and thyroid, even without cortisone, bring about considerable improvement. Cortisone is valuable in diminishing the risk of sudden hypoglycæmia. If thyroid alone is given, it may be poorly tolerated and acute adrenal crisis may develop. If a patient with recognised Simmonds's disease become comatose, hypoglycæmia must first be suspected and intravenous glucose should be given at once. Coma may, however, occur without hypoglycæmia or obvious adrenal crisis. It is called hypothermic crisis, and hot baths may revive the patient.

### FRÖHLICH'S SYNDROME

**Synonyms.**—Dystrophia Adiposo-Genitalis; Babinski-Fröhlich's Syndrome.

**Definition.**—Failure of sexual maturation, associated with dwarfism and adiposity.

**Ætiology.**—This is usually destruction of the anterior pituitary gland by a craniopharyngioma with involvement of the adjacent hypothalamus causing adiposity. It occurs in either sex. Fröhlich's original case was a boy of 14 with a craniopharyngioma.

**Pathology.**—The lesion is usually a craniopharyngioma. More rarely it is a chromophobe adenoma and sometimes a gross lesion cannot be discovered.

**Symptoms.**—It is important to realise that the condition is very rare. The failure of development of sexual and secondary sexual characteristics is absolute and not merely delayed. The adiposity involves the face and trunk, and the limbs are slender. Such adiposity, as judged by photographs, was not of any severity, in the original cases of Fröhlich and Babinski. For clarification, it is better to regard inadequate somatic growth as an essential part of the syndrome and, as a corollary, not to make the diagnosis in patients whose height is normal or above normal. The complexion is pallid as in pituitary deficiencies and not plethoric.

**Complications.**—Rarely the syndrome is complicated by the additional features of retinitis pigmentosa, mental deficiency, polydactylism and familial incidence. It is then called the Laurence-Moon-Biedl syndrome.

**Diagnosis.**—The three main features of the disease are failure of sexual development, dwarfism and adiposity. An enlarged sella turcica and optic atrophy give support to the diagnosis but are not essential. By definition the diagnosis cannot be made before puberty, in the absence of an intracranial neoplasm, except as a speculation.

**Prognosis.**—The condition does not improve in the absence of treatment.

**Treatment.**—Craniopharyngiomata are treated surgically. It is logical to prescribe pituitary gonadotrophic hormones supplemented by thyroid; boys should also receive methyl testosterone and girls œstrogens and progesterone.

## DIABETES INSIPIDUS

**Definition.**—Diabetes insipidus is a disturbance of water balance, characterised by polyuria and polydipsia, and it is due to a destructive lesion of the posterior lobe of the pituitary gland, or of the adjacent part of the hypothalamus.

**Ætiology.**—The condition is sometimes familial. It is due to a deficient secretion of the antidiuretic hormone by the posterior lobe of the pituitary. This results from destruction of the lobe, or any interruption of its normal connection with the supra-optic nucleus of the hypothalamus. Such a lesion is followed by degeneration of the pars nervosa, but not of the pars intermedia.

**Pathology.**—In the majority of cases there is no obvious cause. It is sometimes due to trauma, a vascular lesion, syphilis, tuberculous meningitis, a primary or metastatic brain tumour, a pituitary or parapituitary neoplasm involving the posterior lobe, or Hand-Schüller-Christian's disease. The condition may also follow shock, via the hypothalamic mechanism.

**Symptoms.**—The symptoms are polyuria and polydipsia, with the passage of large quantities of urine, e.g. 12 litres in 24 hours, of pale colour, and low specific gravity, e.g. 1002. The polyuria leads to disturbed sleep and anxiety. The patient loses weight and strength, and may become very emaciated and even bedridden if untreated.

**Diagnosis.**—Hysterical polyuria may be difficult to differentiate apart from the hysterical background. There is a tendency in this condition, however, for the polyuria to be more marked during the daytime and the patient may sleep throughout the whole night, whereas the polyuria of diabetes insipidus is most troublesome at night. The hysterical patient remains in reasonably good health in spite of the poly-

dipsia and polyuria. Some individuals have a familial hypersensitivity to caffeine and, if much tea or coffee is drunk, they have polyuria and frequency. Diabetes mellitus is easily distinguished by hyperglycemia and glycosuria. In chronic nephritis the urine may be voluminous and of constantly low specific gravity, but it contains albumin and renal casts. A Wassermann reaction will exclude tertiary syphilis. Radiographs of the skull, and examination of the optic disks and visual fields should exclude pituitary and parapituitary tumours. The Hand-Schüller-Christian disease is congenital and familial and characterised by exophthalmos, a large liver and spleen, yellow-tinted skin and irregular areas of xanthomatous infiltration in the skull.

**Prognosis.**—The disease is protracted, and if treatment is inadequate the patient becomes emaciated and dies from intercurrent infection.

**Treatment.**—The best replacement therapy consists of Pitressin tannate in oil, 5 mg. in 1 ml., injected intramuscularly, the effect lasting 24 to 48 hours. This is preferable to aqueous Pitressin, 10 or 20 units in 1 ml. given 2 or 3 times in 24 hours. Powdered Pitressin, 50 mg. insufflated or snuffed intranasally, may be effective in milder cases or used as supplementary therapy. Pallor, headaches, intestinal cramps and precipitate bowel action may complicate treatment when large doses are necessary.

## DIABETES TENUIFLUUS

**Definition.**—A condition of supernormal secretion of the posterior pituitary antidiuretic hormone, manifested by diminution in the volume of urine excreted and an absence of thirst. Tenuifluus means "flowing slenderly", and the condition is the opposite of diabetes insipidus (tasteless urine). The latter condition might be better termed diabetes multifuus (copious urine—flowing greatly).

**Ætiology and Clinical Features.**—It is due to excessive secretion of the antidiuretic hormone of the pars nervosa of the pituitary, is probably rare as an uncomplicated entity and on the comparatively few occasions that it has been observed, it has appeared to be part of a pituitary syndrome. It may be found with pituitary or parapituitary tumours, with Fröhlich's syndrome, and with other varieties of pituitary adiposity. Acromegaly may be associated either with diabetes insipidus, or with diabetes tenuifluus, and one may give place to the other according to the phase of the disease. In one such case of the latter, Ellinger, Hare and Simpson demonstrated, for the first time, that there was an excess of antidiuretic hormone in the cerebrospinal fluid. The daily intake of fluid was small, and the output of urine even smaller, the difference apparently being explained by an obviously excessive perspiration, in contrast with the dry skin of diabetes insipidus. It is interesting to note that irradiation of the pituitary gland resulted in a normal and balanced fluid intake and output, and a disappearance of excessive perspiration and of the excess of antidiuretic hormone from the cerebrospinal fluid.

Water retention with resulting extensive œdema may occur in hysteria or the anxiety neuroses, possibly via hypothalamic stimulation of the pars nervosa. Premenstrual water retention is not infrequent, the mechanism being via the posterior pituitary or the adrenal mineral corticoids. Low calorie diets in adiposity may cause phases of water retention.

**Complications.**—E. I. Jones described a syndrome, in a man of 26, which he attributed to hyperactivity of the posterior lobe of the pituitary gland. The main features were hypertension, hyperchromic anæmia, achlorhydria and impaired carbohydrate tolerance. Melanophore-expanding, vasopressor and antidiuretic substances were present in the urine (Noble and others).

**Diagnosis.**—An abnormally small daily excretion of urine in the absence of

cardiac or renal disease suggests diabetes tenuifluus, especially if accompanied by excessive perspiration for which no ordinary cause is obvious.

**Treatment.**—Irradiation of the pituitary gland may be beneficial.

## DISEASES OF THE THYROID GLAND

The essential function of the thyroid gland is to control the metabolic rate of the body but it also has an important influence on growth, sexual function, the cardiovascular system, nitrogen and carbohydrate metabolism and fluid balance. The essential principle, thyroxine, was isolated by Kendall in 1919; shown to be an amino acid derived from tyrosine, 3 : 5 : 3' : 5'-tetraiodothyronine, by Harington in 1926; and synthesised by Harington and Barger in 1927. The *lævo*-rotatory form, L-thyroxine, is ten times more active than the *dextro*-rotatory form. In 1952, a substance 3 : 5 : 3'-L-triiodothyronine was found to be a normal constituent of plasma by Gross and Pitt-Rivers in England, and Roche, Lissitzky and Michel in France, and its activity in animals and man to be some three times that of L-thyroxine. It has been separated from thyroglobulin and is probably the form of thyroid hormone that is active in the tissues. Thyronine has a similar basic structure to thyroxine. It is quite inactive without its iodine atoms. Thyroglobulin is a protein of large molecular weight and is the form in which thyroxine is stored in the colloid of the thyroid gland. Diiodotyrosine is present in thyroglobulin and is an intermediate product in the natural synthesis of thyroxine but is itself inactive.

The normal thyroid gland contains 5 mg. of thyroxine and 8 mg. of iodine. Intake requirements of iodine for equilibrium are estimated as 15 micrograms per day per adult and 50 micrograms for a child. Protein-bound iodine in blood is a measure of the thyroxine content, the normal range being 4.0 to 8.0 micrograms per 100 ml., values being higher in thyrotoxicosis and lower in myxœdema. The average daily requirements of L-thyroxine in a completely thyroidectomised adult are 0.3 mg.; 0.1 mg. thyroxine is equivalent to 1 grain of thyroideum siccum. An inadequate intake of iodine produces goitre, due to an ineffective attempt by the thyroid to produce thyroxine. An old observation that cabbage produced goitre in rabbits, led to the discovery that thiourea and thiouracil are also goitrogenic and that they act by preventing the synthesis of thyroxine. Since iodine deficiency or thiouracil can produce ineffective thyroid hyperplasia without hyperthyroidism or with hypothyroidism, it is obvious that hyperplasia is not synonymous with hyperfunction. This explains some difficulties in interpreting the histology of pathological thyroid tissue. The administration of iodine causes a reduction in the degree of hyperplasia and of hyperthyroidism and increases the amount of colloid in the gland. This also influences the interpretation of pathological histology.

Pituitary thyrotrophic hormone causes hyperplasia and hyperfunction of the thyroid gland. Marine showed that subtotal destruction of the adrenal gland has a similar effect, and more recently it has been found that cortisone, conversely, inhibits thyroid function. Both these effects are mediated through the pituitary gland.

Clinically there are two main types of hyperthyroidism, exophthalmic goitre, and toxic adenoma. Hypothyroidism may result in cretinism, or myxœdema, according to whether the deficiency is already present at birth or develops after a period of normal thyroid function.

## EXOPHTHALMIC GOITRE

**Synonyms.**—Graves's Disease; Parry's Disease; Basedow's Disease; Primary Thyrotoxicosis.

**Definition.**—Hyperactivity and hypersecretion of the thyroid gland, usually manifested by tachycardia, tremor, loss of weight, nervousness, sweating, exophthalmos, enlargement of the thyroid and raised basal metabolic rate.

**Ætiology.**—The disease is more common in females than males, in the ratio of 6 to 1. This is probably associated with the greater lability of the endocrine system in the former, as indicated by the not infrequent physiological transient enlargement of the thyroid at puberty, at menstruation and the menopause. The malady is commonest in the second and third decades, but it may occur in childhood or old age. Symptoms may first appear at puberty or the menopause.

Mental stress, anxiety, shock and sexual neurosis are often precursors of the disease, but a constitutional vulnerability of the thyroid to such stimuli is probable. The latter is also indicated by a familial predisposition. Infection aggravates pre-existing hyperthyroidism.

**Pathology.**—The cuboidal epithelial cells undergo hypertrophy and become columnar. They also divide and multiply (hyperplasia), and may project in folds into the follicles, giving a lace-like pattern. The follicles are almost emptied of colloid unless iodine has been given. There is a generalised lymphatic hyperplasia and lymphoid infiltration of the thyroid itself. The thymus is usually enlarged. The liver may show areas of necrosis or atrophy, and is often depleted of glycogen. Experimentally, pituitary thyrotrophin will produce similar thyroid hyperplasia and a raised basal metabolic rate in guinea-pigs and man. Nevertheless, it has not been possible to demonstrate such a hormone in the blood of patients with hyperthyroidism.

**Symptoms.**—The excessive secretion of thyroxine has wide systemic effects, and also disturbs the nervous stability of the patient. Many of the symptoms appear to result from overactivity of the sympathetic nervous system.

**Cardio-vascular system.**—Tachycardia in some degree is invariable, and is usually associated with palpitation. Extra-systoles may be present, and if the disease is of long standing or in people over 40, auricular fibrillation is not infrequent. Capillary pulsation may be seen, and vasomotor instability is evidenced by a tendency to blush or the appearance of a characteristic patch of redness over the neck and upper sternum. The carotid and brachial vessels pulsate visibly and forcibly. The systolic pressure is usually raised and the diastolic is normal or diminished, resulting in an increased pulse pressure.

**Nervous system.**—There is a characteristic tremor of the hands, noticeable on being asked to hold out the hands, or in writing, or in lifting a cup. Anxiety is a frequent and almost invariable accompaniment of exophthalmic goitre. The patient is also restless and unstable, and finds it difficult to remain in one position for any length of time. Conversation too is desultory and, although there is often a hyper-acuity of perception and conception, this is offset by an inability for sustained effort or concentration. Increased sensitivity and sensibility trouble the patient and her associates or family, and emotional distress is common. Occasionally psychotic manifestations develop, especially paranoia and acute mania, with suicidal tendencies, but rarely does this happen in the absence of a constitutional predisposition. Sweating is often excessive, manifested by the hot, moist handshake, and it may be soaking undergarments or bedclothes. Severe muscular weakness and wasting may be present, associated with excessive katabolism of muscular tissue and creatinuria. Myasthenia gravis, acute bulbar palsy and progressive muscular atrophy may be simulated.

**Gastro-intestinal.**—The paradox of an insatiable and voracious appetite with progressive loss of weight is a source of wonder and concern to patient and relatives. The explanation is a raised metabolic rate. Excessive thirst is an effort to compensate for loss of fluid by profuse perspiration. Attacks of dyspepsia occur, sometimes with vomiting, and this may be due to hepatic disturbance, but achlorhydria and hypochlorhydria are not infrequent. Loose stools or diarrhoea may occur.



*Ocular signs.*—Upper lid attraction is characteristic, giving a glint to the eye or a coquettish look when it is mild in degree, or a frightened stare in more severe cases. True exophthalmos is indicated by the appearance of sclera between the cornea and the lower lid, and by orbital bulging and tension. Exophthalmic ophthalmoplegia occurs with severe thyrotoxicosis, but also in middle-aged patients with euthyroidism (a term indicating normal thyroid function) or mild hyperthyroidism. The condition may at first be unilateral. The conjunctiva is swollen and congested and histological examination shows oedema and lymphatic infiltration of the ocular muscles and orbital contents. Exophthalmic ophthalmoplegia (malignant or progressive exophthalmos) is thought to be produced by the thyrotrophic hormone of the pituitary, which explains its occurrence with hypothyroidism after too radical thyroidectomy.

*Thyroid gland.*—This is almost invariably enlarged, although the degree is by no means proportional to that of the thyrotoxicosis. The enlargement usually affects both lobes, and not infrequently the isthmus. The swellings are smooth and roughly symmetrical, but one lobe may be larger than the other. Small degrees of enlargement may be missed unless the proper technique of palpation is observed. The thumb should compress the site of one lobe of the thyroid against the trachea, and the opposite lobe then becomes palpable to the thumb or fingers of the other hand. This procedure is best carried out with the patient lying flat without a pillow. A systolic bruit over the thyroid may be heard on auscultation.

*Metabolism.*—Increased basal metabolism is characteristic and is a good indication of the degree of thyrotoxicosis. The occasional near-normal value, with reliable technique, must be explained by the patient's previously normal metabolism being below average. There is a negative nitrogen balance with creatinuria, due to pathological breakdown of muscle tissue, the fat depots of the body tend to disappear and the serum cholesterol to be low, e.g. 90 mg. per 100 ml. Loss of fat is not always an essential feature and may sometimes be overcompensated due to an increased appetite.

The liver is depleted of glycogen, and transient or persistent glycosuria may appear. This rarely indicates true diabetes mellitus, which is not more common among thyrotoxic patients than among the rest of the population. Nevertheless, thyroxine is antagonistic to insulin. In thyrotoxic glycosuria, the resting blood sugar level is normal, but following 50 grammes of glucose there may be a high and prolonged blood sugar curve. In the absence of gastrointestinal symptoms, or partial starvation, ketosis rarely occurs. There may be a negative calcium balance and, although the serum calcium is not raised, as in hyperparathyroidism, the renal excretion of calcium is not infrequently excessive. There results a decalcification of the bones, sometimes to a severe degree.

*Other features.*—Relative impotence may be present in the male, and amenorrhœa or scanty menstruation is common in females. Pigmentation is rare, and is usually confined to the orbital regions, but it may occasionally be diffuse. Premature whitening of the hair sometimes occurs. There are no characteristic blood changes, but a lymphocytosis may be present. Dyspepsia and diarrhœa may be troublesome features. Occasionally abdominal pain may be severe enough to simulate an acute abdomen, and on laparotomy acute congestion of the pancreas has been observed. Crises are an alarming feature of thyrotoxicosis, sometimes precipitated by infection, or occurring in the first few days after thyroidectomy, but often without obvious cause. There is an acute exacerbation of the condition, with manifestations predominantly cardiac, cerebral or gastro-intestinal, and patients may die unless the condition is promptly recognised and treated. Cerebral forms of crises are particularly dangerous, and are manifested by acute excitement and irritability, acute mania, delusions and hallucinations. There is also a comatose form.

**Diagnosis.**—When the classical features of tachycardia, exophthalmos, enlarged thyroid, tremor of the hands and loss of weight are present the diagnosis usually offers no difficulty.

"Masked" forms of hyperthyroidism, or "*formes frustes*", in which the presenting feature appears to indicate some other disease, may offer difficulty, but awareness of the possibility of hyperthyroidism usually prevents a mistaken diagnosis. Thus, it is important to look out for a possible thyroid basis in cases of auricular fibrillation, and it would seem that the latter may occur in paroxysmal form before the clinical picture of hyperthyroidism is well developed, while occasionally fibrillation may supervene some years after the disease is apparently arrested.

Loss of weight, sweating and rapid pulse may suggest pulmonary tuberculosis; or wasting combined with glycosuria give rise to a diagnosis of diabetes mellitus. The muscular wasting and weakness of hyperthyroidism may simulate the myopathies, or myasthenia gravis. The latter is an extremely rare complication of thyrotoxicosis, and is differentiated by the selectivity for groups of muscles and the response to neostigmine. Some patients are treated for an associated neurasthenia before the thyrotoxicosis is recognised. An overactive sympathetic nervous system at the climacteric may produce many features simulating thyrotoxicosis, but only a small proportion of such patients have true thyrotoxicosis. Neuro-circulatory asthenia may simulate hyperthyroidism, and the thyroid gland is often somewhat enlarged, but in the former the tachycardia is more dependent upon emotion and change of position, and the pulse-rate at rest, or when sleeping, is usually not raised.

In hyperthyroidism the basal metabolic rate is raised and the blood cholesterol is diminished. There is a high value for the protein-bound serum iodine, the uptake by the thyroid of radioactive iodine is increased and its urinary excretion during a 24-hour or 48-hour test period is reduced.

**Course and Prognosis.**—The natural course of the disease, in the absence of treatment, is progressively downhill, but waves of remission and exacerbation occur. Nevertheless, some patients recover spontaneously, or even become myxoedematous. The chief dangers are cardiac failure, intercurrent infection and mental disorder. The results of treatment are good. Although pathological upper lid retraction usually disappears following treatment, some degree of exophthalmos not infrequently persists.

**Treatment.**—Mild cases may respond to sedatives, rest and reassurance. To these may be added small doses of iodine, *e.g.* 5 min. of Lugol's iodine daily. This is not curative but it lowers the degree of thyrotoxicosis. Spontaneous recovery or even transition to myxoedema is possible.

Severe cases may be treated with subtotal thyroidectomy or with radioactive iodine. Pre-operative treatment with methyl thiouracil, or propyl thiouracil, has replaced pre-operative Lugol's iodine because it is more effective. Methyl thiouracil is given as a tablet, 200 mg. *t.d.s.*, for some 14 days or until the basal metabolism is normal or the clinical features of thyrotoxicosis have largely disappeared, and no patient should undergo thyroidectomy before their thyrotoxicosis is so controlled. Methyl thiouracil is replaced by Lugol's iodine, 10 min. *t.d.s.*, for some 7 days before operation, in order to minimise the tendency to congestion and hæmorrhage which it produces.

Methyl thiouracil may be used as an alternative to operation. It is then given as 100 mg. *t.d.s.* and the dose is gradually tapered off to 50 mg. once daily and stopped entirely 6 months after the symptoms have been completely controlled. The great disadvantage is the danger (2 per cent.) of agranulocytosis which may come like a bolt from the blue two days after a normal blood count. All patients are warned to stop tablets and report if malaise, sore throat or fever develops. Agranulocytosis is treated with corticotrophin (A.C.T.H.) and penicillin. The other disadvantages are

the persistence of the goitre, the tendency to relapse in some 50 per cent. of cases and the prolonged uncertainty. Propyl thiouracil is alleged to be less liable to produce agranulocytosis. Thiouracil acts by blocking the synthesis of thyroxine in the thyroid gland. The resulting increased secretion of pituitary thyrotrophic hormone may initially aggravate the degree of exophthalmos and enlarge the existing goitre but amelioration of both may follow later.

Radioactive iodine is, in the opinion of the writer, the treatment of choice, although warnings of the possibility of injury to the ovaries and late development of thyroid carcinoma are still voiced but not substantiated. The bombardment of metallic tellurium in a cyclotron transmutes the tellurium into radioactive iodine, the principal isotopes being  $I^{130}$  (which loses half its activity in 12 hours) and  $I^{131}$  (which loses half its activity in 8 days). Radioactive iodine,  $I^{131}$ , which looks and tastes like stale water, is given in a single dose by mouth. It is selectively taken up almost entirely by the thyroid gland and then gives off electrons (beta rays) which cause atrophy of the hyperplastic gland. Clinical cure results after some 8 weeks, except for a persistent exophthalmos; but, if necessary, a second dose can be given after 3 months. Overdosage may result in myxedema. The latter is very liable to occur if thyroidectomy is attempted after an initial dose, which was thought to be inadequate. Dosage is determined by preliminary tracer studies, measuring iodine uptake by the thyroid by means of a Geiger-Muller counter, and its urinary excretion; and by clinical estimation of the size of the goitre.

## TOXIC ADENOMATOUS GOITRE

**Synonyms.**—Secondary Thyrotoxicosis; Thyrotoxic Nodular Goitre.

**Definition.**—Hyperthyroidism associated with, and usually superimposed upon, a nodular goitre.

**Ætiology.**—Thyrotoxic symptoms occur in some 15 per cent. of nodular goitres. The cause is usually unknown, but occasionally iodine appears to provoke thyrotoxicosis in a quiescent gland.

**Pathology.**—Plummer's term, Toxic Adenoma, might be thought to indicate a single adenoma, but only rarely is this the case. More commonly multiple adenomas are found throughout the glands, and, apart from these, other areas of the gland may show hyperplasia, indistinguishable from that found in exophthalmic goitre, as well as areas of colloid vesicles.

**Symptoms.**—This condition can be differentiated clinically from exophthalmic goitre by the absence or mildness of upper lid retraction and exophthalmos, the absence of the general anxiety so characteristic of Graves's disease, the rarity of thyrotoxic crisis and the rarity of recurrence of thyrotoxicosis after thyroidectomy. It is also more likely to affect an older age group, namely over 40 years of age, and the brunt of the thyrotoxicosis appears to fall on the cardio-vascular system. When the thyroid gland is obviously nodular to palpation, or when the goitre has been present for some years before thyrotoxic symptoms develop (*i.e.* secondary thyrotoxicosis), clinical differentiation from Graves's disease on either of these grounds is clear. In their absence, differentiation is relative rather than absolute and cannot necessarily be decided by thyroid histology since the general hyperplasia of the thyroid in Graves's disease may be accompanied by microscopic adenomata and the nodular adenomatous goitre may contain areas of hyperplasia. Nevertheless clinical differentiation appears justifiable.

**Prognosis.**—Inadequately treated, the condition deteriorates rapidly and cardiac failure results. The response to thyroidectomy is excellent and the percent recurrence is less than 1 per cent.

**Treatment.**—Thyroidectomy is indicated for large or grossly nodular

**Diagnosis.**—When the classical features of tachycardia, exophthalmos, enlarged thyroid, tremor of the hands and loss of weight are present the diagnosis usually offers no difficulty.

"Masked" forms of hyperthyroidism, or "formes frustes", in which the presenting feature appears to indicate some other disease, may offer difficulty, but awareness of the possibility of hyperthyroidism usually prevents a mistaken diagnosis. Thus, it is important to look out for a possible thyroid basis in cases of auricular fibrillation, and it would seem that the latter may occur in paroxysmal form before the clinical picture of hyperthyroidism is well developed, while occasionally fibrillation may supervene some years after the disease is apparently arrested.

Loss of weight, sweating and rapid pulse may suggest pulmonary tuberculosis; or wasting combined with glycosuria give rise to a diagnosis of diabetes mellitus. The muscular wasting and weakness of hyperthyroidism may simulate the myopathies, or myasthenia gravis. The latter is an extremely rare complication of thyrotoxicosis, and is differentiated by the selectivity for groups of muscles and the response to neostigmine. Some patients are treated for an associated neurasthenia before the thyrotoxicosis is recognised. An overactive sympathetic nervous system at the climacteric may produce many features simulating thyrotoxicosis, but only a small proportion of such patients have true thyrotoxicosis. Neuro-circulatory asthenia may simulate hyperthyroidism, and the thyroid gland is often somewhat enlarged, but in the former the tachycardia is more dependent upon emotion and change of position, and the pulse-rate at rest, or when sleeping, is usually not raised.

In hyperthyroidism the basal metabolic rate is raised and the blood cholesterol is diminished. There is a high value for the protein-bound serum iodine, the uptake by the thyroid of radioactive iodine is increased and its urinary excretion during a 24-hour or 48-hour test period is reduced.

**Course and Prognosis.**—The natural course of the disease, in the absence of treatment, is progressively downhill, but waves of remission and exacerbation occur. Nevertheless, some patients recover spontaneously, or even become myxædematous. The chief dangers are cardiac failure, intercurrent infection and mental disorder. The results of treatment are good. Although pathological upper lid retraction usually disappears following treatment, some degree of exophthalmos not infrequently persists.

**Treatment.**—Mild cases may respond to sedatives, rest and reassurance. To these may be added small doses of iodine, e.g. 5 min. of Lugol's iodine daily. This is not curative but it lowers the degree of thyrotoxicosis. Spontaneous recovery or even transition to myxædema is possible.

Severe cases may be treated with subtotal thyroidectomy or with radioactive iodine. Pre-operative treatment with methyl thiouracil, or propyl thiouracil, has replaced pre-operative Lugol's iodine because it is more effective. Methyl thiouracil is given as a tablet, 200 mg. t.d.s., for some 14 days or until the basal metabolism is normal or the clinical features of thyrotoxicosis have largely disappeared, and no patient should undergo thyroidectomy before their thyrotoxicosis is so controlled. Methyl thiouracil is replaced by Lugol's iodine, 10 min. t.d.s., for some 7 days before operation, in order to minimise the tendency to congestion and hæmorrhage which it produces.

Methyl thiouracil may be used as an alternative to operation. It is then given as 100 mg. t.d.s. and the dose is gradually tapered off to 50 mg. once daily and stopped entirely 6 months after the symptoms have been completely controlled. The great disadvantage is the danger (2 per cent.) of agranulocytosis which may come like a bolt from the blue two days after a normal blood count. All patients are warned to stop tablets and report if malaise, sore throat or fever develops. Agranulocytosis is treated with corticotrophin (A.C.T.H.) and penicillin. The other disadvantages are

indistinct and rather toneless. The whole attitude is apathetic and lethargic, with a tendency to somnolence and even coma.

*Metabolism.*—The basal metabolic rate is usually of the order of  $-40$ , the temperature is subnormal, and the patient hypersensitive to cold, being especially intolerant of the winter months. There is an almost constant hypercholesterolaemia, e.g. 380 mg., and the blood protein bound iodine is very low. The fasting blood sugar may be normal or slightly below normal, and there is apparently an increased carbohydrate tolerance in some patients. The injection of 4 units of insulin intravenously is followed by a slower rate of fall of blood sugar than occurs in normal individuals, although the subsequent rise in blood sugar is often retarded. Occasionally diabetes mellitus occurs as a complication of myxœdema, the pancreatic islets, as well as the thyroid, being atrophic. The urinary excretion of 17-ketosteroids is low because of secondary depression of pituitary adrenotrophic and gonadotrophic functions.

Inadequacy of adrenal function secondary to the thyroid deficiency is shown by a positive Kepler test and very low values for urinary 17-ketosteroids and 11-oxysteroids.

*Blood.*—There are three types of anæmia found in myxœdema: (1) Hypochromic low colour index anæmia. This variety responds to iron. It differs from other iron-deficiency anæmias, however, in the absence of microcytosis. (2) Hyperchromic megalocytic high colour index anæmia. This responds to liver, and is comparable to pernicious anæmia. (3) Simple hyperchromic macrocytic high colour index anæmia. It differs from Addisonian anæmia in the absence of megalocytosis and failure to respond to liver. Neither does it respond to iron, but thyroid has a specific effect, although a gradual one. The three types may be associated with achlorhydria, which is not uncommon, but type (3) is a specific thyroid deficiency anæmia. Either of the first two types may, on treatment with iron or liver respectively, change into the last type (simple hyperchromic). It is generally assumed that thyroid is a direct haemopoietic agent essential for maturation of red cells, but the partial atrophy of the erythron in hypothyroidism may be an adaptation to the diminished need of the tissues for oxygen.

*Other features.*—Constipation is common, in contrast to the diarrhoea of thyrotoxicosis. Similarly, appetite and thirst are diminished. Deposits of mucoid material may impair hearing, smell, taste and swallowing. There may be menorrhagia, and in the male relative or absolute impotence is not infrequent. Vague generalised pains may be a feature, and some recognise a subthyroid form of chronic rheumatism.

*Diagnosis.*—Even though well-developed myxœdema presents a characteristic clinical picture, it is perhaps the most frequently missed endocrine disorder, and this is certainly true of the early or slight cases. The best method of avoiding this is constantly to bear in mind the existence of the disorder, especially when dealing with menopausal women. Sluggish mental response, with thick dry skin and loss of hair, failure of memory and sensitivity to cold are characteristic.

Many patients will first be seen by the psychiatrist, although the disease must have been present for some time. Others will present themselves to the gynaecologist on account of menorrhagia. Again, the appearance of the patient may lead to the diagnosis of anæmia, confirmed by blood examination, but the other features should not be missed. The pale, puffy face with baggy eyes also resembles the facies of parenchymatous nephritis, and albuminuria may complicate myxœdema if the kidneys are involved in the mucoid infiltration; a further resemblance between the two conditions is the high blood cholesterol. Myxœdema may be difficult to differentiate from hypothyroidism in Simmonds's cachexia, both having a low B.M.R. and sensitivity to cold. In the latter condition, however, mucoid infiltration of the skin is rare, the skin being thin and wrinkled, and thyrotrophic hormone will raise the metabolism and uptake of radioactive iodine to normal, whereas it has no such effect in myxœdema, the atrophied thyroid gland being unable to respond.

Localised myxœdema may paradoxically be a complication of hyperthyroidism,

Others may be treated with radioactive iodine. The condition is not unresponsive to methyl thiouracil.

## MYXŒDEMA

**Definition.**—A primary condition of hypothyroidism, associated with low basal metabolism, and manifested by sensitivity to cold, mental hebetude, loss of hair and mucoid infiltration of the skin and subcutaneous tissue. It does not include hypothyroidism secondary to pituitary hypofunction, and the term pituitary myxœdema is best avoided.

**Ætiology.**—Myxœdema usually occurs sporadically and without obvious cause, although there is occasionally a history of preceding infection. It is more frequent in women than men, in the ratio of 8 to 1, and is most common in middle age. Perhaps the condition in women is comparable to the cessation of ovarian function, which also takes place in the fifth decade. The disease, however, may have its onset in old age, or even in childhood—when it is known as juvenile myxœdema. There would also appear to be a constitutional predisposition, as several cases may occur in the same family. Myxœdema may follow partial thyroidectomy for thyrotoxicosis, or complete thyroidectomy for non-thyroid cardiac disease, the term *cachexia strumipriva* sometimes being given to post-operative myxœdema. Apart from operation or excessive radiation, myxœdema may arise spontaneously following chronic thyrotoxicosis. It may also occur endemically and usually with goitre, the ætiology being a relative or absolute iodine deficiency.

**Pathology.**—The thyroid is atrophic, and the secreting epithelium is largely replaced by fibrous tissue. The skin and subcutaneous tissue are infiltrated with a mucoid-like material, which was wrongly thought to be mucin, and hence the name myxœdema. There is an abnormal accumulation of extra-cellular and extra-vascular protein, the osmotic pressure of which leads to a transfer of saline from plasma to interstitial tissues. The mucoid infiltration may be widespread and implicate the nasal, pharyngeal, buccal and auditory mucous membrane, salivary glands, the larynx and the œsophagus. The kidneys are sometimes extensively involved, and there may be deposits in the vulvo-vaginal region. The heart and coronary vessels not infrequently show atheromatous changes, with some cardiac dilatation, but contrary to general belief, actual mucoid infiltration is a rarity.

**Symptoms.**—The onset is usually insidious, and at least half the patients have had the disease for some years before it is recognised. The general condition is comparable to hibernation, all the physical, metabolic and mental processes being sluggish and reduced much below the normal.

**Integument.**—The facies is pale and puffy, with baggy eyelids and a characteristic malar flush. There is thinning of the outer half of the eyebrows, and the hair of the head is dry and lustreless and falls out, sometimes with resulting patchy alopecia. The skin is dry and rough, and gives a swollen œdematous appearance, especially in certain regions, *e.g.* face, neck, supraclavicular areas, hands, legs and feet; but there is no pitting on pressure. In contrast to hyperthyroidism, obvious sweating is minimal or absent.

**Cardio-vascular.**—The pulse-rate is characteristically slow, *e.g.* 50, but there may be tachycardia with cardiac insufficiency. The blood pressure may be raised but not necessarily so. Angina sometimes occurs. Radiography usually shows enlargement of the heart, and in the electrocardiogram the voltage is low, with flattening or inversion of T waves.

**Mental changes.**—Apart from the psychoses, especially melancholia, which may complicate advanced or chronic cases, there are characteristic abnormalities of behaviour. The intellectual processes appear dimmed, and memory is poor. There is a noticeable latent period before questions are answered, and speech is slow, thick,

always deficient and cretinism is a variety of dwarfism. The facies is characteristic, being pale and pasty, with a thick skin, wrinkled forehead, a broad nose with depressed bridge and big nostrils, and thick lips separated by a protruding enlarged fissured tongue. The hair on the head is dry and scanty, and the eyebrows and eyelashes frequently deficient. The body is characterised by a protruding, pendulous abdomen, with umbilical hernia, supraclavicular pads of fat and some degree of scoliosis and lordosis. The hands are spatulate, with square finger tips, and the limbs lack muscular tone. Deafness is not infrequent, and speech is often impaired. Genital development is always retarded, and ultimate sexual maturity a rarity. As in the case of myxœdema, there is a low basal metabolic rate, subnormal temperature, sensitivity to cold and constipation.

**Diagnosis.**—To those who have seen the characteristic appearance, the diagnosis of cretinism rarely offers difficulty. In contrast, a Mongol has mongoloid eyes, with epicanthic folds, a good skin and complexion, fine but profuse hair, and a restless, bright manner.

**Course and Prognosis.**—If untreated, cretins remain semi-idiot and incapable of self-sufficiency, intercurrent infection in childhood or adolescence being a common termination. Infants, treated early, can be made normal, but delayed treatment leads to irreversible changes. Further, mental deterioration may occasionally supervene in later life on approximate normality, which has been maintained by adequate thyroid treatment.

**Treatment.**—Prophylactic treatment in endemic areas consists of small doses of iodine (see Goitre).

Treatment of the individual patient is specific, namely thyroid. One to 3 grains daily of thyroideum, B.P., or more, may be required, as judged by the general effects and the cardiac rate. If given in infancy or early childhood, an approximation to normal may be attained, but sometimes a harmless, apathetic idiot is merely changed into a mischievous, truculent semi-idiot.

## GOITRE

**Definition.**—A goitre is a pathological enlargement of the thyroid gland, which may be endemic or sporadic, symptomless or associated with hyperthyroidism or hypothyroidism. The contour of the gland may be smooth or nodular.

**Ætiology.**—Endemic goitre occurs in many regions throughout the world, including certain areas in this country, e.g. Derbyshire and Somerset. In Switzerland, where earlier investigations were undertaken, one factor found to be common to goitrous regions was a deficiency of iodine in the water and soil. This is not always the case in other parts of the world, and goitrogenic agents in an infected water supply have been implicated, although the deleterious effect may be obviated if the iodine content of the water is higher. Vitamin deficiency and a preponderance of calcium over iodine are other possible factors.

The ætiology of sporadic goitre is obscure. Apart from a possible relative iodine deficiency, a familial predisposition is sometimes apparent. The increased demands of the body for thyroxine at puberty may be indicated by a transient physiological thyroid enlargement, but this sometimes persists or increases in size. Endemic goitre is usually obvious in childhood, and its peak incidence is at puberty. This is also true of sporadic goitre, which may however be met with at all ages. The sex incidence of goitre is about equal in childhood, but, after puberty, females are more often affected than males—about 8 to 1.

**Pathology.**—The smooth diffuse goitres may be divided into the parenchymatous and the colloid, although both histological features are not infrequently present in the same gland. The parenchymatous goitres often show degenerative changes in

usually in a recurrent or post-operative phase. The B.M.R. may have changed from above to below normal, but is sometimes still raised. Thick œdematous plaques appear on the front of the shins, or the whole leg may be thickened. The overlying skin is often wrinkled and hairy, and the skin may itch or burn. Nodular lesions may also involve the face, arms, back or scrotum. The pathogenesis of localised myxœdema is uncertain, for the response to thyroid is poor.

**Course and Prognosis.**—In the absence of specific treatment the course is slowly but progressively downhill, and many patients end in the asylum. The response to treatment, however, is usually excellent though by no means necessarily so if a psychosis has already developed.

**Treatment.**—The specific treatment in myxœdema is thyroid, given as L-thyroxine, 0.3 mg. daily, or thyroideum siccum, gr. 3 daily. It is, however, prudent to commence with smaller doses, especially because of the extra strain that may be thrown on the heart by the increase in metabolism and the rate of circulation. A heart that was previously adequate may be unable to meet the extra demand, and cardiac failure or angina may supervene if the initial dosage is too large. In the long run, however, thyroid in appropriate dosage has a beneficial influence on the cardio-vascular system. If an untreated myxœdematous patient is first seen with some cardiac insufficiency and a rapid pulse (in contrast with the usual bradycardia), there may be hesitation to give thyroid; but in small and gradually increasing dosage the drug has a beneficial if paradoxical effect, the cardiac rate diminishing as the heart and coronary circulation improve. With the more usual bradycardia, thyroid has the effect of increasing the pulse-rate, and should this rise above 76 the dose of thyroid should be reduced. More exact criteria of dosage may be obtained by estimations of the basal metabolic rate or the blood cholesterol. It is useful to remember that thyroid, even if administered intravenously as a single dose of thyroxine, requires 24 to 48 hours to begin to act, has its maximum effect at the end of a week, and continues to act for several weeks. There is therefore no point in giving thyroid more often than once daily, and a cumulative effect may be guarded against by missing one week in four. Thyroxine has no advantage over the dried gland, and its intravenous administration is not without danger as the initial reaction may be alarming, e.g. nausea, vomiting, angina, pyrexia, aching muscles, loss of hair and peeling skin. Hypothermic coma may be treated by placing the patient in a warm water bath, or by any other measures which will raise the body temperature.

Hypochromic anæmia will respond to iron, simple hyperchromic anæmia to thyroid and true Addisonian anæmia to liver or vitamin B<sub>12</sub>.

## CRETINISM

**Definition.**—This is a condition of hypothyroidism beginning in foetal life. In contrast, childhood myxœdema is superimposed on a normal infancy and early childhood. The disorder is endemic or, more rarely, sporadic in incidence.

**Ætiology.**—The endemic form occurs in goitrous areas, the mother usually having a goitre. Iodine deficiency of the soil and water, and other theories are discussed in the Goitre section. No cause for the sporadic form is known. The sex incidence in both varieties is about equal.

**Pathology.**—In the endemic form, the goitre is usually the nodular adenomatous variety. In sporadic cretinism, a goitre is rare, the thyroid being atrophic, with flattened irregular epithelial cells, small alveoli and connective tissue overgrowth.

**Symptoms.**—The untreated cretin is mentally deficient, apathetic and somnolent, and tends to lead a vegetative existence. All the stages of childhood development are retarded, the fontanelles remain open for years, centres of ossification appear late, and the epiphyses remain ununited for long periods. Growth, however, is



Some symptomless endemic goitres, however, become hyperactive even without treatment.

The therapeutic, as distinct from the prophylactic, use of iodine in goitre without thyrotoxicosis, endemic or sporadic, is not as beneficial as the iodine-deficiency theory might lead one to expect; and even an initial increase in size may be produced. Thyroid extract to the point of tolerance leads to involution of the goitre in some patients. In others thyroidectomy is indicated for cosmetic reasons or because of pressure symptoms. In children or adolescents thyroidectomy for symptomless goitre is best avoided or deferred as there may be a tendency to recurrence.

## DISEASES OF THE PARATHYROID GLANDS

The parathyroids are four in number, and are usually situated symmetrically in the posterior aspect of the thyroid gland. They secrete a hormone, parathormone, which gives protein colour reactions, is soluble in water and 80 per cent. alcohol, but is insoluble in ether or acetone. The chief function of the glands is the regulation of calcium and phosphorus metabolism. Excess of the hormone leads to osteitis fibrosa diffusa, and deficiency to tetany.

### HYPERPARATHYROIDISM

**Synonyms.**—Generalised Osteitis Fibrosa Cystica; Osteitis Fibrosa Diffusa.

**Definition.**—A disease due to the excessive secretion of parathormone, and manifested clinically by hypercalcaemia, negative calcium balance, muscular atony, weakness and wasting, and decalcification of bones resulting in deformities and fractures.

**Ætiology.**—The disease, which is rare, is due to a neoplasm or hyperplasia of the parathyroid glands. The latter may be secondary to a pituitary stimulus, but a parathyrotrophic hormone has not been demonstrated in the blood. It affects women twice as frequently as men. The average age incidence is about 40, but it also occurs in childhood and old age.

**Pathology.**—A circumscribed adenoma of one parathyroid gland is the commonest lesion, the remaining three glands being normal or hypoplastic, but two adenomas have been found at operation. There may, however, be general hyper-trophy and hyperplasia of all glands, which is usually obvious to the naked eye, and may even be of extreme degree, e.g. one weighing 5 g. compared with a normal of 60 mg. Such changes are comparable to the hyperplasia, with or without adenomatous formation, in the thyroid gland of thyrotoxicosis. The parathyroid cells are greatly enlarged, and the cytoplasm highly vacuolated. The essential skeletal changes are softening, replacement of bone marrow by fibrous tissue, rarefaction of the cortex, and the presence of numerous osteoclasts and osteoblasts, with osteoclastic giant cells and cyst formation. Deposits of calcium as fine granules may be present in all the viscera, especially the kidneys and lungs. Occasionally hyperplasia of the parathyroid glands is secondary to chronic renal insufficiency.

**Symptoms.**—These are all the direct or indirect result of excessive calcium mobilisation and excretion. The long bones may be bent and deformed, with perhaps osteoclastic tumours, and in some cases pathological fractures. The vertebræ

the epithelial cells, and areas of fibrosis. The colloid goitres contain low cuboidal epithelium lining vesicles, filled with colloid. Nodular goitres usually contain multiple capsulated adenomas, which may show cystic or hæmorrhagic change. Occasionally there is a single adenoma, which may be of colloid type or of parenchymatous type. In the latter case, it is thought by some to arise from solid masses of embryonic cells that may be seen in normal glands, and for this reason is termed "foetal adenoma".

The above pathological changes occur both in endemic and sporadic goitres.

**Symptoms.**—When goitre is associated with hyperthyroidism, the symptoms may be those either of Graves's disease or of secondary thyrotoxicosis. When associated with hypothyroidism, the clinical picture is that of cretinism or myxœdema.

In all varieties of goitre, including those which are endocrinologically inactive, pressure symptoms may be the major manifestations, especially so in the case of nodular goitres, and when goitres are low down in the neck or behind the sternum (intrathoracic), pressure symptoms may be the only indication apart from that given by radiological examination. Pressure on the trachea may produce difficulty in breathing, irritating cough, alteration in voice and stridor. For mechanical reasons, the dyspnoea is worse on lying down, and attacks of dyspnoea with cyanosis may be fatal. The voice is also affected by paralysis of the recurrent laryngeal nerve, this, however, being rarely bilateral. Pressure on veins may produce dilatation of those of the head and neck, with cyanosis, and in the case of intrathoracic goitre, dilated veins may be evident over the chest. Oesophageal pressure and resulting dysphagia are rare, as also are bradycardia due to vagus involvement, and mydriasis and sweating from cervical sympathetic stimulation.

**Complications.**—Malignant change is said to supervene in 1·6 per cent. of all goitres, and in 2·7 per cent. of nodular goitres. It is usually only after some years that malignancy develops, and clinical indications are a rapid increase in size and hardness of the goitre over a period of weeks or months, the development or increase of pressure symptoms, especially dysphagia, and lack of mobility in relation to the adjacent structures, *e.g.* the trachea. Metastases in the lungs, liver and bones, may unfortunately be the first recognised indication in some patients. The commonest age of onset of malignant changes is from 50 to 70, and such a change is nearly always superimposed on a pre-existing goitre. In cases in which malignant changes supervene, 35 per cent. are correctly diagnosed before operation, 30 per cent. at operation and the remainder only on histological examination.

**Diagnosis.**—This is usually obvious on inspection. Intrathoracic goitre may be simulated by thymus or mediastinal tumours. Sometimes auricular fibrillation in a middle-aged or elderly person may draw attention to a small pre-existing goitre which has been symptomless for years. Pressure symptoms on the trachea may simulate asthma, perhaps with the complication of bronchitis, and some of these cases are not diagnosed for years.

**Course.**—A goitre may remain symptomless and innocent throughout life, but at any time symptoms of hyperthyroidism or hypothyroidism may appear.

**Treatment.**—In Switzerland the addition of iodide to salt, 1 part in 100,000, has enormously reduced the incidence of endemic goitre. In areas of endemic goitre in France, 1 min. of Lugol's iodine daily, has been employed, and in America iodised salt, 1 : 10,000, both with varying and on the whole satisfactory results. As might have been anticipated, the results are best if iodine has been administered to the mother throughout the pregnancy, but even when first given in childhood, the incidence of goitre is considerably reduced. It is to be pointed out that in the case of symptomless endemic goitre, especially of the nodular variety, the use of iodine is not free from the danger of inducing thyrotoxicosis. This is also true in the case of sporadic goitre, although in simple diffuse goitre the risk is probably insignificant.

segmentally distributed in relation to nerve roots, with corresponding patches of pigmentation. The disorder is found mostly in girls and is associated with sexual precocity. There are no changes in calcium, phosphorus or phosphatase values, the ætiology is uncertain, and parathyroidectomy useless.

Osteoporosis may also be found with prolonged immobility, in old age, in thyrotoxicosis and in eunuchoidism.

**Prognosis.**—In the absence of surgery, the course of the disease is progressive, and death occurs within a few years. Weakness, wasting and deformities confine the patient to bed. Intercurrent respiratory infection may terminate life, while others die from uræmia or pyelonephritis.

**Treatment.**—Primary hyperparathyroidism can only be adequately controlled by removal of a parathyroid adenoma or, in the case of hyperplasia, of two or more parathyroid glands. Irradiation is usually ineffective, and a high calcium and phosphorus diet is only mildly beneficial and not without danger in the presence of renal insufficiency. If at operation no adenoma is discovered, the exploration should be continued above and below the thyroid region, behind the œsophagus and into the upper mediastinum, for a parathyroid tumour is sometimes found in such aberrant positions. Even if an adenoma is found in the usual situation, the posterior aspects of the thyroid gland should be completely explored to see if a second adenoma is present, as may be the case. Where there is diffuse hyperplasia of all four glands, no less than three should be removed, and some surgeons remove a portion of the fourth as in subtotal thyroidectomy. Tetany may follow operation for adenoma or hyperplasia, and may appear within a few days of operation, or after a latent period of some weeks. If controlled medically it will tend to disappear after some weeks or months, when the remaining parathyroid tissue has undergone compensatory hyperplasia. It is obviously illogical to give parathormone, which would further decalcify the already softened bones. Following parathyroidectomy, the general symptoms, e.g. pains, weakness, anorexia, improve almost at once, but the bones may take several months to become normally calcified. The serum calcium immediately falls to normal or below normal, but the phosphatase tends to remain high for some months, being an indication of osteoblastic activity. The sudden change from high to low serum calcium may cause transitory visual and mental disturbances with apprehension.

## HYPOPARATHYROIDISM

**Synonym.**—Parathyroid Tetany.

**Definition.**—A disease characterised by neuro-muscular irritability due to a subnormal serum calcium, the latter being the result of deficient secretion of parathormone. All forms of tetany are due to subnormal concentrations of ionised calcium in the serum, but this is not necessarily the result of parathyroid hypofunction.

**Ætiology.**—Idiopathic hypoparathyroidism occurs sporadically, and may do so at any age, but it is comparatively rare, or perhaps not sufficiently well recognised. A familial incidence of hypoparathyroidism has been recorded, including examples of onset in infancy. The majority of cases follow thyroidectomy, and although this may be due to removal of parathyroid tissue, it is more often due to interference with blood supply. Hypoparathyroidism may also follow the removal of a parathyroid tumour, or two or more hyperplastic glands in osteitis fibrosa diffusa. Parathyroidectomised animals show decreased urinary phosphorus excretion and rise in plasma phosphorus before changes in calcium metabolism are apparent. Later, however, there is a fall in serum calcium in spite of a positive calcium balance, and the animal dies in tetanic convulsions. Parathormone injections will prevent or correct the changes in phosphorus and calcium metabolism. Tetany also occurs in conditions

are compressed, and not infrequently height is diminished by several inches. Osteoclastic swellings may deform the jaw. The shape of the skull is rarely distorted clinically. The bones and osteoclastomatous swellings are often tender, especially on pressure. The teeth are not decalcified. The muscles show atony, fatigability and atrophy. Gastro-intestinal symptoms are nausea, vomiting, constipation, abdominal pains and cramps. Polyuria and polydipsia are associated with the increased calcium excretion. Urinary symptoms are common. The calcium may be deposited diffusely, giving rise to the presence of chronic nephritis and renal insufficiency, or even multiple renal calculi, the latter consisting chiefly of calcium and phosphorus. Renal colic and pyelocystitis are complications. In some patients the presenting symptoms are those of renal calculus, without any indication of hyperparathyroidism. In clinics where all such cases undergo investigation of calcium metabolism a number (1 to 5 per cent.) have been shown to be due to primary hyperparathyroidism. It is also important to remember that bone changes may be relatively slight and in acute cases undetectable radiographically, although the serum calcium is raised. Acute hyperparathyroidism may present itself as weakness, wasting, drowsiness or semi-coma, nausea or vomiting, and cardiac failure. The condition can be produced experimentally by the injection of parathormone.

*Metabolic changes.*—The calcium and phosphorus are mobilised from the bones, and excreted in excess in the urine and to a much less extent in the faeces. The serum calcium is usually raised, e.g. 15 mg. per cent. (normal 10 mg.), and the plasma phosphorus is diminished, e.g. 2 mg. per cent. (normal 3.5 mg.). A normal serum calcium does not necessarily exclude the disorder, providing that the serum phosphorus is persistently low, and the calcium balance negative. In the presence of advanced renal disease, however, there may be phosphorus retention and a raised serum phosphorus. The alkaline serum phosphatase is raised, e.g. 24 King-Armstrong units compared with the normal values, 3 to 13 units, and it is a measure of the degree of osteoporosis. Rarely and in the absence of gross osteoporosis the phosphatase may be within normal limits.

*Diagnosis.*—Radiography shows generalised osteoporosis, with granular mottling in the skull; but an absence of demonstrable radiographic bone changes in itself does not exclude the diagnosis. Multiple calcium deposits, minute and diffusely scattered or large enough to be called calculi, may be shown in skiagrams of the kidneys, and sometimes of the lungs. If estimations of serum calcium, phosphorus and phosphatase are inconclusive, the intake and output of calcium must be measured over a few days to determine if a negative calcium balance is present.

When urinary symptoms are prominent, the underlying primary hyperparathyroidism may be unsuspected in the absence of metabolic investigation. Rarely, hyperparathyroidism of severe degree is secondary to long-standing chronic nephritis, and, in such patients, although the total urinary and faecal calcium excretion is above normal, the serum calcium is normal or slightly less than normal and the phosphorus raised. *Differential diagnosis may be very difficult if there is inadequate evidence of the sequence of events.*

Gout and arthritis may be simulated, especially if there are tender deposits of calcium in the joints, and some patients are treated for vague rheumatic pains or lumbago. In Paget's osteitis deformans, a disease of middle or old age, there is great deformity of the skull, normal calcium and phosphorus metabolism, but an increased serum phosphatase. Osteomalacia, or adult rickets, is very rare in England and America, and is due to deficient intake of vitamin D or lack of sunshine. The bones are soft and deformed, the plasma phosphatase is raised and the plasma phosphorus is low, but the serum calcium is never above normal and is often below.

Albright has described a syndrome of multiple bone cysts and areas of rarefaction,

and the plasma phosphorus is above the normal 3.5 mg. (e.g. 7 mg.); there is decreased urinary excretion of phosphorus and calcium. In a doubtful case, a high phosphorus diet will depress the serum calcium and produce symptoms; this does not occur with normal parathyroids. It is interesting to note, however, that in cattle there is a form of tetany, which is the result of excessive phosphorus in the diet.

**Treatment.**—The logical treatment of hypoparathyroidism is solution of parathyroid, U.S.P. (parathormone), which acts by increasing the excretion of urinary phosphorus and mobilising calcium from the bones thus raising the serum calcium. This form of treatment, however, has several disadvantages. It is useless in acute tetany because subcutaneous or intramuscular injections may take 8 or more hours to be effective and are variable in their effect. While intravenous injection is quicker it takes a few hours to act and, moreover, by this route there is a danger of a protein shock-like reaction in some patients. Four-hourly injections of 1 ml. of parathyroid solution (20 units) intramuscularly or subcutaneously may, however, be effective after the initial latent period. Rarely, overdosage of injected parathyroid hormone results in nausea, vomiting, diarrhoea, failing circulation, dehydration, increased viscosity of blood, coma and death. With controlled serum calcium estimations, however, overdosage is a rarity and 40 units daily may sometimes not be adequate to control the disorder. Even when solution of parathyroid is effective at first, a refractory state sets in after some weeks. The latter is probably not due to the production of anti-hormonic substances in the blood, as in the case of other hormones, but to local tissue immunity since an intravenous injection of solution of parathyroid may still be effective. Nevertheless, this refractory state renders prolonged therapy with solution of parathyroid impracticable.

The immediate treatment of acute tetany is the intravenous or intramuscular injection of calcium gluconate, 20 ml. of a 10 per cent. solution, the effect being rapid and dramatic, but only lasting some hours. The injections must be administered slowly, but a little leakage from a vein has not the local deleterious effects of calcium chloride. It is necessary to follow this emergency injection by large doses of calcium gluconate or lactate by mouth, e.g. 12 g. daily in divided dosage. Calcium chloride is less pleasant to take, and in practice the theoretical value of the resulting acidosis is hardly significant. This is perhaps less true of the addition of 3 g. of ammonium chloride, daily, in 1 g. capsules. In many cases calcium gluconate or lactate by mouth is sufficient to control the tetany. If not, vitamin D should also be given. It acts by increasing calcium absorption from the intestine and secondarily by increasing phosphorus excretion in the urine. The dosage of vitamin D, or calciferol, should be high; 50,000 to 200,000 units daily may be required. In severe cases these measures may still be ineffective, and then a derivative of irradiated ergosterol, dihydrotachysterol (A.T. 10) is of great value. It is not antirachitic, probably because it also causes considerable excretion of phosphorus from the urine, but it produces a great increase in calcium absorption from the intestine and a rise of serum calcium to normal or above normal. Like vitamin D it is of no use in emergency, the effect not being produced for some 24 to 48 hours. It is, however, cumulative in action, and the dosage should be controlled by periodic serum calcium estimations if hypercalcaemia is to be avoided. The urinary test of Sulkowitch is a useful indication of dosage. The reagent consists of oxalic acid and ammonium oxalate in glacial acetic acid, and equal amounts of urine and reagent are mixed. If no precipitate occurs, the serum calcium is probably below 7.5 mg. per 100 ml., as the renal threshold for calcium varies between 7.5 and 9; if there is a fine white cloud, the serum calcium is probably normal, about 10; if the precipitate is milky, the serum calcium is abnormally high. Using this technique Albright gives 3 ml. of dihydrotachysterol a day by mouth until calcium appears in the urine, after which 1 ml., 3 to 5 times a week is usually adequate. Dihydrotachysterol is prepared in

other than hypoparathyroidism if the concentration of calcium in the blood falls below normal.

Thus in rickets, osteomalacia and steatorrhœa there is a deficient absorption and utilisation of calcium. The increased demands for calcium in pregnancy and lactation may render a latent tetany manifest. Tetany may be found in alkalosis, the total serum calcium being normal, but the ionised fraction below normal; alkalosis may result from excessive vomiting, hysterical hyperpnoea, or treatment with alkalis.

**Pathology.**—In idiopathic hypoparathyroidism, the parathyroid glands may be atrophic, or replaced by fibrous or fatty tissue with round-celled infiltration; in post-parathyroidectomy tetany, too much parathyroid tissue has been removed, or the residual parathyroid tissue has not yet had time to undergo compensatory hypertrophy.

**Symptoms.**—Following thyroidectomy and parathyroidectomy, symptoms may appear within the first 48 hours or may be delayed for weeks or months. There is often irritability, nervousness and apprehension in addition to weakness. Paræsthesiæ, and muscular cramps and stiffness are common in the hands, especially on the ulnar aspect, but may also occur in the feet. They are followed or accompanied by muscular contractions of the hands and feet, giving the classical picture of carpo-pedal spasm. The "obstetric hand" is produced by flexion at the metacarpo-phalangeal joints, extension at the interphalangeal joints and adduction of the thumb. Spasm of the laryngeal muscles may produce hoarseness and stridor, and, if the bronchial muscles are also involved, respiratory distress and cyanosis result, sometimes with fatal convulsions or coma. A form of chronic pseudo-asthma associated with bronchial spasm is also a manifestation of hypoparathyroidism. Tetanic muscular spasms are not infrequently painful and may cause the patient to cry out in distress.

In long-standing hypoparathyroidism, ectodermal defects become apparent, with brittleness and ridging of the nails, loss of hair and transverse ridging of the decalcified teeth. Blurring of vision, perhaps leading to blindness, is due to opacity of the lens, minor degrees of which may be detected by means of a slit-lamp even in the absence of ocular symptoms. Muscular spasm may involve ocular muscles.

Various cerebral and mental disturbances may be due to chronic hypoparathyroidism. They include changes in character, mental instability, anxiety, depression, impairment of memory and intellect, and more rarely hallucinations, confusion, manic-depressive states, paranoia and dementia. Major epilepsy and petit mal are rare. Migraine may be a presenting feature. Skull radiographs may show calcium deposits in the basal ganglia of the brain.

Gastric spasm may cause pain and vomiting, and spasm of the bile passages simulate cholelithiasis, especially if associated with transitory jaundice. Laparotomy has been performed for symptoms suggesting appendicitis or perforated peptic ulcer; and ileal spasm may produce fatal ileus. Cardiac pain or a sense of constriction with palpitation may occur; the electrocardiogram shows a characteristic prolongation of the Q-T interval.

**Diagnosis.**—Although in most cases diagnosis is obvious, mild degrees of hypoparathyroidism with general irritability, weakness and paræsthesiæ and only slight ectodermal deficiencies, may not be suspected. The following classical signs are of diagnostic value. Chvostek's sign is the production of contraction of facial muscles by tapping the facial nerve below the zygoma; Trousseau's sign is the production of carpal spasm by a sphygmomanometer band on the arm at a pressure just above systolic; Erb's sign is an exaggerated muscular contraction in response to minimal electrical stimuli. The failure to elicit one or more of these signs does not exclude the diagnosis. Biochemical evidence is often conclusive. In hypoparathyroidism the serum calcium is always below the normal value of 10 mg. per 100 ml. (e.g. 6 mg.)

highly potent in maintaining the electrolyte and water balance in adrenalectomised animals. This fraction is far more potent, weight for weight, than is 17-hydroxy-11-desoxycortone (deoxycortone), a substance synthesised by Reichstein in 1938 and used therapeutically in Addison's disease, but which is probably not a natural constituent of the adrenal gland. Deoxycortone has largely been used for its influence on water and mineral metabolism. It causes retention of sodium and an excretion of potassium, with a lowering of tissue and plasma potassium, and thus it is capable of reversing the changes found in the adrenalectomised animal. Chloride tends to behave as sodium, although not invariably, and water tends to be retained with the sodium chloride. Fluid balance is a complicated subject and it requires the consideration not only of total retention or loss, but of the distribution of fluid between tissues and plasma and between intracellular and extracellular fluid.

The glucocorticoids have some action on water metabolism, which varies with circumstances, causing retention during overdosage, but producing diuresis in Simmonds's and Addison's disease. They also cause excretion of potassium and retention of sodium. By chromatographic studies and using the Na/K ratio in the urine of adrenalectomised mice, after injecting Na and K isotopes, J. F. Tait and S. A. Simpson have separated a mineral-corticoid fraction in beef adrenal extracts of far greater potency than that of deoxycortone or of any previously separated adrenal glucocorticoid. Its relationship to the amorphous fraction is unknown.

(3) *Sex hormones.*—The urine of castrated men and women contains androgens derived from the adrenal cortex. In normal men two-thirds of the urinary androgens come from the adrenals and only one-third from the testes. The whole of the urinary androgens in females come from the adrenals. A number of androgens have been isolated from the adrenals, the chief being androsterone. Urinary androgens may be assayed by a chemical colour reaction and are measured as 17-ketosteroids, the latter possessing a ketone group at the 17th carbon atom. 17-ketosteroids are divided into alpha and beta ketosteroids according to the position of the 3-hydroxy group. The alpha group includes androsterone and the beta group includes dehydroisoandrosterone, which is found in large quantities in the urine of patients with adrenal neoplasms. Although it is uncertain whether, or to what extent, the adrenals secrete oestrogens and progesterone in normal men and women, there is no doubt that such hormones are secreted, often in large quantities, by adrenal tumours, especially in males.

## ADDISON'S DISEASE

**Synonyms.**—Hypocorticalism; Adrenal Cortical Insufficiency.

**Definition.**—A disease due to destruction and hypofunction of the adrenal cortex, and manifested by pigmentation, weakness, myasthenia, anorexia, loss of weight and hypotension. It was first described by Thomas Addison in 1849.

**Ætiology.**—The disease is found among all races, and in all climates. Males and females are affected about equally. It is commonest between the ages of 20 and 40, and rare in childhood and old age. Tuberculosis is the most common cause. Severe infections, primary or secondary carcinoma, hæmochromatosis, arsenic poisoning and hæmorrhage are rarely responsible.

**Pathology.**—In tuberculosis both the medulla and cortex are usually destroyed, except for small islets of surviving tissue. The gland is replaced by caseous tissue, with areas of fibrosis, giant cells and lymphocytes. Other organs may also be affected, but pulmonary tuberculosis is rare. A history of gland or bone tuberculosis in childhood or in other members of the family is not uncommon. The next most common cause is atrophy of the cortex, of unknown origin, the medulla being scarcely affected. The cortex is almost entirely replaced by connective tissue and dilated capillaries,

an oily solvent containing 5 mg. of the drug per ml., and is administered by mouth.

Diet in hypoparathyroidism is a matter of controversy. High calcium diets (milk, cheese, egg yolk) have the serious disadvantage of also being high phosphorus diets. It is better, therefore, to prescribe a normal diet, or preferably a low phosphorus diet, and to supply the extra calcium as calcium lactate or gluconate. A diet containing no milk, cheese, egg-yolk, meat or nuts, but a liberal amount of fruit, vegetables, carbohydrates, fats and white of egg contains little phosphorus.

## DISEASES OF THE SUPRARENAL GLANDS

The suprarenal gland consists of cortex and medulla. The cortex is of mesoblastic origin, while the medulla is ectodermal. The cortex is composed of lipid-containing epithelial cells, arranged from without inwards in three zones, zona glomerulosa, z. fasciculata and z. reticularis. The inner portion of the latter contains brightly staining granules (pigment zone). The medullary cells have an affinity for chromic acid stains, and are termed chromaffin cells. The adrenal glands are supplied by sympathetic nerves from the splanchnic and celiac ganglia, but they are cholinergic.

The medulla is not essential to life. It secretes adrenaline and nor-adrenaline and its function will be discussed under the heading Phæochromocytoma. It is anatomically separate from the cortex in fishes but a functional relationship exists in that adrenaline can stimulate the secretion of adrenocorticotrophic hormone by the pituitary. This probably occurs only in emergencies.

The adrenal cortex is essential to life, and bilateral adrenalectomy results in death within 7 to 10 days. The steroids secreted by the cortex may be divided into three main groups, the glucocorticoids, the mineralocorticoids and the sex hormones.

(1) The glucocorticoids (11-oxysteroids) are diabetogenic and catabolise protein. Gluconeogenesis results from the excessive breakdown of protein (or failure of anabolism), the glucose being transformed into hepatic glycogen and also into fat. There is also a decreased rate of utilisation of glucose. Protein breakdown is also reflected in creatinuria and increased excretion of uric acid. There is a shift of fat from the extremities to the face and trunk and the liver also contains an excess of fat. Ketosis may result. Other effects are involution of lymphoid tissue, decrease of blood lymphocytes and disappearance of eosinophil cells.

Kendall of the Mayo Clinic and Reichstein of Zurich identified many of these corticosteroids. Kendall gave them alphabetic names, e.g. Compound A (11-dehydro-corticosterone), Compound B (corticosterone), Compound E (11-dehydro-17-hydroxy-corticosterone) and Compound F (17-hydroxycorticosterone). Compound F appears to be the main constituent of the adrenal venous blood of dog and man, and Compound B is present in lesser degree. Compounds A and E are found only in traces. Compound E is also called cortisone and is very similar in chemistry and action to Compound F. Compound F has been isolated in large quantities from the urine in Cushing's disease with associated severe diabetes. Compound E has been synthesised from bile and from stigmasterol, a steroid found in the soya bean. Compound A and, less so, Compound B are very potent in producing a deposition of fat in mice.

(2) Mineral corticoids—corticosteroids with influence on electrolytes and water balance. After the glucocorticosteroids (Group 1) have been crystallised from an extract of adrenal cortex, there remains an amorphous residual fraction which is



highly potent in maintaining the electrolyte and water balance in adrenalectomised animals. This fraction is far more potent, weight for weight, than is 17-hydroxy-11-desoxycortone (deoxycortone), a substance synthesised by Reichstein in 1938 and used therapeutically in Addison's disease, but which is probably not a natural constituent of the adrenal gland. Deoxycortone has largely been used for its influence on water and mineral metabolism. It causes retention of sodium and an excretion of potassium, with a lowering of tissue and plasma potassium, and thus it is capable of reversing the changes found in the adrenalectomised animal. Chloride tends to behave as sodium, although not invariably, and water tends to be retained with the sodium chloride. Fluid balance is a complicated subject and it requires the consideration not only of total retention or loss, but of the distribution of fluid between tissues and plasma and between intracellular and extracellular fluid.

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**Pathology.**—In tuberculosis both the medulla and cortex are usually destroyed, except for small islets of surviving tissue. The gland is replaced by caseous tissue, with areas of fibrosis, giant cells and lymphocytes. Other organs may also be affected, but pulmonary tuberculosis is rare. A history of gland or bone tuberculosis in childhood or in other members of the family is not uncommon. The next most common cause is atrophy of the cortex, of unknown origin, the medulla being scarcely affected. The cortex is almost entirely replaced by connective tissue and dilated capillaries,

with infiltration of lymphocytes, plasma cells and leucocytes. The picture is more like a toxic necrosis than a simple atrophy. Rare lesions are syphilis, amyloid disease, hæmorrhage, infarction, hæmochromatosis and malignant growth. The last may apparently produce the disease even when it involves the sympathetic nerve supply only, sparing the actual glands.

**Symptoms.**—Weakness, loss of appetite, loss of strength and pigmentation are the usual presenting features.

The onset is often gradual. Occasionally the patient is not seen until a grave crisis has developed. This is especially so when pigmentation is not a conspicuous feature. Usually the patient complains of feeling vaguely unwell. He (or she) may be languid, lacking in strength and easily tired. Appetite is poor, and there may be a special aversion to fatty foods. In more severe insufficiency, nausea and even vomiting are distressing features, while abdominal pain, rarely sufficiently severe to simulate an acute abdomen, is occasionally present. Abdominal pain is rare during the less acute phases but there may be aching in the loin or referred to the shoulder due to irritation of the diaphragm. Constipation is common, but there may be intermittent attacks of diarrhoea, either spontaneous or following purgatives, and these may initiate a crisis. Hiccups, yawning and conjunctivitis suggest deterioration in the patient's condition. There is progressive loss of weight, myasthenia and general weakness.

Generalised pigmentation, due to the deposition of melanin in the mucous membranes as well as the skin, is a classical sign of the disease. In the skin it is deposited in the basal layer of the epidermis, and in amounts greater than normal. Brown patches and streaks may be found on the inner aspects of the cheeks, the soft palate and posterior portion of the hard palate, the sides of the tongue, the gums and the mucous surface of the lips, especially at the corners of the mouth. The distribution of skin pigmentation is partly determined by exposure to light and irritation. Thus, it is most marked on the face and neck, dorsum of the hands and forearms, waist-line, garter area, axillary folds and vulva, and in areas of skin overlying bony prominences, e.g. knuckles, ischial tuberosities and ankles. The palms show no evidence of increased pigmentation, except in the interphalangeal creases. Occasionally there are scattered pigmented spots on the face and body and the nails may also be pigmented and striated. Although pigmentation is a classical sign of Addison's disease, it may be inconspicuous or even absent in fair-skinned people, or when the onset is acute. There may be associated leucoderma.

There is considerable variation in the degree of interference with sex function. In some there is none, while in others there is amenorrhœa or impotence. Hypogonadism is certainly not an essential feature. Many patients feel the cold badly, especially in more severe insufficiency. The body temperature may be normal or subnormal, with perhaps intermittent pyrexia, and the basal metabolism is rarely appreciably lowered, except in crisis. The systolic blood pressure is characteristically below 100 mm. of mercury, but this does not necessarily give rise to symptoms, and a normal blood pressure may persist for some time. Although in some patients the fasting blood sugar and carbohydrate tolerance curves may be normal, in others there is a persistent or intermittent hypoglycæmia which may even be fatal if unrelieved by glucose or adrenaline. There is an increased sensitivity to infections, shock, surgical trauma, hæmorrhage and drugs.

In crisis, the patient is collapsed and cold. Stupor and apathy are characteristic but there is also irritability, intractability and restlessness. The patient tends to curl up deep in the bed beneath the covering, and to resent interference. The pulse is rapid and of poor volume, and the blood pressure tends to fall acutely. Nausea, vomiting and diarrhoea may be persistent, thus adding to the dehydration that has resulted from the increased loss of salt and water through the kidneys. The veins are collapsed and the blood viscous. Ultimately urine becomes scanty in

amount, and terminally may contain casts and albumin. Pigmentation tends to increase in the more severe degrees of insufficiency, and crops of discrete deeply pigmented spots may appear. The blood sugar falls during crises, the serum sodium, plasma chloride and alkali reserve become even lower than previously and the serum potassium concentration higher.

**Complications.**—Addison's disease may rarely be complicated by thyrotoxicosis, myxœdema or diabetes. Other tuberculous lesions or intermittent infections, such as pneumonia, are not uncommon.

**Diagnosis.**—Clinically, this depends upon the classical features of pigmentation, weakness, wasting, anorexia and hypotension. Cutaneous pigmentation may also be found in other conditions, including hæmochromatosis, Hodgkin's disease, exophthalmic goitre, Cushing's syndrome, pernicious anæmia, arsenical poisoning, malignant cachexia, ochronosis, argyria, parasitic irritation, leucoderma and pregnancy. In Simmonds's cachexia, a condition which has many features in common with Addison's disease, pigmentation is usually absent and is hardly ever diffuse, or marked. It is important to note that pigmentation of the mucous membranes is practically pathognomonic of Addison's disease. It is said by some to occur very rarely with pernicious anæmia, malignant cachexia and arsenical poisoning. Of the first, I wish to record that two authorities on pernicious anæmia have never met with pigmentation of the mucous membranes in this disease; of the second and third I would presume infiltration of the adrenal glands by metastases or by arsenic. In people of the negro race, or in those with an antecedent negroid admixture, pigmentation of the mucous membranes may occur normally. It may also occur in intestinal polyposis.

Laboratory aid should more often be sought to exclude Addison's disease than to confirm a diagnosis, confidently made on clinical grounds. One should be very hesitant about discarding such a diagnosis because of normal or atypical chemical findings. Normal values are: serum sodium, 315 to 350 mg. per cent. (140 to 150 meq. per litre), serum potassium, 18 to 21 mg. per cent. (4.6 to 5.0 meq. per litre), plasma chloride as NaCl, 560 to 630 mg. per cent. (95 to 110 meq. per litre) and plasma bicarbonate, 53 to 77 vols. CO<sub>2</sub> per 100 ml. (25 to 35 meq. per litre as H<sub>2</sub>CO<sub>3</sub>). In severe adrenal insufficiency the blood sodium and chloride are low, the potassium raised and the alkali reserve low. Blood urea is raised in severe phases partly due to hæmoconcentration associated with electrolyte and water balance and partly due to poor renal function. Hæmoglobin and hæmatocrit values are also raised as an expression of hæmoconcentration, and when anæmia is present a low hæmoglobin may not be revealed until hæmoconcentration has been corrected by treatment. There may be relative lymphocytosis, eosinophilia and an increased sedimentation rate.

The Kepfer test is a measure of the rate of the elimination of water and to a lesser degree of chloride and urea. The night urine is measured and in the morning a litre of water (20 ml. per kg. body weight) is drunk and the urine collected hourly for 4 hours. If none of these hourly specimens is greater than the total night urine the diagnosis of Addison's disease is confirmed (Part I). Further confirmation (Part II) is sought by withdrawing venous blood and calculating Factor A—

$$A = \frac{\text{Urine Urea}}{\text{Plasma Urea}} \times \frac{\text{Plasma Chloride}}{\text{Urine Chloride}} \times \frac{\text{Day Urine}}{\text{Night Urine}}$$

Urea and chloride are expressed as mg. per cent. Day urine represents the largest volume in 1 hour; night urine the total night urine (10 p.m. to 7 a.m.). If A is greater than 30, the diagnosis of Addison's disease is not supported, the usual value for adrenal insufficiency being less than 15. The test is only slightly modified by deoxycortone but is reversed to normality by cortisone which produces normal diuresis.

The carbohydrate tolerance curve is not necessarily abnormal but the physiological hypoglycæmia at the end of the test period may be accentuated. The insulin sensitivity test is midway between normality and that of Simmonds's disease. The urinary 17-ketosteroids are very low in the female and reduced in the male. The 11-oxysteroids tend to be low but are a less reliable index.

The response to pituitary corticotrophin is the basis of a test devised by Thorn. Corticotrophin (A.C.T.H.) is injected in doses of 25 mg. at intervals of 6 hours for 48 hours. The urinary 17-ketosteroids are measured for 24 hours before the test and during the last 24 hours of the test. In Addison's disease there is no appreciable increase in 17-ketosteroid excretion as there is little or no healthy adrenal cortex left to respond. Neither is there a decrease in eosinophil cells in the blood, either after 4 hours, or after 48 hours, in contrast to a normal response of over 50 per cent. decrease in 4 hours and almost complete disappearance in 48 hours.

When tuberculous lesions of the adrenal glands have become calcified, radiology may be of diagnostic help by revealing calcareous shadows in the costo-vertebral angle.

**Prognosis.**—In the absence of treatment, there is progressive deterioration and death within months or years. With adequate substitution therapy, life may be prolonged, but the sensitivity to intercurrent infection is always a danger. Very rarely there is a spontaneous recovery of adrenal function sufficient to permit the cessation of substitution therapy.

**Treatment.**—Until cortisone became available, treatment consisted of deoxycortone acetate (D.O.C.A.) given by intramuscular daily injections or by subcutaneous implantation, in either case supplemented by salt by mouth. Salt alone was adequate for mild cases. Patients, however, were very liable to intercurrent infection and/or hypoglycæmic attacks and these caused death in some 50 per cent. of patients within 10 years. Cortisone should now be considered an essential part of treatment for the majority of cases. It makes the patient less liable to infection and hypoglycæmia, and increases appetite, strength and well-being, abolishing at the same time the depression, apathy and negativism which characterise the behaviour pattern. In large doses, cortisone may reactivate tuberculous lesions, but in Addison's disease, with doses less than the physiological requirement of 50 mg. daily, this does not appear to be the case. For safety the basic dose should be 25 mg. daily, given as half a tablet by mouth twice daily; and the maximum daily dosage should not exceed 37.5 mg.

In so far as cortisone has some action on electrolyte and water balance, mild cases will not require supplementary therapy with deoxycortone, but most patients will require extra salt in the form of capsules of 1 g. three times a day. Others may require as much as 12 g. of salt a day and in the more severe cases it will be necessary to give deoxycortone as well. This can be done in several ways—

- (1) By subcutaneous daily injections in oil, the average dose being 2 to 5 mg.
- (2) By intramuscular injection of a suspension of trimethyl acetate deoxycortone Crystules, the average dose being 50 to 100 mg. and the effect lasting some 4 weeks.
- (3) By implantation of tablets into the subcutaneous fat of the lower abdomen or upper thigh, the average dose being between 200 and 400 mg., and the effect lasting 6 months. This dose is calculated on the basis of one 100 mg. tablet for each 1 mg. of deoxycortone acetate, in oil, required by daily injection for maintenance.

Where deoxycortone is used, it may be unnecessary to take extra salt except on occasions, e.g. when long-acting Crystules or implants are almost completely absorbed. Where cortisone is not available, deoxycortone, with or without salt, is reasonably effective although it is qualitatively an incomplete form of therapy. In so far as deoxycortone, in large doses, can produce excessive elimination of potassium, with a fatal outcome, initial therapy should be with smaller doses and the danger of over-dosage should always be borne in mind. In this connection it should also be remem-

bered that tissue potassium may be lowered before the blood shows any change. Apart from general malaise, nausea and rapid pulse, a cough with frothy sputum and flaccid muscular paresis are features of deoxycortone over-dosage. The physical signs include hypertension, œdema and crepitations at the bases of the lungs, but the blood pressure may fall with cardiac failure.

The treatment of crisis is much the same as the treatment of chronic adrenal insufficiency described above, except that it is more intensive. Cortisone is essential, particularly in the presence of hypoglycæmia. Cortisone by mouth acts within an hour and unless the patient is comatose this is the best route of administration. Intramuscular or subcutaneous cortisone takes several hours to become effective but the effect lasts for some 24 hours. In the presence of complete collapse, with or without hypoglycæmia, the intravenous administration of glucose and saline is called for. In crisis the veins are collapsed and difficult to enter and it may be necessary to expose a vein by incision. As previously stated, active treatment may transform a state of adrenal insufficiency to one of over-dosage so that if a patient recovers from the initial crisis and then appears to relapse in the face of active treatment, the possibility of over-dosage must be considered.

### ACUTE SUPRARENAL DEFICIENCY

Apart from Addison's disease, there is some clinical and pathological evidence that acute adrenal insufficiency occurs with certain infections, such as meningococcal septicæmia, diphtheria, typhoid fever and pneumonia. At necropsy, the suprarenals show congestion, œdema, hæmorrhage and necrosis. Such lesions may also be found in fatal eclampsia.

The onset is sudden. Malaise, restlessness, headache, vomiting, fever, chills, sweating, abdominal pain, cyanosis, scattered petechiæ and stupor or coma, are the main features. When the underlying lesion is acute bilateral suprarenal hæmorrhage, the term Waterhouse-Friderichsen syndrome has been applied to the clinical condition. This syndrome is usually associated with meningococcal septicæmia, and is more common in infants than in adults.

Acute suprarenal insufficiency may also complicate surgical shock and severe burns, the biochemical changes in the blood resembling those found in the more severe phases of Addison's disease.

**Diagnosis.**—The diagnosis of acute suprarenal insufficiency as a complication of infections, surgical shock and burns, is often a matter of assumption, based on experimental evidence. That of the Waterhouse-Friderichsen syndrome is only occasionally made in life, but is suggested by early cyanosis, collapse and fall of blood pressure in a patient suffering from a meningococcal infection. Subacute adrenal insufficiency may develop with any severe infection but the diagnosis is not easily substantiated.

**Treatment.**—Treatment is similar to that described for the crises of Addison's disease.

### ADRENO-GENITAL SYNDROME

**Synonym.**—Virilism.

**Definition.**—A combination of hirsutism with amenorrhœa, or oligomenorrhœa. There are two clinical types, adipose or muscular.

**Ætiology.**—The immediate cause is hypersecretion of androgenic hormone by the adrenal cortex, and this is the only type of hypersecretion in the muscular variety of the disease. In the adipose variety there is also hypersecretion of glucocorticoid

and it is not always possible to differentiate between this adipose type and incomplete forms of Cushing's syndrome, particularly when the latter is associated with coincident androgenic features. The excess of androgen inhibits pituitary gonadotrophic function. There appears to be a greater incidence among Jewish, Celtic and Mediterranean people. There is, however, no sharp dividing line between milder cases of the disorder and accepted normality.

**Pathology.**—The lesion is an adenoma, a carcinoma or a bilateral hypertrophy of the adrenal cortex. The cells have an affinity for the Ponceau-fuchsin stain, and are thought to arise from the inner androgenic zone of the cortex. There may be a general lymphoid hyperplasia, and a large thymus. The ovaries tend to be atrophic and cystic.

**Symptoms.**—The changes usually begin at or soon after puberty, but may not become prominent until the late teens, or sometimes in the twenties, or later. The essential feature is an excessive growth of hair on the side of the face, the upper lip and chin, the forearms, thighs, buttocks and legs and on the trunk. The last may be only slightly affected in the form of a linear growth of hair extending from the usual feminine horizontal upper limit of pubic hair upwards along the linea alba to the umbilicus; or the hair may cover the abdomen and chest, and tufts of hair surround the nipples. Menstruation may cease altogether, or there may be oligomenorrhœa. The uterus may become small or may fail to develop, but more usually there is no gross change in its size. The clitoris may be normal or appreciably enlarged, sometimes resembling a small penis. The breasts may be atrophic or undeveloped, but when there is adiposity this feature is obscured. The adipose type is more common. Fat is deposited on the face, neck, breasts, abdomen, pubes and thighs, leaving the legs and forearms thin. In the muscular type the normal feminine contours fail to develop, or may be lost through disappearance of adipose tissue and the muscles are strongly developed with broad shoulders and narrow hips as in the male.

**Complications.**—There may be some degree of pigmentation around the eyes. Psycho-neurosis and psychosis, with loss of heterosexual desire and homosexual tendencies, may be complications. A complete feminine mentality, however, may be associated with virilism, giving rise to a fear of sex conversion and of feminine inadequacy.

**Diagnosis.**—A combination of hirsutism and amenorrhœa makes the diagnosis probable. A tumour should be suspected if the disease has started after the twenties in a person hitherto quite normal, and in no case can it be excluded without investigation. Appreciable enlargement of the clitoris is common with a tumour, or with purely androgenic hyperplasia. An intravenous pyelogram may demonstrate a neoplasm. A more certain method, though not without danger, is perirenal insufflation of 450 ml. of air, the neoplasm being shown surrounded by air in the skiagram. Ovarian tumours (arrhenoblastoma) may produce virilism; they are not always palpable on vaginal examination, and may be revealed by laparotomy.

Androgenic hormone is usually secreted in excess in virilism. If the quantity of 17-ketosteroids excreted in 24 hours is greater than 30 mg. (normal 5 to 12 mg.) an adrenal tumour should be suspected, although higher values than this may be found with simple hyperplasia. Occasionally enormously high values, 180 mg., may be found with an adrenal tumour. If, after removal of an adrenal tumour, the values for 17-ketosteroids fall and then rise again to high levels, malignant metastases or a tumour of the opposite adrenal gland should be suspected. The presence of dehydroisandrosterone in large quantities in the urine indicates neoplasm rather than hyperplasia. Virilism complicating acromegaly is due to hypertrophy of the adrenal cortex. It may also be a feature of gigantism or may be present in big-boned but otherwise normal individuals. These facts justify the concept of a pituitary type of virilism due to an excessive pituitary adrenocorticotrophic stimulation of androgenic type.

Diabetes is not a feature of the adrenogenital syndrome, but in the adipose type

carbohydrate tolerance may be impaired. This is probably due to excessive secretion of glucocorticoids. Values for blood electrolytes are usually normal. Idiopathic or genetic hirsutism is attributed to hypersensitivity of the hair follicles to a normal stimulus and adrenal androgens are assumed not to be secreted in excess. Such patients, however, may later develop oligomenorrhœa or amenorrhœa and it is difficult to make a clear-cut division. Further, moderate cases of adreno-genital syndrome may have values for urinary 17-ketosteroids which are within the normal range, but this does not necessarily mean that the androgens secreted by the adrenal cortex are not in excess of normal.

**Prognosis.**—In the case of hyperplasia, the condition may be stationary or only slightly progressive for many years. Sterility is the rule, but this is not invariable. The successful removal of an innocent tumour may produce a reversion to normal. Carcinoma of the adrenal cortex is very malignant, and metastases or recurrences are common.

**Treatment.**—A tumour should obviously be removed surgically. The opposite adrenal is rarely atrophied in the case of an adrenal tumour that is entirely, or predominantly, androgenic in character. Nevertheless, for safety, cortisone should be given before and for a short time after operation, as in the case of adrenal glucocorticoid-secreting tumours.

The commonest cause of the adreno-genital syndrome, however, is bilateral hyperplasia of the adrenal cortex. Unilateral adrenalectomy often produces a return of menstruation but rarely affects the hirsutism to any appreciable degree and certainly does not affect adiposity. Experience with bilateral subtotal adrenalectomy for this condition is still limited and such a procedure should not be advocated except for very severe cases. One cannot guarantee that the hirsutism will necessarily disappear, because, unfortunately, such disappearance of hirsutism does not always follow even the removal of an adrenal tumour.

Cortisone in large doses, e.g. 50 to 100 mg. daily produces an amelioration of hirsutism and development of the breasts and a return of menstruation. It also causes the disappearance of acne. These ameliorating effects are associated with a reduction of the urinary excretion of 17-ketosteroids to normal and such assays can be used to determine the effective dose of cortisone. The effects only last as long as the cortisone is continued, however, and cortisone given in large doses over long periods has its own disadvantages. Larger doses of œstrogens have been advocated but in the writer's experience their effect is little or nil. Where an ovarian androgenic tumour is present it should be removed. As to local methods of removing hairs, electrolysis has a definite but limited value, but irradiation is contraindicated because of the danger of scars and even of carcinoma. Shaving is acceptable to some women and has some advantages.

## FEMINISATION

This condition is rare compared with virilism. It is due to a tumour of the adrenal cortex in the male, usually malignant. There is a loss of libido and sexual potency, with a general increase in fat deposition and a hyperplasia of the glandular tissue of the breasts. The latter become enlarged, the nipples pigmented and the superficial veins dilated. There may even be some secretion, which can be expressed from the nipples as in incipient lactation. The patient usually dies from malignant metastases, but in one case successful removal of the tumour led to a return to normal. The testes on section show atrophy. It is interesting to note, and of diagnostic significance, that whereas adrenal cortical tumours, producing virilism in women, secrete very large quantities of androgens, similar tumours (not capable of histological differentiation) producing feminisation in man, secrete enormous quantities of œstrogens, e.g. 4000 mouse units in 24 hours. There is a return to normal values, e.g.

200 mouse units, on removal of the tumour, and increasing values if malignant recurrence or metastases follow.

## HERMAPHRODITISM

True hermaphrodites have both male and female gonads, namely, one testis and one ovary, or an ovo-testis in one organ. They are extremely rare, and it is probable that up to the present time not more than 30 cases have been described. Hermaphroditism is normal for some of the lower species, e.g. the worm, and is not a rarity among pigs and goats. In the hen, the right gonad is rudimentary, but if the left ovary is removed the right gonad becomes a testis and the hen grows a comb. Further, any remnant of the left ovary that is left behind may grow into testicular tissue, since the medulla of the ovary is the homologue of the testis. The change of sex in the hen may be so complete that the mother of chicks may become the father of chicks. In man the external genitals may give no indication of the internal genitals. Young, in 1933, described what he regarded as the twelfth case of true hermaphroditism on record. A young "male", tall and athletic, with penis and scrotum, and masculine hair, came to operation for undescended left "testicle". On opening the left inguinal canal, it was found to contain a uterus, Fallopian tube and functional ovary. A portion of the right gonad in the scrotum was excised, and a section showed normal testicular tissue.

True hermaphroditism is genetically determined and is not primarily due to hormonal imbalance. This is well illustrated by the bullfinch, which may have a testis on the right and an ovary on the left, with masculine plumage on the right half of the body and feminine plumage on the left half. Huggins, Cohen and Harden reported another type of true hermaphroditism in which the patient was brought up and behaved as a woman, one gonad was a testis and the other an ovo-testis. Both were removed from the inguinal canal and examined histologically. The patient was athletic and slightly hirsute, had a normal vagina and uterus, and began to menstruate at the age of 14, at which time the clitoris became grossly enlarged and assumed the size of a small penis.

## PSEUDO-HERMAPHRODITISM

**Synonym.**—Inter-sex.

**Definition.**—Pseudo-hermaphroditism is a condition in which there is only one type of gonad, testis or ovary, but in which the external genitals are a mixed representation of male and female characteristics, or characteristic of the opposite sex to the gonads. Strictly the term should be applied only to those cases in which the condition is present from birth, and not to those instances of virilism or feminisation which appear in later life. It is also not intended to include under this heading sexual precocity in the female due to an adrenal tumour and associated with hirsutism. Classification according to the type of gonad is the simplest, *i.e.* testicular pseudo-hermaphroditism and ovarian pseudo-hermaphroditism.

**Ætiology and Pathology.**—Pseudo-hermaphroditism is sometimes due to genetic factors unrelated to hormones, when, for example, there is failure of development of genital structures or persistence of rudimentary features. Of more classical importance are the types which are due to excessive secretion of hormones, commencing in foetal life. Experimentally the embryo can be influenced by the injection into the mother of androgens or of oestrogens.

Ovarian pseudo-hermaphroditism (where the gonad is the ovary) is due to excessive secretion of adrenal androgens, both in foetal life and subsequently, although



maternal androgens may well play a part. It can be shown clinically and by hormone assay that an excess of adrenal androgens is secreted after birth. Androgens produce enlargement of the clitoris or phallus, enlargement of the prostate, atrophy of the testes by inhibiting pituitary gonadotrophins, growth of facial and bodily hair and muscular development with relatively broad shoulders. Testicular pseudo-hermaphroditism, due to excessive secretion of adrenal oestrogens, is less definite an entity.

**Main clinical types: (A) OVARIAN PSEUDO-HERMAPHRODITISM.**—The female pseudo-hermaphrodite possesses ovaries, but has a masculine configuration, with the external genitals simulating those of the male. The basis of the condition is difficult to explain unless it is assumed that it is comparable to the adrenal virilism of the adult, and due to hyperfunction of the adrenal cortex commencing in foetal life. Although to be within our definition such cases should show abnormalities at birth, these may not be gross until later childhood and may be further accentuated at puberty. The psychic and sexual behaviour of the pseudo-hermaphrodite varies in different individuals, and is often independent of the physical or endocrine basis. Thus the hirsute, testicular pseudo-hermaphrodite may be essentially feminine in outlook and libido, and capable of functioning to complete satisfaction of herself and partner in coitus. Some are ambisexual. Apart from indisputable pseudo-hermaphroditism, it is obvious that a number of people have the physical characteristics (apart from genitals), emotional reactions and libido of the opposite sex.

**(B) TESTICULAR PSEUDO-HERMAPHRODITISM.**—The commonest and most easily understood type is the male in whom the formation of the external genitals is incomplete, the two scrotal folds remaining ununited (cf. hare lip), and enclosing a vagina-like cavity, one or more inches in depth. The penis may be incomplete, or *hypospadias of varying degree may be present, or the penis may be so inadequately developed as to represent a clitoris.* The patient is then brought up as a girl, until the appearance of masculine hair at puberty and the failure to menstruate lead to further investigation. The vagina is found to be false, the uterus absent and the gonads testicles. The last, being retained in the abdomen, have the characteristics of cryptorchid testicles, namely, absence or destruction of the spermatic tubules, and increase in the interstitial cells. Nevertheless, the secretion of male hormone may be deficient, and the patient be of eunuchoid type. Chapple has described the case of a young, beautiful woman, with no hirsutism, with a female figure, well-developed breasts and normal feminine libido, who in spite of a short vagina had satisfying intercourse with males. She came under observation for painful lumps in the groin, which were found to be testicles. No uterus could be detected. It is more usual, however, for the testicular pseudo-hermaphrodite to have hirsutism and other secondary male sexual characteristics. It is difficult to understand why, of two pseudo-hermaphroditism with testes and female external genitals, one should have male hair and bodily form and another be a beautiful female. Obviously the genetic factors are more important than the endocrine. As regards the sexual organs other than the gonads there is considerable variation, e.g. *hypospadias only; with a vagina; with a vagina and Fallopian tubes; with a vagina, uterus and tubes.* The testes may be in the pelvis, the inguinal canals, the labia or in the scrotum.

**Diagnosis.**—The recognition of pseudo-hermaphroditism is not difficult, although it may not become evident to the lay person until late childhood or puberty. Urethroscopy may give evidence of value. In adrenal pseudo-hermaphroditism there is a *common urogenital sinus, without a separate external urethra.* In addition, if the excretion of 17-ketosteroids in the urine is appreciably raised, the adrenal origin of the condition can be strongly suspected. The elucidation of the underlying pathology may, however, be impossible unless laparotomy is undertaken. Many patients present themselves with lumps in the inguinal canal, and it is only removal and section of these gonads that the real sex can be determined. W

pseudo-hermaphroditism is due to excess of adrenal androgens there may be attacks of adrenal insufficiency of Addisonian type, occurring either spontaneously or during the course of infections. Some, however, are more prone to attacks of hypoglycaemia. The probable explanation in both cases is that the androgen-secreting cells have displaced those which secrete the mineralocorticoids and glucocorticoids.

**Prognosis.**—When the disorder is due to an excess of adrenal androgens it may be modified by cortisone or bilateral adrenalectomy before puberty.

**Treatment.**—If help is not sought before adult life, treatment should depend upon the sexual inclinations of the patient. If these are female, the clitoris should be amputated and, if necessary, the vagina enlarged. The removal of testes may diminish the hirsutism. In the child the removal of testes would prevent hirsutism, but in view of some testicular pseudo-hermaphrodites having beautiful feminine configuration without hirsutism and the fact that the testis does secrete oestrogens, it is considered by some better to wait until puberty gives an indication of what is likely to develop. When the outlook and libido are masculine, a plastic operation can repair or create a scrotum and abolish the hypospadias.

Pseudo-hermaphroditism due to excessive secretion of adrenal androgens can be treated with cortisone or bilateral subtotal adrenalectomy. This operation should be performed before puberty, and when it proves inadequate it may still render the condition more susceptible to moderate doses of cortisone. Cortisone acts by suppressing the secretion of androgens by the adrenal. It also prevents attacks of adrenal insufficiency, although, surprisingly, these attacks are also abolished or minimised by bilateral subtotal adrenalectomy.

## CUSHING'S SYNDROME

**Definition.**—A condition of plethoric adiposity of the face and trunk, associated with weakness, hypertension, diabetes, scanty menstruation, osteoporosis, red lineæ distensæ and a negative nitrogen balance.

**Ætiology.**—It is more common in females. It often begins during pregnancy but occurs also at puberty and the menopause. It may occur at any age. The symptoms are due to hypersecretion of glucocorticoids by the adrenals. Androgens are also secreted in excess in some cases.

**Pathology.**—There may be adrenal cortical hyperplasia, an adenoma or a carcinoma. In simple hyperfunction the size, weight and even histology of the adrenals may be normal. Nodular adrenals, due to adenomata, may be found in children. When there is a neoplasm in one adrenal the opposite gland may be atrophied, as excess of cortisone in the blood inhibits the secretion of pituitary corticotrophin. Cushing found a pituitary basophil adenoma in some patients and postulated this as the primary lesion, but the finding is by no means constant. Crooke found hyalinisation and vacuolisation of the pituitary basophil cells in all cases, but these changes are produced by an excess of cortisone in man and experimental animals and are not ætiological. However, in the case of adrenal hyperplasia, the primary stimulus is probably the pituitary and an excess of corticotrophin has been found in the plasma (Parrott). The source of corticotrophin is probably the transitional basophil cells but the eosinophils are also implicated, as in acromegaly. There are probably two varieties of corticotrophin. An ovarian tumour consisting of adrenal cortex type cells, may rarely cause Cushing's syndrome; and carcinoma of the thymus has been found. The liver is loaded with fat. The pancreatic islet cells are hypertrophic in the young.

**Symptoms.**—The face is rounded, plethoric and adipose. Fat is also deposited on the chest, the breasts, the buttocks and the abdomen. The distal extremities are thin, except in children, and even the thighs and upper arms may have lost fat. Thus

there is mobilisation as well as deposition of fat. Not all patients are grossly fat. The breasts may be enlarged and acrocyanosis may be a conspicuous feature. Red or purple lineæ distensæ are often present on the lower abdomen, in the groins, the lumbar regions, the axillæ and on the breasts, but they are not constant. There may be amenorrhœa or impotence and the latter may be associated with gynæcomastia and testicular atrophy. Hirsutism is found in women when there is also excessive secretion of adrenal androgens. Muscular weakness and osteoporosis are associated with excessive catabolism of protein and a negative nitrogen balance. Parathyroid function is usually normal.

The bones are rarefied and softened, so that the vertebræ are compressed, and the patient develops kyphosis and round shoulders, with a diminution in height. Lordosis helps to accentuate an adipose pendulous abdomen, and may give rise to troublesome backache; but sometimes pathological fractures of the vertebræ and ribs have escaped attention. The blood pressure is raised, and there may be a secondary ischæmic nephritis. In a few patients, fatal malignant nephrosclerosis has been recorded. Diabetes mellitus may be present in varying degrees of severity, and those patients who manifest no diabetic symptoms invariably show a delayed fall in blood sugar in the carbohydrate tolerance test. Pigmentation of the orbits and nipples may be present. Migrainous headaches are not infrequent, but changes in the optic nerves or visual fields are rare, since basophil adenomas are usually microscopic in size. The thyroid gland may be enlarged, but there is rarely evidence of hyperthyroidism.

**Complications.**—The patients are liable to intercurrent infections, due especially to staphylococci.

**Diagnosis.**—The clinical picture is not difficult to recognise. Osteoporosis can be shown radiologically and the sella turcica is rarely enlarged. Perirenal insufflation may reveal an adrenal tumour and, when the kidney is displaced, depression of the renal calyces may be demonstrated in the intravenous pyelogram. An excess of urinary 11-oxysteroids (glucocorticoids) may be shown by the Talbot copper reduction method, formaldehydogenic assays or chromatography, and methods of assay of blood corticosteroids are being evolved. 17-ketosteroid excretion in the urine is usually normal; high values suggest neoplasm. A relative polymorphonuclear leucocytosis, absence of eosinophils, a low blood potassium and alkalosis are found in some cases. The serum calcium and phosphorus are normal but the phosphatase may be raised.

**Prognosis.**—The condition is usually progressive, ending in death from cardiac failure or intercurrent infection.

**Treatment.**—An adrenal or ovarian tumour should be removed. When there is no tumour, irradiation of, or the insertion of, radon seeds into the pituitary may cause improvement or recovery. The author believes, however, that subtotal adrenalectomy is the treatment of choice. The operation can be done in one stage with two lumbar incisions. One-eighth of the adrenal gland is left behind. Cortisone, 200 mg. daily by mouth, is given the day before operation and continued for 5 days. The dose is then gradually reduced. Adrenal insufficiency is indicated by anæmia, anorexia, nausea, weakness and rapid pulse. Autogenous adrenal grafts, which have been stored at very low temperature, can be inserted in such cases, although cortisone should still be given in the acute stage. Cortisone should also be prescribed when an adrenal tumour is being removed, since the opposite adrenal may be atrophic. Cortisone has made adrenal surgery safe and is invaluable.

## ADRENAL MEDULLARY TUMOURS

Three distinct types of tumour arise in the adrenal medulla; phæochromocytoma, derived from chromaffin cells, neuroblastoma, derived from embryonic sympathetic nerve cells, and ganglioneuroma, derived from adult ganglion nerve cells.

## PHŒOCHROMOCYTOMA

**Synonyms.**—Paraganglioma; Hyperadrenalism.

**Definition.**—A condition in which there is excessive secretion of adrenaline and nor-adrenaline by an adrenal medullary tumour, arising from the chromaffin cells in the adrenal medulla, or occasionally from ectopic chromaffin cells in other parts of the body, e.g. para-aortic, thoracic or cervical.

**Ætiology.**—This is unknown. A small percentage of cases are bilateral.

**Pathology.**—The tumours are usually innocent, only a small percentage being malignant; but even when malignant, such tumours rarely metastasise. They are usually, but not invariably, small and the size of the tumour is no indication of its degree of functioning. The cells stain yellow with salts of chromic acid as in the case of the chromaffin cells of the normal adrenal medulla. Phæochromocytomata secrete adrenaline and nor-adrenaline in quantities greatly in excess of normal and the secretion may be continuous or paroxysmal. The proportion of adrenaline and nor-adrenaline secreted varies in different cases and cannot be predicted on clinical grounds. Their pharmacological actions are not identical, and perhaps the most important difference is that adrenaline causes acceleration and nor-adrenaline slowing of the pulse. Nor-adrenaline also differs from adrenaline in having a relatively slight glycogenolytic action. Both can be extracted from the tumours. In the clinical description, the term adrenaline will be used to include both adrenaline and nor-adrenaline, unless otherwise specified.

**Symptoms.**—Characteristically these are due to paroxysmal secretion of excess adrenaline which floods the blood-stream, producing a hypertensive crisis. Attacks may occur at any time with variable intervals. The systolic blood pressure may rise from 130 to 300 mm. and the change in the diastolic is usually of a smaller order. Other features are sub-sternal pain or angina, pallor, perspiration, nausea, vomiting, agonising headaches, cold clammy hands which are sometimes cyanosed, shivering, cramps of the calf muscles, mydriasis, pyrexia, anxiety and fear of death. The beat of the heart may be so forceful as to shake the chest and the bed. Tachycardia is common, but bradycardia occurs in some cases. There may be left ventricular failure with cardiac asthma. The thyroid is not uncommonly enlarged during an attack. Sweating is often a prominent and characteristic feature, although sweat glands are said to be cholinergic and not adrenergic. The fundi may show papilloedema, retinal hæmorrhages and exudates. The urine may be normal but frequently contains albumin and granular casts. Malignant nephrosclerosis has been recorded. The basal metabolic rate is increased in attacks and there is often pyrexia. Leucocytosis also occurs. The paroxysms last for 5 to 30 minutes and the patient is left in a state of exhaustion from which it may take hours, or days, to recover.

In other cases, as has been indicated above, the excessive secretion of adrenaline is constant and the condition may resemble essential hypertension or malignant progressive hypertension. Where paroxysmal attacks are added to a pre-existing chronic hypertension, the dangers of such attacks are obviously greater. Although emotion, excitement, straining at stool, exertion and other happenings may precipitate an attack, there is often no obvious initiating factor.

**Diagnosis.**—The condition can occur at any age and in either sex. The diagnosis can be made, with a considerable degree of certainty in the paroxysmal variety, on the basis of the clinical picture. Tomography or intravenous pyclography may provide confirmation, at the same time indicating the site of the tumour which, strangely, is much more common on the right side than on the left. Peri-renal insufflation is inadvisable because it may precipitate an attack. The same applies to attempted manipulation in the lumbar area for this express purpose, although it is rare for it

to be successful in producing an attack. During paroxysms, there is hæmoconcentration with increased hæmoglobin and hæmatocrit values and the serum potassium may be raised.

When a phæochromocytoma is present the intravenous injection of 0.025 mg. of histamine di-phosphate in 2.5 ml. of normal saline will cause an enormous rise of blood pressure, sometimes amounting to a hypertensive crisis, which is one reason for avoiding the test unless the diagnosis on clinical grounds is improbable. Its mechanism of action is unknown. A simple and safe test, evaluated by Pickering and colleagues, is the measure of heat elimination from the hand by the change of temperature of water in a calorimeter in which the hand is immersed. Because of vasoconstriction the calories produced, under comparable standard conditions, are approximately only one-third of the normal. Another type of test depends on the use of adrenergic blocking substances like piperoxane and dibenamine, which have a greater affinity for the adrenaline receptor end organ than has adrenaline. Thus they both produce a fall of blood pressure, in the presence of a phæochromocytoma, in contrast to the mild increase in blood pressure which occurs when hypertension is not due to adrenaline. Both are injected intravenously and are preferably added to a slow intravenous saline infusion. Piperoxane is injected in doses of 0.25 mg. per kg. body weight over a period of 2 minutes. It may also be given in 2 ml. of normal saline injected slowly and the maximum dose should not exceed 20 mg. The injection may have to be stopped because of headache, nausea or sub-sternal pain. Dibenamine hydrochloride is given in doses of 7 mg. per kg. of body weight dissolved in 300 ml. of a 5 per cent. solution of glucose in normal saline over a period of 1 hour. The fall of blood pressure lasts for 24 hours and this makes it suitable also for therapeutic control. This also applies to phentolamine (Regitin), given in doses of 0.08 mg. per kg. body weight during 1 to 2 minutes. It produces a rapid fall of blood pressure which lasts a few hours. These various adrenergic substances have clinical formulæ very closely related. Another test, which has been developed by Peart and colleagues, based on the work of Euler and Goldenburg, is the measurement of adrenaline-like pressor substances in the urine. After hydrolysis with hydrochloric acid, so that only the free amines are estimated, these are selectively adsorbed on alumina. They are assayed biologically, using the blood-pressure response of the *anæsthetised rat* and measuring the response against known solutions of adrenaline and nor-adrenaline. The fact that dihydro-ergotamine reverses the action of adrenaline but not that of nor-adrenaline permits a measurement also of the relative quantities of each. This ratio varies considerably in different cases. As an indication of the value of this test the quantity of pressor amines, found in the presence of a phæochromocytoma, may be 10 to 40 times that in control cases or in the same case after operation. It is much more reliable than the adrenergic blocking test which may give unreliable results in some cases for no apparent reason.

**Treatment.**—The tumour should be removed. During its manipulation there may be a rapid and dangerous rise of blood pressure which can be controlled by piperoxane, the effect of which lasts some 15 minutes. After removal of the tumour there is a dangerous drop in blood pressure and this is controlled by nor-adrenaline in strength of 10 to 20 mg. per litre of normal saline, the rate being adjusted according to the blood pressure. Atropine should not be used before operation, as it appears to interfere with the response to nor-adrenaline. In some patients the ultimate blood pressure after operation does not fall to normal and in others it may continue to rise. If assays of urinary adrenaline become normal, any residual hypertension can be attributed to irreversible changes in the peripheral vascular system. Even so, the general symptoms and the fundi always show improvement. If, however, adrenaline is still present in high concentration in the urine, a tumour on the opposite side should be suspected.

## NEUROBLASTOMA OR SYMPATHOBLASTOMA

This highly malignant tumour is found usually in young children but it can arise at any age, and on rare occasions, when it is congenital, it can be large enough to obstruct labour. Symptoms and signs are more often due to metastases than to the primary growth. In the Pepper type, which affects children under 1 year, the liver is enormously enlarged and the disease is rapidly progressive. In the Hutchison type, which is more common in older children, metastases are found in bones and the progress of the disease is more gradual. The skull is invaded, especially in the region of the orbits, and bruising of the eyelids followed by exophthalmos are amongst the commonest presenting symptoms. Skull radiograms are indistinguishable from those in sarcoma, showing fine spicules of bone radiating from the outer table. Secondary tumours of the long bones are usually palpable and radiograms are here diagnostic. The periosteum is raised by subperiosteal growth which does not involve the cortex until the later stages of the disease.

**Prognosis.**—Death is usual within a year, but examples of spontaneous recovery are on record.

**Treatment.**—Excision of the primary growth can be combined with radiotherapy, but the results are unsatisfactory.

## GANGLIONEUROMA

This is a rare benign tumour which produces symptoms only because of its size. It is found in childhood and in adult life.

## THE SEX GLANDS

Hypogonadism may be secondary to failure of pituitary function, as has been described in previous articles, *e.g.* Simmonds's disease and Fröhlich's syndrome; or it may be a primary failure of gonadal function, *e.g.* eunuchoidism; climacteric. The latter condition in males is not generally recognised, but is met with in some men over 50, with loss of libido and potency, hot flushes, anxiety and inability to concentrate; the symptoms are ameliorated by testosterone therapy. Impotence in man is not infrequently met with at all ages, and is usually psychogenic. Whereas organic impotence, *e.g.* after traumatic castration, responds dramatically to testosterone, psychogenic impotence does not. The latter may be ameliorated but rarely cured by psychotherapy. Temporary functional impotence is more common than is generally realised, and is caused by excessive anxiety or fatigue.

## EUNUCHOIDISM

**Definition.**—A condition of primary hypogonadism, or agonadism, originating in embryo, or before puberty. The term is usually restricted to males and this will be observed in the description of this section, but female eunuchoidism does occur. The term eunuchism is sometimes applied to complete absence of gonadal function.

**Ætiology.**—The condition is often genetically determined, and there is no obvious cause for the failure of gonadal development; or it may result from bilateral testicular atrophy following mumps, or, rarely, operation for bilateral inguinal hernia. Very rarely, also, both gonads may be involved in strangulated hernia, and be removed. In certain religious sects, castration is performed before puberty in all males, and this

operation was at one time carried out to provide eunuchs (meaning "guardian of the couch") in harems.

**Symptoms.**—The epiphyses of the long bones remain open until the third or fourth decade, or longer, and as there is no deficiency of growth hormone, all true eunuchoids tend to be tall, often very tall. The length of the limbs is much greater than the measurement from the head to the pubis; in normals such measurements are approximately equal. The testes are absent, atrophic or infantile, and the penis small and flaccid. Libido and potency are absent. The secondary sexual characteristics are absent and the patient has a smooth hairless face and high-pitched voice. The pelvis may be of neutral type, or unusually broad for a man. Pubic hair may be present, but it is scanty and limited horizontally. There is a thin type and a fat type, which fact complicates our conception of the disease, but this appears to depend on an inherent endocrine constitution. Thus, whereas in cattle, sheep and oxen, castration is undertaken to produce fatness and invariably does so, in dogs early castration produces fatness in only some 50 per cent. Even the thin eunuchoids tend to put on weight after the age of 40.

**Complications and related Syndromes.**—A syndrome consisting of gynæcomastia, very small testes, azoospermia and increased amounts of gonadotrophins has been described by Klinefelter, Reifenstein and Albright, biopsy of the testes showing hyalinisation of varying degree in the spermatid tubules. The interstitial cells of Leydig appear numerous and prominent, but staining methods show that they are abnormal. The urinary 17-ketosteroids are usually decreased and most of the patients show some degree of eunuchoidism. Heller and Nelson described a similar group, but in which gynæcomastia was a less common finding. These contributions led to the theory that the seminiferous tubules secrete a substance called "inhibin", which inhibits the secretion of anterior pituitary gonadotrophins. Inhibin is said to be a hypothetical oestrogen-like secretion of the seminiferous epithelium. These conditions should be regarded as varieties of eunuchoidism in which some pathological process affects both the seminiferous tubules and the interstitial cells, although the near normal appearance of the latter may be deceptive. The clinical picture is fairly obvious and can be confirmed by the demonstration of an excess of pituitary gonadotrophins in the urine and by failure of the testes to respond to gonadotrophic injections. Biopsy of the testes is important for a complete evaluation, in particular in those rare cases where the size of the testes is not appreciably decreased. True eunuchoidism occurs only when the genetic or pathological processes are evident before or at puberty, but an incomplete post-puberty type is recognised. Primary anterior pituitary insufficiency may be associated with a eunuchoid-like condition, but the author does not think the term "pituitary eunuchoidism" should be permitted as it is confusing and conflicting with definition. It is obvious that in such a condition there is an *absence rather than an excess of pituitary gonadotrophins in the urine.*

Testosterone can be given by injection, 50 mg. of testosterone propionate in oil, twice or thrice weekly; or more conveniently by using the long-acting testosterone phenyl-propionate, injected once weekly or every 2 weeks in the same dosage. By subcutaneous implantation, 8 tablets of 100 mg. each, the effect will last for some 8 months. Methyl testosterone, 10 to 25 mg. tablets by mouth or under the tongue, three times a day are also effective. Sublingual absorption ensures the maximum potency, but swallowing the tablet is quite practicable and efficient, although only two-thirds as effective.

## IMPOTENCE AND INFERTILITY

Apart from the association of impotency with obvious major endocrine disorders, organic endocrine impotency can be due to deficiency or absence of testicular androgenic secretion. Defined as such, it is a rarity, and it can be ruled out when secondary

sexual characteristics are well developed or when nocturnal erections and ejaculations are experienced. Impotency associated with diabetes mellitus is believed to be due to local neuro-vascular pathological changes rather than to deficiency of any androgenic hormone. The commonest cause of impotence is psychological and wherever there is no obvious organic defect, psychological impotence should be strongly suspected. It is a form of sexual neurosis and is usually only part of a general neurosis or anxiety state. Temporary lack of libido and impotence are by no means uncommon and respond to lessening of the strain and effort of daily life, where such is possible, and to reassurance and encouragement. More severe forms of psychological impotence are often refractory to any form of psychotherapy. Testosterone, or methyl testosterone, will produce an almost immediate response in cases of impotence due to deficient secretion of testosterone, but will be ineffective in cases of psychological impotence. This can be used as a therapeutic test in doubtful cases.

Sterility in the male can be due to azoospermia or oligospermia. Biopsy of the testes will show destruction or disorganisation of the seminiferous tubules but the interstitial cells are intact and functioning well. The commonest cause is mumps, but any infection may be responsible. The seminiferous tubules are much more sensitive to toxins than are the interstitial cells. Apart from a drastic decrease in the number of sperm cells, the deficiency or absence of motility and a high percentage of abnormal shapes are evidence of probable infertility. By the nature of the pathological lesion, hormone therapy is unlikely to be effective in male sterility. It is prudent never to declare a patient completely sterile but to use the term "relative infertility".

## CLIMACTERIC

**Synonym.**—Menopause.

**Definition.**—The climacteric, or "change of life", occurs in women about the age of 45 to 50, and its manifestations are due to the cessation of ovarian function and associated changes in the pituitary and adrenal glands. Menopause refers more precisely to the cessation of menstruation. It is one feature of the climacteric.

**Ætiology.**—The primary disorder appears to be cessation of ovarian activity, the ovaries ceasing to respond to gonadotrophic stimuli. There is a secondary hyperactivity of the anterior pituitary gland and of the adrenal cortex. The pituitary secretes an excess of follicle-stimulating hormone, but apparently ceases to secrete luteinising hormone. The ovaries become atrophic and fibrosed.

**Symptoms.**—A great deal depends on the endocrine constitution of the individual. Some women experience almost no symptoms or signs. Others may suffer severe disturbance. Vasomotor instability is manifested by hot flushes over the face and neck, alternating with cold sweats. There is an increase in fat and weight, sometimes very considerable. Hair may grow or increase on the lips and chin, a manifestation of increased activity of the adrenal cortex. Anxiety, nervousness, irritability, emotionalism, tremors and palpitations, may change personality and behaviour pattern. Hypertension may develop at this time, and may disappear spontaneously after months or years, or may be permanent. Pruritus is often troublesome. Many diseases, such as exophthalmic goitre, diabetes mellitus, rheumatoid arthritis and migraine, may have their onset at this time of life, although not necessarily caused directly by the endocrine changes occurring at the climacteric.

The climacteric changes and symptoms often go on for a period of several years, and may even recur after an interval of several years' freedom from disturbance. That they are not entirely brought about by cessation of ovarian activity is indicated by the effects of bilateral ovariectomy in younger women, e.g., 30. The operation may or may not be followed by climacteric symptoms, but in any case at the age of 45 to 50, although menstruation ceased 15 years previously, climacteric symptoms may make their appearance.



**Prognosis.**—Vasomotor, neurotic and hypertensive symptoms tend to disappear spontaneously after some months or years, but adiposity and hirsutism may remain.

**Treatment.**—When there are vasomotor symptoms oestrogens should be given in the smallest dose that proves effective. The synthetic oestrogen, ethinylœstradiol, can be given in an initial dose of 0.01 mg. twice daily or 3000 units or more of the natural oestrogen, œstrone, can be given daily. It is recognised that some patients may require much higher dosage and then nausea may result, especially with synthetic preparations. Although oestrogens are carcinogenic in laboratory animals this should not prevent their administration in the climacteric when they are indicated. A more realistic disadvantage is the possibility of uterine bleeding during the time of administration or on withdrawal. For this reason minimal doses are advised and when the oestrogen is to be discontinued withdrawal should be gradual. Should uterine bleeding take place in a post-menopausal patient, receiving oestrogens or not, uterine carcinoma should be excluded. Sedatives and simple psychotherapy are often beneficial and adiposity and hirsutism are dealt with on the lines advocated in previous sections.

## SEXUAL PRECOCITY

**Synonyms.**—Pubertas Præcox; Macrogenitosomia.

**Definition.**—The attainment of sexual maturity in childhood some years before the normal time of puberty. True sexual precocity is due to pituitary or hypothalamic-pituitary gonadotrophic stimulation. Pseudo-sexual precocity is due to hyperactivity of the adrenal cortex, or of a gonadal tumour, in childhood, leading to premature but incomplete sexual maturity.

**Ætiology and Pathology.**—Sexual precocity may be due to a variety of causes, which ultimately belong to one of three groups, primary gonadal; primary adrenal; primary pituitary or hypothalamic-pituitary. Thus the underlying lesion may be an adenocarcinoma of the testis, a granulosa cell tumour of the ovary, an adenoma or adenocarcinoma of the adrenal cortex, a pineal tumour (which acts pathologically by mechanically stimulating the hypothalamic pituitary mechanism and not by producing any specific hormone of its own), encephalitis, internal hydrocephalus or a third ventricle tumour. There is also an idiopathic familial type of sexual precocity. Whatever the mechanism, the result is a hypersecretion of androgenic or œstrogenic hormone.

**Symptoms.**—In boys, the sexual precocity is shown by enlargement of the penis, development of hair on the pubis and to some extent on the face, and often considerable strength, the Hercules type. In true sexual precocity the testicles are enlarged in proportion to the penis, whereas in pseudo-sexual precocity the testicles, except when there is a testicular tumour, are small and atrophic. This is due to the fact that adrenal androgens inhibit pituitary gonadotrophins. The boys will show obvious sexual behaviour, even running after and attacking adult women, masturbating against their legs, which they may clasp with great strength and may bite with anger if frustrated. Seminal emission is rare with pseudo-sexual precocity. The precocity may begin in very early childhood.

With girls, there are clinically two main types. When the condition is due to ovarian hyperactivity, either primary or secondary to a hypothalamic-pituitary stimulus, it is manifested by qualitatively normal sexual development, pubic hair, well-formed breasts, menstruation and even pregnancy, the last having been recorded as early as 6 years of age. With adrenal tumours, menstruation is usually absent, the clitoris enlarged, the voice deep, and hirsutism occurs on the face and body, as in virilism. These manifestations are due to the secretion of androgenic hormone by an adrenal tumour but adrenal oestrogens may also be secreted.

In both sexes, sexual maturity is associated with premature dentition, and early union of the epiphyses. The latter results in ultimate dwarfism although initial growth is well above average. Although the instincts may be adult, the intellectual activity usually corresponds to the chronological age.

**Diagnosis.**—In girls, an enlarged clitoris and hirsutism suggest an adrenal tumour, whereas homosexual precocity, without hirsutism, may be due to an ovarian granulosa cell tumour, or, more commonly, bilateral adult development of the ovaries, or multiple cystic ovaries. Although, in the two latter instances, the initial stimulus is probably a pituitary one, there is often no gross detectable pituitary or hypothalamic pituitary lesion. In boys with an adrenal tumour, the testes remain infantile, although the penis is big, whereas with a primary pituitary, or hypothalamic-pituitary lesion, the testes tend to be developed to adult size and function. Pineal tumours may be manifested by ocular palsies, papilloedema, somnolence and other hypothalamic features such as polyphagia, adiposity, diabetes insipidus and disturbances in temperature. Precocious puberty may also occur with third ventricle tumours, aqueductal block following encephalitis lethargica, tuberculous or syphilitic meningo-encephalomyelitis, post-measles encephalomyelitis, supra-sellar tumours, neoplasms involving the floor of the third ventricle and tumours of the mamillary bodies and tuber cinereum. Ventriculograms and exploratory cranial operations may be necessary.

**Prognosis.**—Idiopathic or familial sexual precocity may proceed to a normal adult state. Adrenal and testicular tumours are usually malignant, whereas ovarian tumours are generally not so. Intracranial lesions may be fatal. Removal of adrenal or gonadal tumours tends to produce a reversion to normal in the absence of metastases.

**Treatment.**—Adrenal, testicular or intracranial neoplasms should, if possible, be excised. Oestrogens may control sexual behaviour in males with idiopathic or hypothalamic-pituitary precocity.

S. LEONARD SIMPSON.

SECTION VIII  
DISEASES OF THE DIGESTIVE SYSTEM  
DISEASES OF THE MOUTH  
STOMATITIS

CATARRHAL STOMATITIS

**Ætiology.**—Catarrhal stomatitis is common in ill-nourished children during dentition and in association with gastro-intestinal disturbances. In adults it may result from excessive consumption of alcohol or highly seasoned food or excessive smoking. It is sometimes present in the specific fevers, and may also be caused by septic teeth and a dirty or badly fitting plate. It develops rapidly in very ill people whose mouths are not kept clean, especially if they sleep with the mouth open.

**Symptoms.**—The gums and lips may alone be affected. In other cases the whole mouth, including the tongue, is involved. The mucous membrane is red and dry, but excess of mucus may be secreted by the small buccal glands. The tongue is swollen and furred.

The mouth is uncomfortable, and occasionally actual pain is present, especially on mastication. The patient complains of a nasty taste, especially on waking, and fetor oris may be present. The general health is unaffected.

**Treatment.**—The teeth should be cleaned with special care, and the tongue kept as free as possible from fur by scraping. A mouth-wash should be used after each meal, and glycerin of borax should then be applied to the inflamed parts.

ULCERATIVE STOMATITIS

**Ætiology.**—Ulcerative stomatitis is not a specific disease, but is, like catarrhal stomatitis, produced by the action of various irritants. It can develop from neglected cases of catarrhal stomatitis, and is a prominent symptom of mercurial poisoning and scurvy. The following are special varieties of the condition.

(a) RECURRENT ULCERATION IN ADULTS.

Single or multiple superficial ulcers may occur on the mucous membrane of the cheeks, lips, tongue and gums. They have a grey surface with a red, but not raised, border, and the intervening mucous membrane is generally healthy. In severe cases, however, the ulcer is deeper and its base bright red. Each ulcer generally lasts only a few days, but a patient may have one or more in his mouth for months, or even years, without an interval. They are often very painful, especially on chewing, and they may make it impossible to take any acid food. Their ætiology is most obscure; the condition is aggravated by oral sepsis and ill-fitting plates, and some ulcers may begin as abrasions produced by the careless use of a tooth-brush, but it appears to depend primarily upon some obscure constitutional defect. It is not associated with any disturbance in digestion or with any special form of gastric secretion. The saliva is not acid and the ulcers do not appear to be infective in origin. In some cases there is an undoubted nervous element in causation, and immediate cure may follow relief from anxiety, suspense or emotional strain.

No treatment beyond scrupulous attention to oral hygiene and the application

of silver nitrate to each ulcer as it appears is, as a rule, of any use. Cures have been reported from the use of nicotinamide, 100 mg., three times a day for a month.

(b) APHTHOUS (OR VESICULAR) STOMATITIS.

**Ætiology.**—Aphthous stomatitis occurs especially in children, either alone or associated with some febrile or digestive disorder. It is due to a filterable virus which is latent until activated by such an infection as pneumonia.

**Symptoms.**—The aphthæ consist of small slightly raised vesicles, each surrounded by a red areola. Within 24 hours the vesicles rupture, leaving grey ulcers, 2 to 4 mm. in diameter, with bright-red margins. The ulcers heal rapidly. They occur especially on the inner surface of the lips, the edges of the tongue and the inside of the cheek. In severe cases the pillars of the fauces may be affected. The mouth feels sore, and the child is unwilling to take food. Salivation is frequently present.

**Treatment.**—The mouth must be carefully washed after meals with potassium chlorate solution (gr. 10 to 1 fl. oz.). In severe cases the ulcers may be treated with silver nitrate.

(c) FOLLICULAR STOMATITIS.

**Ætiology.**—Follicular stomatitis may occur at any age, but especially in nursing women.

**Symptoms.**—The mucous follicles of the lips and cheeks become inflamed and swollen; the epithelium over them breaks down, and ulcers, 3 to 5 mm. in diameter, result. They may cause no symptoms, but more commonly they give rise to a considerable amount of pain on taking food and to reflex salivation.

**Treatment.**—The ulcers heal rapidly after being touched with silver nitrate.

(d) MERCURIAL STOMATITIS.

See pp. 233 and 381.

(e) ULCERO-MEMBRANOUS STOMATITIS (VINCENT'S STOMATITIS).

**Ætiology and Pathology.**—Severe ulcero-membranous stomatitis is a contagious disease, caused by infection with the same spirochaetes and fusiform bacilli which cause Vincent's angina (see p. 537).

**Symptoms.**—All parts of the mouth and pharynx may be involved, but the margins of the gums are specially liable to be affected. The stomatitis is similar to that caused by mercury, and the gums may be so swollen and bleed so readily that scurvy is simulated. The breath has a characteristic fetid odour, and the tender gums may make mastication painful.

The disease is sometimes acute, but more often runs a chronic course and is often followed by pyorrhœa alveolaris. It generally gives rise to but little constitutional disturbance.

**Treatment.**—The teeth should be scaled, and the ulcerated margins of the gums treated by the application of 10 per cent. chromic acid for 1 minute, followed by hydrogen peroxide kept in the mouth for 2 minutes. Penicillin lozenges should be used by tucking one as high as possible into the buccal sulcus above the last upper molar. It will last from 1 to 3 hours and then should be replaced by another. One will last all night. This should be kept up continuously for about 4 days or until a day or two after acute symptoms have subsided. In severe cases intramuscular doses of penicillin should be given, 500,000 units daily for 4 days. The patient should be given 300 mg. vitamin C daily for a fortnight, followed by 50 mg. daily for 6 months. Sodium perborate should be used as a tooth-powder and hydrogen peroxide as a mouth-wash. Smoking should be forbidden.

## (f) GANGRENOUS STOMATITIS.

**Synonyms.**—Cancrum Oris; Noma.

**Ætiology.**—This rare disease occurs in children, especially girls between the ages of 2 and 5, who live under very insanitary conditions. It generally develops during convalescence from an acute fever, especially measles, and less frequently scarlet and typhoid fever. It also forms part of the clinical picture of agranulocytosis (p. 756).

**Symptoms.**—A sloughing ulcer develops in the inside of the cheek or on the gums; it rapidly spreads and leads to brawny induration of the skin of the cheek. Occasionally it heals spontaneously, but more frequently it perforates the cheek or spreads to the tongue, chin, jawbone or eyelid and eye.

Cancrum oris is accompanied by severe constitutional symptoms, the patient being prostrated with a high temperature and rapid pulse. Diarrhœa or bronchopneumonia frequently follows, and death generally occurs between 7 and 10 days from the onset.

**Treatment.**—The only adequate treatment for cancrum oris in children is to destroy the diseased part as completely as possible with the cautery. Intramuscular injections of penicillin should be given in massive doses related to the child's weight. For the treatment of agranulocytosis see p. 757.

## THRUSH

**Ætiology.**—Thrush is most common in weak, emaciated infants with gastrointestinal symptoms, who have been fed with an unsuitable diet, and whose mouths have not been kept clean. Acid fermentation of food remnants leads to catarrhal stomatitis, and this is likely to be followed by thrush. Thrush occurs in epidemic form in badly managed institutions, being spread by dirty feeding-bottles. The disease may also occur in enfeebled adults in the late stages of tuberculosis, cancer and diabetes, and in severe febrile infections.

**Pathology.**—Thrush is caused by infection with *Candida albicans*—a fungus, the filaments of which form a dense felt-work in the superficial epithelial layer of the mucous membrane.

**Symptoms.**—Thrush generally appears first on the tongue, and then on the cheeks, lips, hard palate, tonsils and pharynx. In rare cases the entire buccal mucous membrane is covered, and the infection may even spread to the vocal cords, œsophagus and stomach. It begins as slightly raised, pearl-white spots, which gradually grow and then coalesce. The white material can be readily detached, leaving either intact mucous membrane, or, in more severe cases, a bleeding and ulcerated surface.

**Diagnosis.**—Adherent milk curds may superficially simulate thrush. In aphthous stomatitis the white patches are at first vesicles and then definite ulcers, and salivation is present in contrast to the dry mouth in thrush. A definite diagnosis can be made only with the aid of the microscope.

**Treatment.**—Thrush should be prevented by keeping the mouth clean and babies' bottles sterilised. It is important to improve the patient's general health as well as to give local treatment. The mouth should be washed with sodium sulphite solution (gr. 60 to 1 fl. oz.), after which the fungus can be easily scraped off. Infected patches may be painted daily with a 1 per cent. solution of gentian violet.

## PYORRHŒA ALVEOLARIS; CHRONIC PERIODONTITIS

**Ætiology and Pathology.**—Stagnation of food mixed with pyogenic organisms between the teeth leads to inflammation of the edge of the gums—marginal gingivitis.

The attachment of the muco-periosteum to the neck of the tooth is destroyed, and a pocket develops between the tooth and the gum. The margin of the alveolar process is then slowly eroded as a result of rarefying osteitis, until it may finally be replaced by granulation tissue. Stagnation of infective material in the pocket leads to gradual extension of the disease and aggravation of the gingivitis. Pus is produced, the condition at this stage being commonly known as *pyorrhœa alveolaris*.

**Symptoms.**—In marginal gingivitis the edge of the gum of one or more teeth is red and swollen and bleeds with abnormal ease when brushed, the first part to be affected being usually the interdental papillæ. When *pyorrhœa alveolaris* has developed, pockets are present round the teeth, and pus can generally be seen exuding from the edge of the gum. Even when none is seen on first examining the mouth, beads of pus appear if the edges of the gum are pressed. In chronic cases the teeth are often loose. Reflex salivation occurs, and an excessive quantity of mucus is secreted by the small mucous glands of the mouth. This is a common cause of aerophagy. The accumulation of decomposing food, debris and pus in the pockets round the teeth produces an unpleasant taste in the mouth, most marked on waking in the morning, and is a common cause of foul breath. There is no pain, and the slight discomfort which may be present is generally insufficient to induce the patient to consult a dentist.

**Treatment.**—In early cases the disease can be arrested by scaling and treatment of the pockets with strong antiseptics. When the supporting bone has been destroyed to more than half the depth of the root, extraction is necessary. In intermediate cases the gum should be cut away in order to eradicate the pockets. The patient should then be given instructions regarding oral hygiene.

## DENTAL CARIES

The immediate cause of dental caries is unknown, but two main theories have been put forward. The chemico-parasitic theory postulates that acid produced by bacterial fermentation of carbohydrates causes decalcification of the enamel and dentine, the acid being kept in contact with the tooth by a plaque of debris on its surface. The alternative theory is that the initial change is a degradation of the organic matrix of the enamel by bacterial enzymes and that the inorganic matrix subsequently disintegrates. It is generally agreed whichever theory is correct that caries is due to the activity of bacteria.

**Symptoms.**—Carious teeth are tender, and their presence renders mastication painful. The patient therefore avoids using the affected teeth, and this favours the deposit of tartar and the stagnation of food. If many teeth are affected the food is bolted, so that indigestion is likely to occur owing to insufficient mastication, quite apart from possible infection of the alimentary canal caused by swallowing septic material from the mouth. The irritation produced by the decomposition of stagnant food around the teeth gives rise to marginal gingivitis and *pyorrhœa alveolaris*. Oral sepsis produced in this way is of much more importance than that caused by the caries itself, as the quantity of decomposing material and bacteria swallowed from dental cavities is comparatively small, and no local absorption of toxins or bacteria can occur so long as the pulp cavity is not reached. When the latter becomes infected, absorption of toxins is likely to lead to enlargement of the cervical glands, especially in children, and the chronic inflammation produced in this way is a common precursor of tuberculous infection of the glands. Inflammation of the pulp spreads to the periodontal membrane and may finally produce an alveolar abscess.

Dental caries is the most common cause of toothache, and pain is often referred to various situations more or less remote from the teeth.

**Prophylaxis.**—The incidence of caries can be significantly reduced by the addi-

tion of vitamin D, calcium and phosphorus to a diet which is deficient in these substances, and the improved dentition of British children in the post-war years was attributed to the war-time provision of extra milk and vitamin D. Calcium carbonate was also added to the flour and the vitamin D content of margarine was increased. Refinement of flour is detrimental because it removes phosphorus and increases the content of phytic acid, a substance which interferes with the absorption of calcium. Caries is especially prevalent in regions where there is a natural deficiency of fluorine and it has been shown that the artificial fluoridation of drinking water, to an optimal value of 1.0 to 1.2 parts per million significantly reduces its incidence. Concentrations above this level are liable to cause mottling of the teeth. Fluorides can also be applied directly to the teeth, and four applications of a 2 per cent. solution of sodium fluoride at weekly intervals will usually reduce the amount if not entirely prevent the onset of caries.

*Oral hygiene.*—The teeth should be brushed regularly vertically from the gums to the teeth, and wooden tooth-picks used to clear and massage the gum spaces between them. Tincture of iodine may be applied on a wisp of wool on the end of the tooth-pick. The mouth should be well rinsed after meals. Ideally, sugar and sticky carbohydrates should be eliminated from the diet, and they should be replaced by natural unrefined vegetable foods.

*Treatment.*—This is the province of the dental surgeon. Removal of all the milk teeth in children may cause narrowing of the dental arch and consequent crowding of the permanent teeth, but this can be easily remedied by treatment, whereas the septic condition of the mouth caused by extensive caries may lead to permanent ill results.

#### APICAL INFECTION

*Ætiology.*—Infection of the apex of the root of a tooth can occur only if the pulp is dead, except in rare cases of extensive caries.

*Symptoms.*—Apical infection may be acute or chronic. In the former an alveolar abscess forms, which gives rise to the usual symptoms and signs of inflammation. Chronic apical infection, on the other hand, frequently gives rise to no pain or discomfort, and no signs recognisable on ordinary examination. It can then be recognised only in a good radiograph.

*Treatment.*—In cases of moderate severity the pulp canal should be opened and sterilised by antiseptics, e.g. ammoniacal silver nitrate followed by formalin, or penicillin 25,000 units per ml., or ionisation with zinc chloride, or diathermy applied down the root canal, and the root should be filled to its apex with an impervious material. In more advanced cases, and in all in which secondary symptoms are present, extraction should be performed without delay and the socket should be curetted.

#### HALITOSIS (BAD BREATH)

An offensive odour to the breath is mainly of importance because it may give rise to serious feelings of inferiority and self-consciousness if the sufferer is made aware of his complaint. In most cases of halitosis the individual is, in fact, unconscious of any bad smell—on the contrary, when he is continually complaining of his breath it is often found to be due to an obsessional neurosis and that he has actually no odour at any time. A pungent heavy breath is frequently due to bad teeth, decaying food in dental cavities, pyorrhœa, or to cheesy putrefactive material in the crypts of the tonsils. Ozæna (see p. 956) is a further local cause, as may, rarely, be infected accessory nasal sinuses. Decaying material on the back of the tongue may become

offensive and pulmonary conditions, such as lung abscess or bronchiectasis are other causes.

Hepatic or intestinal causes of halitosis can less easily be demonstrated and, though it is popularly believed that chronic constipation may be a cause, this is, in fact, very doubtful. The odour of garlic when swallowed in capsules may remain in the bile after it has disappeared both from the breath and the intestine, and it seems probable that liver dysfunction may play a part in some cases of halitosis. The sulphur-smelling mercaptan may be smelt strongly in the breath in cases of hepatic necrosis.

**Treatment.**—Some cases of unexplained halitosis are improved by much reducing the amount of fats in the diet. Purgatives are of little use, though saline laxatives are often advocated. Attention must be paid to the mouth, teeth, throat and nose. Chlorophyll tablets taken orally will often remove the odour completely and may be ordered freely without ill effects.

## DISEASES OF THE SALIVARY GLANDS

### PTYALISM

**Ætiology.**—The flow of saliva is increased by reflexes originating in the mouth and also in more distant situations. Thus all pathological conditions in the mouth and its neighbourhood, such as stomatitis, epithelioma of the tongue and carious teeth, especially if associated with pain, are accompanied by salivation. Trigeminal neuralgia, whatever its cause, is frequently associated with a reflex flow of saliva. Mechanical irritation of the œsophagus caused by the passage of a tube into the stomach or by the impaction of a foreign body causes salivation, which is a common symptom in achalasia of the cardia and in simple and malignant ulceration of the œsophagus. Reflex salivation is the cause of waterbrash associated with the hyperchlorhydria of duodenal ulcer.

The salivation which may occur during menstruation and in the early months of pregnancy is also probably reflex in origin. Salivation is a common and sometimes very distressing symptom of paralysis agitans and post-encephalitic Parkinsonism. Ptyalism may result from excessive smoking. It is also caused by the specific stimulating action of certain drugs, such as pilocarpine, and by drugs such as the iodides and mercury, which are partially excreted by the salivary glands.

**Symptoms.**—Every time saliva is swallowed air passes with it into the stomach. In neurotic individuals a spitting or swallowing tic may develop; the latter is always accompanied by aerophagy and the patient consequently complains of severe flatulence with excessive belching (p. 566).

**Treatment.**—In order to cure ptyalism the primary cause must be discovered and removed. As purely symptomatic treatment, belladonna should be given: 5 minims of the tincture, taken three times a day, half an hour before meals may be sufficient, but much larger doses are often required. The drug has the additional advantage of diminishing the secretion of gastric juice when gastric hypersecretion is also present.

### XEROSTOMIA

**Ætiology.**—The dry mouth, which is constantly present in fevers, is due mainly to deficiency in the psychical, chemical and mechanical stimuli to salivary secretion. The associated toxæmia probably also exerts some direct inhibitory action on the gland-cells. Depressing emotions and the loss or perversion of taste, which may occur when the tongue is furred, result in diminution in the psychical secretion. The paralysis of the secretory nerve-endings produced by belladonna, stramonium



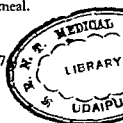
and their alkaloids sets the limit to the dose of these drugs which can be administered. The secretion of saliva is also diminished when excessive quantities of fluid are lost by other channels, as in severe diarrhoea. Diseases of the salivary glands themselves, such as mumps, result in diminished secretion. Severe xerostomia occasionally develops without any obvious cause. A dry mouth is also a common result of sleeping with the mouth open.

**Symptoms.**—Deficient secretion of saliva causes the mouth to become dry and septic, as particles of food remain between the teeth, where they undergo bacterial decomposition. The tongue is furred and dry, and there is often an unpleasant taste in the mouth. It is difficult to chew food sufficiently, and the appetite is impaired as a result of the condition of the mouth and the difficulty in tasting. The insufficiently chewed food is likely to irritate the stomach. In severe cases dysphagia occurs and speech becomes difficult. The loss of the digestion of starch by the ptyalin of the saliva is of no importance owing to the amylolytic activity of the pancreatic juice.

**Treatment.**—A diet should be chosen which stimulates the flow of saliva; acids are most active, then salt and bitters, whilst sweet substances have very little action. The food should be given in as appetising a form as possible and masticated very thoroughly. The taste of a bitter mixture taken immediately before meals may directly stimulate the flow of saliva, and pilocarpine may be tried, but it is rarely of much use, as a dose sufficiently large to increase the flow of saliva generally produces unpleasant symptoms, such as excessive sweating. It is, however, valuable in the treatment of paralysis agitans and post-encephalitic Parkinsonism, as it counteracts the xerostomia (and also the paralysis of the intrinsic eye muscles) often caused by hyoscine and stramonium, without diminishing their effect on the tremor of paralysis agitans and the rigidity following encephalitis. Great care should be taken to keep the teeth clean, and the mouth should be washed after each meal.

SPECIFIC PAROTITIS (MUMPS)—(see p. 17)

## PAROTITIS



**Ætiology.**—Parotitis is usually due to infection ascending Stensen's duct from the mouth. This is particularly apt to occur in the acute parotitis that not infrequently follows operations on the alimentary tract when the mouth has become septic owing to dehydration, the absence of chewing and normal salivation. It may develop secondarily to obstruction from a stone in Stensen's duct, or in the dry mouth of Sjögren's syndrome or diabetes mellitus. It may also follow trauma of Stensen's duct by ill-fitting dentures. Subacute parotitis, which is often recurrent, may also occur in persons with apparently healthy mouths. The infection may be limited to Stensen's duct, when it is referred to as sialodochitis, or it may spread from the ducts to the tissues of the gland. Blood-stream infection may also take place. The subacute recurrent type of infection is relatively common in children and occurs more frequently in women than in men. In children recurrent attacks tend to become less severe as adolescence is reached and usually clear up before adult life.

**Symptoms.**—In acute parotitis following operation one or both glands may be affected. The glands are enlarged and tender, the skin over them reddened, shiny and œdematous. In severe cases, suppuration takes place, the neighbouring lymphatic glands enlarge, the temperature is high and severe constitutional symptoms are present. The mouth is dry and difficult to keep clean; the tongue is covered with a thick fur. The mouth of Stensen's duct is everted and forms a small, red nodule from which a bead of pus can usually be squeezed. In most cases the inflammation

subsides with antibiotic treatment; abscess formation may occur; rarely the condition becomes chronic, the parotid glands remain permanently enlarged and excrete a reduced quantity of saliva.

In the subacute form swelling of one or both glands may occur on a single occasion or repeatedly at intervals of weeks or months, sometimes over a period of many years. The swelling usually lasts for several days but may persist for months. Fluctuation in the size of the swelling takes place, an increase usually accompanying or following mastication. The inflamed gland is tender to pressure and the overlying skin may be reddened and hot. Firm pressure over the gland often causes expulsion of pus or turbid saliva from the reddened orifice of Stensen's duct. The submandibular glands may be affected in the same way, either by themselves or in association with parotid swellings. In these patients radiographic examination of the ducts after injection of lipiodol frequently shows beadlike dilatation of the terminal acini, or there may be irregular dilatation of the main duct and its branches. The condition must be differentiated from leukaemia with infiltration of the parotid and submandibular glands and from uveoparotitis or Heerfordt's disease which is a special form of sarcoidosis.

Microscopic examination of the parotid saliva shows degenerated leucocytes, epithelial cell debris and organisms. In acute parotitis *Staphylococcus aureus* is the organism usually responsible, while in the subacute and recurrent forms *Streptococcus viridans* and *pneumococcus* are commonly found.

**Treatment.**—In acute parotitis treatment with penicillin in full doses usually leads to resolution. Hot fomentations or application of an electric pad may ease the pain of the swollen gland. Mouth washes may be used and steps should be taken to overcome dehydration and to deal with local conditions in the mouth, if these exist. If abscess formation has occurred incision of the gland will be necessary.

In subacute cases penicillin is also useful, local application of heat to relieve the pain, and chewing-gum to assist drainage. When the active phase has subsided short-wave diathermy is often helpful. In long-standing cases with chronic infection and persistent swelling, deep X-ray therapy is sometimes justified, but this treatment, which destroys the secretory mechanism of the gland and induces fibrosis, should never be employed in children whose facial bones are still developing, since in such cases it may interfere with the growth of the mandible.

### NON-INFECTIVE RECURRENT SWELLING OF THE PAROTID GLANDS

**Ætiology.**—This condition may occur at all ages. The cause is often uncertain, but the frequent association with allergic conditions in the patient himself or in his relatives has led to the suggestion that an allergic process is responsible. A number of cases have been described in which this pathogenesis has been demonstrated beyond doubt.

**Symptoms.**—Eating may precipitate attacks, especially when the food is acid in character, and in some patients the parotid glands become swollen whenever food is taken over a period of many years. In others, the swelling is definitely associated with the eating of certain foods to which the patient is specifically sensitive. The swellings are more often bilateral than unilateral. They develop rapidly and are present for a short time only, often subsiding within half an hour and seldom persisting for more than 24 hours. Single isolated attacks may occur, but owing to their brief duration and the absence of after-effects they are seldom seen, and cases presenting themselves for treatment are usually recurrent. Signs of inflammation are absent, the parotid saliva contains no pus, and the swellings are seldom painful.

In most cases secretion can be expelled from the parotid duct by pressure during

the attack. Globules of jelly-like mucus obstructing Stensen's duct may first be forced out, followed by 2 or 3 ml. of clear saliva. It is in this type of case that eosinophil cells have been observed both in the mucous plugs and in the pent-up secretion. This is sterile and contains no pus, but secondary infection may supervene in patients in whom swellings have recurred over a long period. In early cases saliva may be difficult to obtain.

Sialography may show gross fusiform dilatation of the main and branch ducts in long-standing cases; in others the appearance is similar to that seen in infective parotitis, with bead-like terminal dilatations. In early cases the appearance may be normal.

**Treatment.**—Massage over the gland is of value, especially when mucous obstruction is present. In some cases injection of adrenaline subcutaneously leads to subsidence of the swelling. If specific foods cause the swelling, these must be avoided.

THOMAS HUNT

## DISEASES OF THE TONSILS

### ACUTE TONSILLITIS

Tonsillitis has been classified as superficial, follicular or lacunar, and parenchymatous, according to the degree in which the various parts of the gland bear the brunt of the inflammation; the distinction, however, is not a definite one, as the entire organ is necessarily inflamed.

**Ætiology.**—The disease is rare in children below the age of 3, and after middle age; and it is commonest in spring and autumn. It is predisposed to by general ill health, overwork and a polluted atmosphere; and the infection may be carried by water or milk. Cross infection in hospital wards, dormitories and classrooms is often an important factor in spreading the disease. It occurs as a regular symptom of scarlet fever and measles. There is a connection between rheumatism and tonsillitis, and it was formerly believed that tonsillitis was of rheumatic origin; but it is now generally recognised that both acute rheumatic fever and chronic rheumatic pains in joints and muscles are often caused by absorption from infected tonsils. Unhealthy conditions of the teeth or tonsils predispose to further attacks by causing adhesions in the crypts or supratonsillar fossæ, thus promoting the retention of secretion; previous incomplete removal acts in the same way. The usual bacterial cause is a hæmolytic streptococcus (*Str. pyogenes*) of Lancefield's Group A.

**Symptoms.**—The symptoms are those of a feverish attack, together with a sore throat; the former often appears before the latter, and only examination of the throat reveals the cause of the disturbance. The temperature may rise to 103° or 105° F., and there is a variable degree of malaise, backache, headache and pain in the limbs. The soreness of the throat radiates to the ear, and is increased by attempts to swallow; the voice becomes thick, the breath foul and the submaxillary and upper cervical glands are tender and swollen.

The tonsils are swollen, and their purple-red colour extends to the pharynx, palate and uvula—the latter frequently being œdematous. In the follicular type the surface of the tonsils is spotted over with yellowish masses of secretion which have exuded from the crypts; sometimes this secretion becomes confluent on the tonsils, it is soft and readily wiped away. The tongue is coated, and the fauces covered with tenacious mucus. There is usually constipation, and the urine is scanty and high-coloured, but not ordinarily albuminous. Albuminuria is, however, an occasional complication, as are pericarditis, endocarditis and suppurative otitis media.

**Diagnosis.**—The diagnosis from diphtheria is important, and sometimes difficult. The latter is more gradual and asthenic in onset, with less pain, less fever and a more rapid pulse, and the urine frequently contains albumin. The membrane of diphtheria is greyish white rather than yellowish, and frequently spreads to the pillars and soft palate, though it may on occasions be confined to a very small area. The exudation of tonsillitis rarely spreads, and never to any great extent, beyond the surface of the tonsils. The diphtheritic membrane is adherent and, when detached, leaves a raw bleeding surface, while that of tonsillitis is readily removed and more often discrete. In cases of doubt a bacteriological examination should always be made, and an injection of antitoxin should be given while waiting for the result.

**Treatment.**—Complete bed rest is the most important step in treatment. If, as is so often the case, the patient is constipated a suitable aperient should be prescribed. The time-honoured custom of applying hot fomentations to the neck merely irritates and tires a sick patient whose greatest need is rest.

The severely ill patient cannot gargle, and it is foolish to make him try; he will, however, derive some comfort from alkaline mouth washes. Lozenges are often demanded by the patient or his relatives and it may be well to accede to these demands, trochiscus phenolis is harmless and has a certain local analgesic effect. Penicillin lozenges are sometimes of value, but their routine use is not recommended because severe stomatitis may result. Internally aspirin is useful, the following, shaken with an equal quantity of water, may be used as a mouthwash and then swallowed:

Acidi acetyl-salicylici	..	..	..	gr. 10
Pulv. Tragacanthæ Co	..	..	..	gr. 10
Aquæ	..	..	..	to 1 oz.

Feeding is often difficult and the patient must be encouraged to take as much nourishment as his dysphagia permits. Semi-solids are usually easier to swallow than liquids and there is scope for ingenuity in provision of a suitable diet. Junket, meat jellies and thick unseasoned soups are acceptable.

There is little more to be said about the treatment of mild cases. In severe cases sulphonamides, penicillin, or even both, will be indicated. It is important to realise that the earlier a sulphonamide is given the more likely it is to succeed. Dosage must be sufficient to maintain an efficient blood level for 5 days even if the temperature settles early. A generous fluid intake is essential. Penicillin, when prescribed, must be given in full doses for 5 days. It is usually not worth while to take cultures and test organisms for sensitivity to antibiotics since Group A hæmolytic streptococci are always penicillin-sensitive.

There is yet no evidence suggesting that other more recently discovered antibiotics are better than penicillin.

## PERITONSILLAR ABSCESS OR QUINSY

**Ætiology.**—This condition can be defined as inflammation with pus formation in the loose areolar tissue *outside* the tonsil. Infection in the supratonsillar fossa or in the depth of a crypt bursts through the capsule. This process is favoured by adhesions obstructing the mouth of the supratonsillar fossa or the crypts, wherefore previous attacks of tonsillitis and imperfect surgical removal are predisposing causes. The abscess is usually situated above and external to the tonsil, but in rare cases is behind it.

**Symptoms.**—The affection is unilateral; but sometimes the opposite side is attacked as the first recovers. It begins with a feeling of malaise, fever, often a rigor, and severe pain radiating from one side of the throat up to the ear and into the neck;

the cervical glands are enlarged and tender, and the neck stiff. Dysphagia is intense, the tongue thickly coated, and the breath foul. The mouth cannot be opened widely, and a good light is required for examination, when the typical large deep-red swelling is to be seen bulging one side of the soft palate. Pus forms in 2 to 4 days and, if left alone, will eventually burst through the supratonsillar fossa or occasionally through the soft palate; relief is then immediate, but occasionally the opening closes prematurely and the abscess refills. A much less acute, almost insidious, form of quinsy is sometimes seen when a patient suffering from acute tonsillitis has received sulphonamide treatment too late and in ineffectual doses.

**Diagnosis.**—Occasionally diphtheria simulates quinsy when swelling is disproportionately great and when only a tiny area of diphtheritic membrane is present. Malignant disease of the tonsil and tonsillar stone have been mistaken for quinsy.

**Complications.**—Although one of the most painful and distressing of acute diseases, complications are uncommon, and death is very rare; it has occurred from rupture of the abscess, and inspiration of the pus, during sleep. Severe hæmorrhage may take place after spontaneous or surgical evacuation of the abscess when, as the blood may come from the internal carotid or from a branch of the external carotid artery, ligature of the common carotid is called for. Suppuration of the cervical glands is a rare complication, as are pneumonia, septicæmia and pyæmia.

**Treatment.**—The general treatment is the same as that of severe acute tonsillitis, and the pain sometimes calls for an occasional injection of morphine. In the early stage, before pus has formed (peri-tonsillitis), systemic penicillin may be given in full doses with good prospects of aborting abscess formation. The treatment should be continued for 5 days even if improvement is obvious. If pain and trismus persist beyond the third day it must be assumed that pus has formed and the abscess should be opened without delay. Even experienced physicians often find difficulty in making a confident diagnosis of pus formation, in such cases it is usually wise to continue penicillin treatment for 24 hours and re-examine the throat on the following day.

The procedure of opening a quinsy is not always easy for the patient will not be able to open his mouth wide and a good light is essential. An adult should not be given an anæsthetic, though the throat may be sprayed with cocaine 5 per cent.: an alternative plan is to allow him to suck an amethocaine hydrochloride (Decicain) lozenge. He must be seated bolt upright and his head rigidly supported. A thin-bladed scalpel adequately guarded is thrust into the most prominent part of the swelling, the cutting edge should lie upwards and the blade held in the sagittal plane. The scalpel should not be introduced deeper than  $\frac{3}{4}$  inch. Whether or not pus is struck at once a sinus forceps is introduced into the wound and opened widely to assist evacuation. Children must be given an anæsthetic but the mouth gag must be introduced before induction and a sucker must be at hand lest the abscess bursts spontaneously before full anæsthesia is obtained. The patient's head must be extended (chin to ceiling) before the incision is made.

When the acute illness is over the patient must be told that the tonsils should be removed to prevent recurrence. It is very unwise to operate until at least a month has elapsed.

## CHRONIC TONSILLITIS

Many attempts have been made to classify chronic tonsillitis and much unnecessary confusion has arisen. Pathologists disagree about the definition of chronic infection whilst physicians have accepted clinical distinctions which are often non-existent. It has been the custom for years to speak of chronic parenchymatous tonsillitis and chronic follicular tonsillitis; in the former there is parenchymatous hyperplasia and overgrowth of lymphoid tissue, whilst in the latter crypts become

distended with epithelial debris and pus. It is easier and much more logical to refer to chronic tonsillitis in the knowledge that the picture presented may vary. If chronic infection is present it matters little whether the tonsils themselves are large from parenchymatous hyperplasia or small and fibrotic with pus leaking from distended crypts.

Accepting this simplification makes it possible to refer to enlarged tonsils without inferring infection. Many healthy children have large tonsils which never give rise to trouble and are best left alone. It is proposed to refer to the problem of chronic tonsillitis as it affects children and adults separately.

### CHRONIC TONSILLITIS IN CHILDREN

Infected tonsils in children are usually enlarged and associated with enlarged adenoids, though gross hypertrophy of adenoids may exist when tonsils are small. Healthy tonsils and adenoids tend to atrophy at puberty and hypertrophy seldom takes place *de novo* after that age.

**Ætiology.**—The condition occurs chiefly in children between the ages of 4 and 14 and, as a rule, results from repeated acute attacks. The first throat infection may have arisen as a manifestation of scarlet fever or measles. Unsuspected infection of the maxillary antra may lead to chronic tonsillitis.

**Symptoms.**—The symptoms are often overshadowed by those primarily due to enlarged adenoids, mouth breathing, toneless speech, snoring, recurrent otitis media and deafness of varying severity. Between recurrent attacks children seldom complain of sore throat. Cervical lymph nodes are easily palpable and sometimes become visibly enlarged; suppuration in the glands is now uncommon. It is well to remember that in some cases the enlarged nodes are tuberculous.

The objective appearances are very variable, and it is extremely difficult to estimate the healthiness of a tonsil by inspection. Slightly enlarged tonsils may be prominent and may readily meet on gagging, while big tonsils are often largely buried in the palate or hidden beneath the plica triangularis—in which case a bulging can be seen at the side of the soft palate corresponding to the site of the upper pole.

**Treatment.**—It is important to realise that no local treatment to chronically infected tonsils is of value. Paints, gargles and lozenges may have to be prescribed but only to ease the minds of anxious parents. Recognition and treatment of maxillary sinusitis is important.

When it is considered that the degree of chronic infection is not severe enough to warrant surgical removal, an open-air life in the country or at the seaside can be advised if domestic circumstances permit. The well-disciplined child who is sent to bed at reasonable hours does better than the spoiled child.

Unhealthy tonsils should be removed when there have been repeated attacks of tonsillitis, after a quinsy, when there is chronic enlargement of the cervical glands and when rheumatic fever or chorea has occurred. Definitely unhealthy tonsils should also be removed in cases of chronic or recurrent otitis media, whilst recognising the even more important rôle of enlarged adenoids in the causation of this complication. When chronic cervical adenitis is present, and is not due to some other obvious cause, such as pediculosis or dental caries, the tonsils should be removed whether they appear diseased or not; in these cases about one-third of the tonsils are tuberculous, and this latent tuberculosis cannot be recognised by inspection, many of these tonsils, indeed, being quite small.

The reader is referred to surgical works for details of the operation, but it may be said here that, if a tonsil requires removal, it must be removed completely in its capsule, for the deeper portion of a diseased tonsil is quite as unhealthy as the superficial; trouble in the remaining portion is very common, and the previous operation only adds to the surgeon's difficulties.

## CHRONIC TONSILLITIS IN ADULTS

In older subjects, when fibrosis has followed hypertrophy, the stenosed crypts become filled with yellowish-white caseous masses. The patient complains of an offensive taste, foul breath, often of recurrent attacks of sore throat and of gastric disturbances. Not infrequently various forms of chronic toxæmia, such as fibrositis or arthritis, are induced by absorption from these septic foci. In many cases the tonsils are quite small; they may look healthy, but pus can be squeezed out of the crypts on applying pressure at the anterior pillar by means of a flat instrument.

**Treatment.**—The treatment in the more marked cases is removal. There are, however, a good many patients who have only a few unhealthy crypts in the tonsils; such patients may be taught to empty these crypts by pressure on the anterior faucial pillars with the handle of a spoon. The mouths of the crypts may be painted with guaiacol 4 per cent. in glycerin.

## VINCENT'S ANGINA

**Ætiology.**—This affection is believed to be due to two organisms, the fusiform bacillus and spirochaete of Vincent growing in symbiosis; these organisms may be found in many ulcerative conditions of the mouth and throat, but their constant presence in this affection points to their specific character. Affection of the throat is frequently secondary to periodontal infection of the gums. It occurs especially in debilitated persons and under insanitary conditions and, though rather rare in civil life, was common during the War of 1914–1918 and the War of 1939–1945.

**Symptoms.**—The attack begins insidiously, with malaise, general pains and a temperature of 100° to 101° F. The pain in the throat is often slight but in some cases may be severe, but the glands on the affected side become enlarged and tender, and the breath is characteristically offensive.

There is superficial ulceration, which commonly involves tonsils or fauces but may affect the inner surface of cheek, pharyngeal wall or larynx. The ulcers vary in size; their base is covered with a yellowish-grey pseudo-membrane which is not easily detached, and there is marked hyperæmia around the edges. In rare cases the pseudo-membrane is replaced by a heaped-up irregular slough. By the end of a week the membrane ceases to form, and the ulcer begins to heal.

**Complications** are very rare.

**Diagnosis.**—The disease is particularly interesting by reason of its liability to imitate diphtheria in its early stage, and syphilitic ulceration later. In both cases the discovery of numerous spirilla and fusiform bacilli in smear-preparations—they are difficult to cultivate—will help the physician to the correct diagnosis; but these organisms may also be found in syphilitic ulcers, and the Wassermann reaction is occasionally positive in Vincent's angina. The subacute onset, the raised temperature and the tenderness of the glands aid the differentiation from syphilis; and from diphtheria the milder constitutional symptoms, the soft friable character of the membrane and the absence of the diphtheria bacillus. Cases of non-specific superficial ulceration involving tonsil fauces and inner surface of cheek are not unduly rare. One form occurs as a result of semi-starvation or a grossly unbalanced diet. A second form remains entirely unexplained, it is common in women and no specific organism or virus has been discovered. Patients suffering from this mysterious type of ulceration almost always have some unresolved psychological worry: Physicians should be alive to the fact that ulcerative lesions can also occur in the course of agranulocytic angina, leukaemia and glandular fever.

**Prognosis.**—Death hardly ever occurs.

**Treatment.**—The ulcerated areas should be cleaned with hydrogen peroxide, after which topical applications, such as liquor arsenicalis and vinum ipecacuanhæ in equal parts, or neoarsphenamine in the strength of gr. 20 to the oz. of glycerin, may be used. These should be firmly applied on a swab, with due regard to their poisonous nature.

Ascorbic acid and vitamin B complex are valuable, particularly in the treatment of recurrent cases. Dental supervision is important.

The causal organisms are not easy to culture so that bacteriological tests for sensitivity to modern antibiotics are unreliable. It is, however, recognised that the use of systemic penicillin is amply justified by results. Penicillin lozenges are best avoided because their use is too often followed by stomatitis.

W. I. DAGGETT.

## DISEASES OF THE PHARYNX

### DIVERTICULA (see p. 546)

#### ACUTE CATARRHAL PHARYNGITIS

This is not a very well-defined affection, and is usually accompanied by acute rhinitis on the one hand, and by laryngitis on the other; the tonsils also often participate in the inflammation.

**Ætiology.**—The affection is generally the result of coryza, and it is a feature of various acute infectious fevers, such as measles, German measles, scarlet fever, influenza and typhoid.

**Symptoms.**—The discomfort varies from a tickling sensation, or the feeling of a lump in the throat, to severe dysphagia. The voice is husky and thick, and the cervical glands tender and somewhat enlarged. There is slight fever and general malaise.

The pharynx is to a varying degree red and swollen, especially at the sides behind the posterior faucial pillars, where the swelling forms the so-called "lateral bands". The palate is swollen and relaxed, and the uvula elongated. The posterior wall is often covered by a film of tenacious mucus.

**Treatment.**—The patient should stay in a warm room and avoid the irritation of smoking, talking, alcohol or irritating foods. Aspirin, or sodium salicylate, is helpful and it is important to treat any primary cause.

#### ACUTE SEPTIC PHARYNGITIS

This term includes a series of severe infective inflammations; œdematous, phlegmonous and gangrenous pharyngitis and laryngitis, and Ludwig's angina. Any classification must necessarily be a clinical one, based on the severity of the symptoms and their localisation, for they can be produced by a variety of micro-organisms, though they are usually caused by a streptococcus. These severe inflammations are fortunately uncommon, and most often, though by no means invariably, occur in debilitated or alcoholic persons.

**Symptoms.**—These vary greatly with the severity of the infection, which ranges from a mild inflammation to the most severe septic intoxication. They include malaise, sore throat, dysphagia, hoarseness and dyspnoea. The temperature in some cases rises to 105° or 106° F.; but in many of the worst cases it is hardly raised at all, and may be subnormal. Pleurisy, pneumonia and pericarditis may ensue, or death may result from asphyxia; but the worst cases die from general toxæmia and heart failure, even within 24 hours of the onset of the disease.



The objective appearances, also, are very variable. The pharynx and palate are of a deep purplish red, and there may be sloughy pseudomembraneous patches. The entire mucosa may be enormously swollen, and the oedema may involve the upper aperture of the larynx and produce asphyxia. The sublingual region is sometimes occupied by a peculiar brawny swelling, of a hardness like wood, which spreads downwards into the neck to a variable extent, and is known as Ludwig's angina.

**Treatment.**—The patient must be in bed and well nursed, and every care must be used to ensure that he takes as much nourishment as possible. Sulphonamides and antibiotics must be the mainstay of treatment. Adults should receive 60,000 units of penicillin 3-hourly, and this may be combined with full doses of a suitable sulphonamide. A high fluid intake must be assured. Oedema of the glottis may call for emergency tracheotomy. For Ludwig's angina it is now only rarely necessary to make an incision deeply into the neck in the hope of striking pus; the swelling will either subside or a fluctuating abscess will become apparent.

### RETRO-PHARYNGEAL ABSCESS

There are two forms—(1) Acute, and (2) Chronic.

1. The acute form occurs in children up to the age of 3 or 4, but is far more frequently met with in the first 12 months. It is due to suppuration in the pre-vertebral glands situated behind the posterior pharyngeal wall; these glands disappear in later life. The abscess is secondary to nasal, naso-pharyngeal or tonsillar infection and may occur during the course of an infectious fever.

Though rare, the condition is an important one, for it may easily remain unrecognised in a young infant, and may be fatal if the abscess is left unopened. The symptoms are fever and restlessness, a hoarse cry and croupy cough, with difficulty in swallowing and dyspnoea. Such symptoms should arouse a suspicion of retro-pharyngeal abscess, which may be seen on inspection as a rounded swelling of the posterior pharyngeal wall. The abscess is often very large, and must be freely opened in such a way as to avoid aspiration of the pus, without an anæsthetic, and with the child firmly held, either on the side with the face directed somewhat downwards, or on the back with the head hanging almost vertically. A suction apparatus must be at hand. Recovery is rapid, and no after-treatment is required beyond attention to the enfeebled general health.

2. The chronic form, also, is found most frequently in children, but generally after the third year. It is of tuberculous origin, and is due either to tuberculosis of the prevertebral glands, or to caries of the cervical spine. The latter should be carefully excluded, for this abscess should not be opened through the mouth, as secondary infection of the diseased bone is likely to occur. The chronic glandular abscess, however, may be successfully opened by this route, though some surgeons prefer to treat all chronic cases by an incision beyond the sterno-mastoid.

### CHRONIC PHARYNGITIS

#### (PHARYNGEAL HYPERÆSTHESIA)

The symptoms of discomfort in the throat in the conditions grouped as chronic pharyngitis bear little relationship to the intensity of the changes seen on examination. Many people, especially heavy smokers, complain of no discomfort, in spite of showing decided chronic inflammation; whereas others, in particular dyspeptic or anæmic women or those at the menopause, suffer great discomfort, with no apparent local abnormality. Indeed, in many cases the condition is better described as pharyngeal hyperæsthesia; globus hystericus may be considered to be an extreme example of this hyperæsthesia.

**Ætiology.**—Chronic pharyngitis is usually secondary to chronic infection in the nasal sinuses, tonsils and teeth. It is aggravated by mouth-breathing, excessive smoking and over-indulgence in alcohol.

**Symptoms.**—Discomfort may take the form of aching, fullness or feeling of a lump, a hair or a pricking. The voice has a dead tone, and there is usually much hawking and frequent swallowing. The sufferer often becomes depressed, and fears that he has cancer of the throat. The unpleasant sensations are markedly lessened after a meal.

The mucosa of the pharynx and palate is thickened, and there is a loss of the finer modelling of the faucial pillars; the uvula is elongated, often slightly œdematous at its edges and tip, and fails to retract on phonation. The posterior wall is covered by a film of mucus, which puckers up and becomes more obvious on touching it with a probe or swab. The wall of the pharynx is traversed by enlarged venules, and sometimes it is set with slightly raised pink lenticular nodules of lymphoid tissue, constituting a variety known as *granular pharyngitis*. In other cases two elongated masses of lymphoid tissue appear behind and parallel to the posterior pillars; these are the "lateral bands", and this form is called *lateral pharyngitis*. Patients suffering from atrophic rhinitis may complain of dryness of the throat; the posterior pharyngeal wall presents a glazed dessicated appearance, sometimes alluded to as *pharyngitis sicca*.

**Treatment.**—The most important part of the treatment consists in the detection and alleviation of the cause, and should begin with a careful examination of the nasal passages. Cases of pharyngeal hyperæsthesia without obvious local changes are often harmed, rather than helped, by local treatment which directs attention to their trouble. Tobacco should be given up, and alcohol in concentrated forms, indeed the latter should be abandoned completely in plethoric patients; condiments and highly seasoned food should be avoided. This type of patient is benefited by a morning dose of sulphate of soda or magnesia, a teaspoonful in a glass of hot water while dressing, or by one of the natural mineral waters. When the pharynx is dry, or covered with tenacious mucus, an expectorant mixture gives relief, such as tinctura ipecacuanhæ, min. 12, vinum antimoniale, min. 5, potassium iodide, gr. 3, syrup of tolu, min. 60, water, 1 fl. oz., three times a day. The throat may be sprayed with a warm alkaline saline lotion, or protargol 10 per cent. Of local applications in the form of paints, 10 per cent. protargol is the most generally useful, 4 per cent. guaiacol in glycerin is also well tolerated. In cases presenting heaped-up inflamed patches of lymphoid tissue on the posterior pharyngeal wall, the galvano cautery may be of value, but it must be used lightly so that subsequent scarring is minimal. Many patients suffering from this complaint are intelligent yet introspective and neurotic, and alcoholic indulgence makes them impatient and intolerant. It is difficult to explain that constant hawking makes them worse, and the physician's most common mistake is to fix his patient's mind on the throat by over-treatment.

### KERATOSIS PHARYNGIS

In this condition a number of sharply defined white or yellow spikes project from the surface of the tonsils; they also occur, though less profusely, scattered over the lingual and naso-pharyngeal tonsils and on any lymphoid granules in the pharynx. They occur at any age after childhood and the causation is unknown. The projections consist of heaped-up epithelium and detritus containing numerous micro-organisms of the kind ordinarily present in the mouth. On microscopical examination branching fungus mycelium can usually be demonstrated. They sometimes disappear quickly, in other cases they remain for many months, or they may recur. They produce no symptoms, or at most a slight discomfort, and are of interest chiefly

because they are frequently mistaken for the exudation of chronic follicular tonsillitis. Once seen they can, however, be recognised at a glance, for they are hard and adherent, discrete and prominent, and occur beyond the limits of the tonsils, on the pharynx and base of the tongue. They are usually discovered accidentally by the patient, who is naturally alarmed at their appearance. They are quite harmless, and local treatment is useless, for they are removed with difficulty and usually recur; it is wise to reassure the patient by telling him these facts and, if any treatment be required, to trust to attention to the general health, a holiday and change of air.

W. I. DAGGETT.

## DISEASES OF THE ŒSOPHAGUS

### THE NORMAL ŒSOPHAGUS

The act of swallowing occurs in four stages. The first consists in the voluntary *propulsion of food from the mouth to the pharynx*. The second is set in action by a reflex arising from the contact of food with the posterior wall of the pharynx, which leads to closure of the passages leading to the mouth, nose and larynx, together with a rapid peristaltic wave travelling down the constrictors of the pharynx, which is followed by the opening of the hitherto closed pharyngo-œsophageal sphincter formed by the lower division of the inferior constrictor. The third stage consists in the propulsion of the bolus by a peristaltic wave down the œsophagus till it reaches the closed cardiac sphincter, the active opening of which constitutes the fourth and final stage of deglutition. The "suction effect" due to active relaxation of the œsophagus in front of the bolus certainly plays some part in swallowing in addition to the peristaltic contraction from behind.

### DYSPHAGIA

Dysphagia, or difficulty in swallowing, is generally the first symptom in diseases of the œsophagus. Owing to the fixed position of the œsophagus localisation of abnormal sensations is very accurate, and a patient generally points to the exact level of obstruction. In some cases, however, reflex spasm of the pharyngo-œsophageal sphincter occurs in association with lower œsophageal lesions, so that the patient experiences difficulty in initiating the act of swallowing as well as feeling the obstruction in the œsophagus caused by the primary disease.

The causes of dysphagia can best be considered according to whether the difficulty is experienced at the upper extremity, near the middle or at the lower extremity of the œsophagus; the last is the most common.

(a) *Pharyngo-œsophageal dysphagia*.—This is most commonly found in the Plummer-Vinson syndrome. In rare cases it is hysterical and it may also occur in various organic nervous diseases. Upper dysphagia may be caused by carcinoma, especially in women, and by a pharyngeal pouch, especially in old men.

(b) *Mid-œsophageal dysphagia*.—This is almost always caused by carcinoma. External pressure by an aneurysm or mediastinal tumour rarely causes dysphagia.

(c) *Lower œsophageal dysphagia*.—Dysphagia at the lower end of the œsophagus is most frequently caused by achalasia of the cardia and by carcinoma of the œsophagus. Next most frequent is the dysphagia caused by spasm secondary to peptic œsophagitis and œsophageal ulcer, especially in the presence of hiatus hernia, and by carcinoma of the fundus of the stomach. Lastly, the dysphagia may be due to cicatricial stenosis secondary to peptic ulcer or to the phlegmonous œsophagitis resulting from the swallowing of boiling water or corrosive poisons.

## HYSTERICAL DYSPHAGIA

Theoretically there is no reason why hysterical dysphagia should not develop in the form of paralysis or inco-ordination of the voluntary muscles concerned in the first two stages of swallowing, in which food passes through the sensitive bucco-pharyngeal cavity. It would, however, be very unlikely to develop in the œsophagus itself or at the cardia, where the passage is entirely independent of voluntary action and the food under ordinary conditions is not felt, unless it is very cold, very hot or in large lumps.

Hysterical dysphagia is, however, rare. The majority of cases so diagnosed are examples of the Plummer-Vinson syndrome, and others are really suffering from myasthenia gravis. It develops in patients who have become nervous for various reasons, when some trivial incident draws their attention to the voluntary but normally automatic act of swallowing. Much weight is lost. Recovery usually follows simple psychotherapy by explanation and persuasion.

## DYSPHAGIA IN ORGANIC NERVOUS DISEASES

Dysphagia may occur in various organic nervous diseases as a result of paralysis of the muscles concerned in the first and second stages of swallowing. The œsophagus itself and the cardiac sphincter are never involved. In diphtheria the toxin not only invades the blood, but also ascends the nerves from the site of the lesion to the central nervous system, where it puts the cells of the corresponding nuclei out of action. The paralysis of the soft palate, which results in regurgitation of food through the nose, and the rare pharyngeal paralysis which results in severe dysphagia, occur therefore mainly in the common faucial diphtheria and far less often when the primary focus is in a wound, the conjunctiva or elsewhere. The paralysis is nuclear in origin and generally develops in the second week, in contrast with the more widespread paralysis caused by diphtheritic polyneuritis, which usually appears between the third and sixth weeks.

In motor neurone disease, dysphagia may occur if the vagal nucleus is involved in the last stages of the common form beginning in the muscles of the hands. It always occurs in progressive bulbar palsy, the form which begins in the bulbar nuclei. Though myasthenia gravis is a primary muscular disease, it gives rise to a simple upper dysphagia, in which the first as well as the second stage of swallowing is affected. In motor neurone disease the slowly progressive paralysis is unaffected by any treatment, and there is no variation in the course of each day, so that once nasal feeding is begun it has to be continued until death, which is not likely to be long delayed. In myasthenia gravis the dysphagia increases in severity as the day goes on, and considerable spontaneous improvement may occur from time to time, so that a patient who has had to be fed temporarily by nasal tube may later be able to swallow quite well for weeks, months or years. Improvement in swallowing may be a direct result of the complete rest given to the muscles of deglutition by nasal feeding. The response to neostigmine is often dramatic. Neostigmine bromide 15 mg. can be given by mouth or neostigmine methylsulphate 1 mg. subcutaneously. Dysphagia is also a symptom of the acute bulbar paralysis which may follow vascular or inflammatory lesions involving the nucleus ambiguus.

In all forms of dysphagia due to organic nervous disease food of porridgy consistence is most easily swallowed, as fluids require more rapid, and lumps more powerful, action than soft food.

## PLUMMER-VINSON SYNDROME

**Synonym.**—Kelly-Paterson Syndrome.

Upper dysphagia with anaemia is the most frequent cause of difficulty in swallow-

ing involving the junction of the pharynx and œsophagus. It occurs in about 15 per cent. of cases of idiopathic hypochromic anæmia (see p. 732), which is common in women, but very rare in men. The syndrome is the direct result of iron deficiency, which causes not only the anæmia, but also atrophy of the mucous membrane of the tongue and pharynx. The atrophy of the pharyngeal mucosa results in a loss of sensibility, so that the afferent side of the reflex upon which the second stage of swallowing depends is impaired. The orderly activity of the muscles involved in the complicated act is disorganised and swallowing becomes difficult or impossible. The pharyngo-œsophageal sphincter is particularly involved, the normal relaxation which allows the passage of food from the pharynx into the œsophagus failing to take place. By œsophagoscopy an organic stricture may often be seen at the level of the crico-pharyngeal ring, sometimes with a thin crescent-shaped web of mucosa obstructing the lumen.

**Symptoms.**—The patient, generally an edentulous woman between 25 and 50 who has been in poor health for a long period owing to the presence of anæmia, gradually finds difficulty in initiating the act of swallowing, especially of solids. Sometimes, however, the dysphagia begins quite suddenly, and it may occur intermittently. *Severe cases in which dysphagia is the main symptom are rare in comparison with those in which it is so slight that the patient does not mention it unless directly cross-questioned.* The dysphagia is associated with atrophy and sometimes inflammation of the mucous membrane of the tongue and the pharynx. An atrophic condition also involves the lips, which may be thin and inelastic with cracks at the angles of the mouth. Achlorhydria is frequently, but not always, present, and the spleen is occasionally enlarged. The nails are often thin, brittle and spoon-shaped (koilonychia).

A barium swallow using a thick emulsion may show filling defects with retention of some of the opaque material in the pyriform fossa and the œsophagoscope may demonstrate the atrophic, inelastic condition of the pharyngeal mucous membrane, which may contract and aggravate the dysphagia by adding a mechanical obstruction to the neuro-muscular disorder.

This atrophic condition of the mucous membrane predisposes to carcinoma. About 50 per cent. of women with cancer of the mouth and a still larger proportion of those with cancer of the hypopharynx and upper end of the œsophagus give a history suggestive of the syndrome. *The fact that the latter is almost confined to women probably explains why 80 per cent. of cases of carcinoma of the post-cricoid part of the pharynx, which always spreads to and obstructs the mouth of the œsophagus, occur in women, whereas at least 80 per cent. of cases of cancer of the middle and lower end occur in men.*

**Treatment.**—The dysphagia usually responds well to treatment of the anæmia. Large doses of iron, and general treatment as outlined on p. 733, are usually all that is required, but in some cases a large mercury bougie may be carefully introduced into the œsophagus if the condition requires. Sedatives and psychological treatment by encouragement and reassurances are also useful. The atrophic condition of the mucous membrane often responds to iron therapy with additional vitamins, even if there is no anæmia. In rare cases the syndrome occurs in association with true pernicious anæmia, in which case liver must be given in full dosage.

#### CARDIOSPASM: ACHALASIA OF THE CARDIA

**Ætiology.**—Achalasia of the cardia may begin at any age, but most commonly in adults, and males and females are equally affected. A sudden onset following nervous shock occurs in many cases, which suggests that the condition is at least partly due to psychological causes.

**Pathology.**—The hypertrophy of the muscular coat of the œsophagus, which is

always present, indicates that violent efforts must have been made to overcome some obstruction. As no organic obstruction is ever found after death it was at first thought that spasm of the cardiac sphincter was present, and the condition was called *cardio-spasm*. As the symptoms may be present without intermission for many years before death, hypertrophy of the cardiac sphincter should result from the long-continued spasm. In very few necropsies, however, has there been any hypertrophy, and in several cases in which the cardiac sphincter, which is normally about 1 in. long and corresponds with the whole of the abdominal œsophagus, was exposed by operation, the muscle was found to be unusually thin. It was thought, therefore, that the obstruction was due to a failure of the cardia to open reflexly during swallowing, and Hurst suggested the name *achalasia* (*a*, not; *Χάλασις*, relaxation) to indicate the absence of the normal relaxation, which should occur when each peristaltic wave reaches the cardia. Food stagnates in the œsophagus, which dilates as more and more collects in it; the distension of the œsophagus acts as a powerful stimulus to peristalsis, which is excessively violent and continues at intervals throughout the day. This is the cause of the hypertrophy.

Further evidence that the condition is due to achalasia and not to spasm is afforded by the fact that, although strong peristaltic waves are unable to overcome the obstruction, the weight of an indiarubber tube filled with mercury is sufficient to cause it to drop into the stomach, the actual passage through the cardiac sphincter being often inappreciable to the hand holding the mercury bougie, which can be withdrawn with equal ease. It is not gripped, as the finger is gripped when it enters or is withdrawn from a spasmodically contracted sphincter.

The exact cause of the achalasia is uncertain, though disease of the myenteric (Auerbach's) plexus has been suggested; psychological factors are certainly concerned.

The dilated œsophagus may be able to hold as much as 2 pints, and its circumference may exceed 6 in.

**Symptoms.**—Achalasia of the cardia generally develops gradually, a slight attack, lasting for a day or two, being followed by a period of freedom for a few days or even several weeks or months. Attacks then occur at gradually shorter intervals, until finally the condition becomes permanent. The patient feels as if the food "sticks". He often recognises that the obstruction is beneath the lower end of the sternum, but sometimes the sensation is felt in the upper part or middle of the chest. Sometimes actual pain is produced, it is usually burning in character and is localised to the lower end of the sternum, but it may be indistinguishable from angina and may radiate to the neck, the ears or lower jaw. Salivation occurs in every case.

As a rule the patient voluntarily relieves his discomfort within a few minutes of finishing a meal by bringing up the greater part of what he has eaten mixed with saliva. He realises that this comes from his chest and not his abdomen, and, unlike true vomiting, it is not associated with nausea.

The weight of the column of food in the dilated œsophagus after a meal is sufficient to force a small proportion of the fluid present through the cardia as a very narrow stream; but as soon as the height of the column falls below a certain point, generally about 7 in., or the individual lies down, the pressure becomes insufficient and the flow ceases. Consequently, stagnating food mixed with mucus is always present in the œsophagus, and a considerable quantity can be removed from it even after a fast of 24 hours. No regurgitation occurs on lying down as the pharyngo-œsophageal sphincter is always, as in normal people, closed except during the act of swallowing.

The œsophagoscope shows that the entry to the cardiac sphincter, which is generally at the level of the diaphragm but may be within the thorax or within the abdomen, is completely closed. The mucous membrane may be normal, but owing to the prolonged stasis of food it is often chronically inflamed, especially

in the lowest part, and there may be superficial erosions: hæmatemesis may occasionally result.

Even in the absence of treatment the general health may remain good in spite of the fact that weight is often rapidly lost. At a certain stage a condition of equilibrium develops. Though the diet has to be limited the patient loses no more weight, and though he is less strong than formerly, he may continue to remain in this condition for many years and attain old age.

**Diagnosis.**—The patient's description of his symptoms is generally so characteristic, that a diagnosis of obstruction in the region of the cardia can be made with a considerable degree of probability. It is next necessary to decide whether this is due to achalasia, cancer or spasm associated with œsophagitis or peptic ulcer. The comparatively early age of many patients, and, in cases in which an early diagnosis has not been made, the long duration of the illness point to achalasia rather than to growth. Pain is often late in carcinoma. The diagnosis is confirmed by radiography; in achalasia the shadow of the dilated œsophagus narrows abruptly and ends at the entry into the sphincter, either on a level with the diaphragm or a short distance above or below it. As each additional quantity of food is swallowed, a narrow and uniform channel is seen for a moment to join the œsophagus with the stomach before the sphincter closes again. In peptic ulcer of the lower end of the œsophagus the sphincter remains open, but a narrowing is seen just above as a result of spasm with or without cicatricial contraction, and the round crater of the ulcer may be recognisable. In carcinoma the lumen of the cardiac sphincter is replaced by an irregular channel which extends a varying distance up into the œsophagus, the unaffected part of which is never as dilated as in achalasia, and except in the later stages the opaque fluid continues to pass slowly through the narrow irregular channel into the stomach till the œsophagus is empty, whereas it is never empty in achalasia. If there remains any doubt, the diagnosis of achalasia may often be confirmed by inhaling octyl nitrite, which results in dilatation of the sphincter and evacuation of the œsophagus. Œsophagoscopy should be carried out both to confirm the diagnosis and to undertake treatment (*vide infra*).

**Prognosis.**—If the condition is recognised at the onset of symptoms, a permanent cure often results from treatment, but if treatment is instituted only after the œsophagus has become dilated, cure as distinct from mere relief of symptoms is less likely to be obtained. There is practically no spontaneous tendency to cure, but approximately half the patients treated early remain well after dilatation. In the absence of treatment death has occurred at an early stage in very acute cases; but more often the patient survives for a considerable period, even for 40 years. In rare cases a diverticulum may form in the lower end of the dilated œsophagus or cancerous degeneration of a papilloma developing on the chronically inflamed mucous membrane may occur. In long-standing cases respiratory complications may result from pressure by the enormously distended œsophagus, or from regurgitation of the œsophageal contents into the pharynx and aspiration into the lungs.

**Treatment.**—Nitrites are the only drugs which cause relaxation of the closed cardiac sphincter. Unfortunately their effect is evanescent, and in the case of amyl nitrite, the general symptoms produced are so unpleasant that it is rarely of use. Octyl nitrite is more satisfactory, having less smell and causing no side-effects other than some drying of the mouth and the bronchial secretions. It can be sniffed up the nose from a small metal inhaler and, as a rule, two or three sniffs at a time during and just after a meal are sufficient to cause relaxation of the cardia and the passage of the food into the stomach. The food should be soft and as far as possible of high calorific value, such things as vegetable soups thickened with sugar and cream, egg-flips, and malted milks being preferable to tea, meat broths or jellies: additional vitamins should be given, especially if there is much wasting. Many patients may be kept in good health and weight by these means alone, but dilatation often becomes

necessary and is usually very effective. The passing of mercury bougies as introduced by Hurst has been superseded by the use of a distensible bag, which can be gradually inflated with water. By this means the lower end of the œsophagus can be stretched and many of the circular fibres ruptured. The procedure can be controlled endoscopically and is often followed by lasting relief. If not, some form of open surgical operation should be advised. This is best done by simple surgical division of the circular fibres at the œsophageal opening (Heller's operation), comparable to a pyloroplasty. Various alternative and more elaborate operations which lead to permanent incompetence of the cardiac orifice are less satisfactory, since they lead later on in nearly every case to troublesome or serious œsophagitis. In severe cases œsophago-gastrostomy may have to be carried out. Either the abdominal or trans-thoracic route may be employed.

Modern surgical treatment offers an excellent chance of cure, and should not be withheld too long if symptoms are at all severe. Even though the radiological findings after operation do not show great reduction in the dilated œsophagus, the symptomatic result may nevertheless be very good.

## DIVERTICULA OF THE PHARYNX AND ŒSOPHAGUS

**Ætiology and Pathology.**—Diverticula may develop from the anterior wall of the middle third of the œsophagus, by the traction resulting from adhesions between inflamed glands near the bifurcation of the trachea and the wall of the œsophagus; these "traction diverticula" are generally less than an inch in depth and rarely give rise to symptoms.

A diverticulum, which has given rise to no symptoms, is occasionally discovered at the lower end of the œsophagus during routine radiographic examination; these are usually congenital in origin, but occasionally are found in association with achalasia of the cardia.

Pressure diverticula are rare, but of considerable clinical importance. They occur only in adults, especially elderly edentulous men who habitually swallow lumps of unchewed food. They develop at the muscular gap on the posterior wall of the pharynx between the upper and lower divisions of the inferior constrictor of the pharynx at the level of the cricoid cartilage. They are really diverticula of the pharynx and not of the œsophagus, though they are generally described as œsophageal. The lower division of the inferior constrictor of the pharynx (the crico-pharyngeus muscle) forms a sphincter surrounding the entrance to the œsophagus. It is closed at rest, but opens during each act of deglutition the moment the food reaches it. When, as a result of neuro-muscular inco-ordination, it fails to open (achalasia), the food is forced against the weak spot on the posterior wall of the pharynx immediately above the sphincter. A pouch of mucous membrane may thus be formed. This becomes progressively larger towards one side, generally the left, owing to the accumulation of food in it, until it may finally measure as much as 5 in. in depth and be large enough to contain over a pint of fluid, in which case it may extend into the posterior mediastinum. Its wall is formed of mucous membrane and submucous tissue without any muscular covering.

**Symptoms.**—Diverticula of the pharynx sooner or later cause progressive dysphagia, which may be preceded by irritation of the throat and increased secretion of mucus. The patient complains of obstruction in the neck when he swallows, and a small quantity of food is regurgitated at varying intervals after meals. As the sac increases in size, the symptoms become more marked owing to obstruction of the œsophagus by the distended diverticulum, which finally forms a prolongation of the pharynx, the œsophagus opening as a transverse slit in its anterior wall. Increasing quantities of food are brought up, mixed with a large amount of mucus, and food



eaten several days before may be recognised. The patient becomes steadily more emaciated. Distension of the sac often causes pain, which is relieved when it is emptied. An irritable cough is often present, and dyspnœa may result from pressure on the trachea. A large diverticulum containing food may form a visible tumour in the neck, generally on the left side, which can be emptied by pressure, the food returning into the pharynx, but in most cases there is no palpable tumour.

The size, shape and exact position of the diverticulum can be recognised radiographically after a barium meal.

**Treatment.**—The only satisfactory treatment is excision. Whilst waiting for operation the patient should be fed through a catheter, which is introduced over a string swallowed when the sac is empty; if no fluids are taken for 5 or 6 hours the string always reaches the stomach.

## ŒSOPHAGITIS

Two distinct forms of œsophagitis occur, both of which may be either acute or chronic. In one the irritants which cause it are either hæmatogenous or swallowed. In the other form, which, unlike the first, is often associated with ulceration, the essential factor is the presence of acid gastric juice in the œsophagus.

### A. SIMPLE ŒSOPHAGITIS

#### (a) *Acute*

**Ætiology.**—Acute simple œsophagitis is a rare complication of various acute infections and toxæmias, such as scarlet fever. It may also complicate cancer of the œsophagus and spread from acute pharyngitis. In 5 per cent. of fatal cases of diphtheria the inflammation spreads from the fauces into the œsophagus, and in very rare cases the membrane extends as far as the cardia. The impaction of a foreign body in the œsophagus may cause local suppuration. Acute inflammation results from swallowing boiling water or corrosive poisons, taken by accident or in attempted suicide; owing to the obstruction to the passage of the œsophageal contents caused by the narrow cardiac sphincter the lower end is the part most affected, the upper extremity being next most seriously injured.

**Symptoms.**—In mild cases there may be no symptoms, but more or less dysphagia is generally present; in severe cases deglutition is so painful that the patient may be afraid to swallow his saliva or relieve his urgent thirst by drinking. There may also be constant pain beneath the sternum. Attempts to swallow often prove unsuccessful owing to reflex spasm, and the food is immediately rejected. Mucus is expectorated, together with blood and pus in severe cases.

**Treatment.**—In severe cases nothing should be given by mouth, but saline solution must be injected into the rectum or intravenously. Morphine is required for the pain. When the pain begins to subside a tablespoonful of olive oil followed by 5 oz. of milk can be given every 3 hours. Solid food should not be given until swallowing no longer causes pain. Complete obstruction necessitating gastrostomy is likely to occur in severe cases following corrosive poisoning.

#### (b) *Chronic*

**Ætiology.**—Chronic œsophagitis results from the constant swallowing of irritants, the most important of which are strong alcoholic drinks, and from septic conditions of the teeth and nasopharynx. It is also a common sequel of the stasis of food in the dilated œsophagus in achalasia of the cardia (p. 543).

**Symptoms.**—As the condition is frequently associated with chronic pharyngitis and gastritis, it is generally impossible to isolate the symptoms of one of these from the others. The morning vomiting of alcoholics is mainly the result of œsophageal catarrh.

**Treatment.**—The œsophagitis usually disappears when the sources of irritation are removed. The patient should become teetotal, and all septic foci in the mouth and pharynx should be treated.

## B. PEPTIC ŒSOPHAGITIS AND ULCER

### (a) *Acute Peptic Œsophagitis and Œsophageal Ulcer*

**Ætiology and Pathology.**—Acute peptic œsophagitis and acute œsophageal ulcer occur at all ages; the latter is one of the causes of fatal hæmatemesis and melæna in infants. It is always a sequel of severe vomiting in an enfeebled individual with low resistance. The acid gastric contents are retained in the œsophagus just above the closed cardiac sphincter, where their irritant action gives rise to inflammation, the lower end of the œsophagus being generally alone involved. In most cases the acute œsophagitis is associated with the presence of one or more acute ulcers just above the sphincter.

The majority of cases follow post-operative vomiting. Less frequently they result from the vomiting caused by pyloric obstruction secondary to a chronic gastric or duodenal ulcer.

**Symptoms.**—An important symptom of acute œsophageal ulcer is hæmatemesis. It may begin between 24 and 48 hours after an operation which has been followed by severe vomiting. Heartburn and occasionally a burning pain may be felt behind the lower end of the sternum, especially on swallowing. The symptoms rarely persist for more than 10 days after an operation, but in other cases they may continue for long periods, though it is uncertain whether a chronic ulcer ever develops from this condition. Death may occur from hæmorrhage or from perforation of an acute ulcer into the pleural cavity, sometimes without any warning symptoms.

**Treatment.**—The patient should be kept in the erect position and given small milky and semi-solid feeds every 3 hours. Five minutes after each feed he should drink a few ounces of water, and alkalis may be given freely for relief of pain.

### (b) *Chronic Peptic Œsophagitis and Œsophageal Ulcer*

**Ætiology.**—Simple chronic ulcer of the œsophagus was formerly regarded as little more than a pathological curiosity, but a recognition of its clinical features has in recent years shown that it is not uncommon. The incidence is greater among men than women; the majority occur between the ages of 50 and 70.

**Pathology.**—Œsophageal ulcers have all the anatomical characteristics of chronic gastric and duodenal ulcers. In fatal cases heterotopic gastric mucous membrane has sometimes been found in the œsophagus; it probably secretes acid gastric juice, which collects in the lower end of the œsophagus immediately above the closed sphincter, and in course of time an erosion and finally a chronic ulcer develops as a result of peptic digestion of the very vulnerable stratified epithelium. In a large majority of cases, however, the ulcer is associated with a hiatus hernia (q.v.)

**Symptoms.**—Discomfort or pain, often of a burning character and sometimes described as heartburn, occurs under the lower third of the sternum whilst eating solid food, hot drinks or strong alcohol. The pain may also occur on leaning forward and shortly after lying down. It often radiates to the back and occasionally to the left shoulder or left side of the neck. At first the pain lasts for only a few minutes, but later it is prolonged and the patient may become frightened to eat. The food

sometimes appears to stick at the lower end of the œsophagus before passing into the stomach. The spasm which causes the dysphagia sometimes leads to effortless regurgitation of sour material. The pain is relieved by alkalis and can generally be completely prevented by taking only fluid food. Progressive emaciation and anæmia are common in chronic cases. As with chronic gastric and duodenal ulcer, the symptoms at first occur for periods of varying duration with intervals of complete freedom.

Occult blood is present in the stools. Hæmatemesis, which may be severe but is rarely fatal, occurs in about 20 per cent. of cases and may be the earliest symptom. Perforation into the mediastinum, pericardium or peritoneum is rare, but it is a more common cause of death than hæmorrhage. In very chronic cases a fibrous stricture may develop and lead to more or less complete obstruction: much fibrosis and thickening of the œsophageal wall is found on microscopic examination.

The clinical picture may be confused by association with a gastric or duodenal ulcer. Excessive salivation is common. This may lead to aerophagy, which occasionally causes severe pain in the left hypochondrium owing to inability to expel the excess of gas from the stomach on account of œsophageal spasm (*aërogastric bloquée*).

Radiographic examination during the swallowing of a barium emulsion generally shows no abnormality, though the emulsion may be held up by spasm at the lower end of the œsophagus. The œsophagus may be slightly dilated, but there is never anything approaching the characteristic mega-œsophagus caused by achalasia of the cardia. When a semi-solid opaque meal is swallowed, or if the opaque emulsion is swallowed whilst the patient is lying down, a characteristic picture is obtained. This consists of a narrowing caused by spasm near the lower end of the œsophagus; below this is a rounded shadow corresponding with the crater of the ulcer, and below this again is the cardiac sphincter, in which two or three longitudinal folds can often be recognised, passing to the stomach, which is often partially herniated into the chest.

It is advisable to confirm the diagnosis by œsophagoscopy, though occasionally the ulcer itself cannot be reached owing to the spasm just proximal to it. If there is any doubt about the nature of the ulcer, a fragment of its margin should be removed for microscopical examination. The ulcer is always associated with inflammation of the mucous membrane of the lower third of the œsophagus.

**Diagnosis.**—The diagnosis of peptic œsophageal ulcer must be made from a consideration of the symptoms, as the condition is generally missed in a routine radiological examination. The latter, however, serves to exclude cardiospasm and cancer of the œsophagus, which might be regarded as the cause of the dysphagia, though substernal pain and heartburn are rarely present in the former.

Ulcer of the œsophagus is clinically indistinguishable from peptic œsophagitis affecting the lower end of the œsophagus; the latter may be associated with spasm, but no actual ulcer can be recognised either with the radiogram or the œsophagoscope.

**Treatment.**—A patient with severe œsophageal ulcer should be given fluid feeds only and treated in the sitting position so as to lessen stagnation in the lower end of the œsophagus; he should drink a few ounces of water a quarter of an hour after each feed so as to wash its remains into the stomach. Maximal doses of atropine and a tablespoonful of olive oil should be given a quarter of an hour before each feed in order to overcome spasm. The treatment should be continued until not only all pain and dysphagia have disappeared, but also until the radiograms show no trace of a crater and the occult blood has disappeared from the stools. If the ulcer does not heal within a couple of months, or if, when first seen, much cicatricial narrowing with secondary stasis in the œsophagus is present, surgery should be advised without delay. A gastrotomy may be necessary, followed by an anastomosis between stomach and œsophagus, performed through a transthoracic approach, or a partial resection of the œsophagus may be possible. Cases of moderate stenosis may be treated by endoscopic dilatation.

## ŒSOPHAGEAL HIATUS HERNIA

**Synonyms.**—Diaphragmatic Hernia; Thoracic Stomach.

In this condition part of the stomach is herniated into the thorax through the œsophageal opening in the diaphragm. In a few cases this is a congenital abnormality—short œsophagus—but in the majority it is acquired, and results from relaxation or trauma of the tissues at the diaphragmatic opening, with an increase in intra-abdominal pressure due to such causes as pregnancy, obesity or continued coughing. Most œsophageal herniæ are of the sliding type, in which the stomach is drawn through the diaphragmatic opening, the cardiac sphincter is incompetent, and acid regurgitation and œsophagitis occurs. In others, a part of the fundus of the stomach herniates into the chest alongside the œsophagus—paraœsophageal hernia—and there is less chance of acid regurgitating into it. A congenitally short œsophagus and œsophageal inflammation, such as follows the swallowing of caustics, may draw the stomach upwards through contraction of scar tissue, and congenital absence of part or all of one side of the diaphragm may also occur.

An œsophageal hernia may be present intermittently and is usually found in middle-aged women who are overweight. It may remain symptomless or give rise to belching, fullness after meals and epigastric or substernal discomfort. If there is acid regurgitation into the œsophagus, a sensation of burning behind the sternum occurs, which may radiate to the back, arm, neck and ears. With a paraœsophageal hernia there is often a complaint of a lump in the throat, asthma and "wind round the heart".

**Diagnosis.**—The diagnosis may be difficult to make, but the most important characteristic is the relationship of the symptoms to posture rather than to eating. Bending forward as in digging, or doing up a bootlace brings on the discomfort burning or pain, which may also occur when the patient lies down in bed. It is usually relieved by sitting up and by alkalis. It must be distinguished from the pain of angina pectoris, which is more related to exertion than position, and from the symptoms of peptic ulcer, gall-bladder disease and nervous dyspepsia. In any case of suspected hiatus hernia a special radiological examination should be made in the particular position which causes the pain, when gastro-œsophageal regurgitation of barium may be seen and the herniation demonstrated.

**Treatment.**—In treatment much may be done by relieving the patient's mind about the pain and the absence of heart disease, and by advice to avoid bending and to sleep propped up in bed. If there is œsophagitis a régime similar to that advised for peptic ulcer should be given and only if the symptoms are severe should surgery be considered. In this case, operation using the thoracic approach to reduce the hernia and fix the stomach in position may be successful, or more extensive procedures if an œsophageal stricture is present. Anæmia sometimes arises from hiatus hernia in which case iron should be given in full dosage. Symptoms occurring in pregnancy usually improve after delivery, when the intra-abdominal pressure has fallen.

## NON-MALIGNANT STRICTURE

**Ætiology.**—Stricture of the œsophagus is in rare cases congenital; the middle part of the œsophagus may be represented by a fibrous cord, or the lower part may open into the trachea or into one of the bronchi. It may also be a sequel of the acute œsophagitis resulting from caustic poisoning, or the impaction of a foreign body, and of the healing of a chronic peptic ulcer just above the cardiac sphincter. At œsophagoscopy concentric narrowing of the œsophagus may be seen, or irregular scarring with evidence of healed ulceration and peri-œsophageal adhesions. Syphilitic strictures are very rare.

**Treatment.**—Dilatation of the stricture causes bleeding and any persisting inflammation is increased by the trauma leading to still further fibrosis. If the stenosis is sufficient to cause dysphagia, surgical resection of the diseased portion of œsophagus is necessary, which may have to be preceded by gastrostomy. Various methods of restoring the continuity of the œsophagus have been devised.

## CANCER OF THE ŒSOPHAGUS

**Ætiology.**—Cancer of the œsophagus occurs with about one-third the frequency of cancer of the stomach. Over 70 per cent. of all cases occur in men, but 80 per cent. of upper œsophageal growths occur in women (p. 543). Among 100 cases of cancer occurring in the alcohol trades (barmen, cellar-men, waiters and brewers) about 15 affect the œsophagus compared with 7 in men working in other trades, suggesting that the chronic œsophagitis caused by excessive indulgence in alcohol may be a predisposing cause.

**Pathology.**—Most growths of the œsophagus are epitheliomata. They are most common in the lower end and then at the level of the bifurcation of the trachea, these being the narrowest parts, the mucous membrane being consequently most subjected to friction by coarse food. Less frequently they occur at the upper end of the œsophagus; it is then impossible to say whether an epithelioma is a primary growth of the pharynx, from which it has spread into the œsophagus, or a primary growth of the œsophagus which has spread into the pharynx. Ulceration occurs at an early stage. Accumulation of food above the obstruction leads to progressive dilatation, and the efforts of the œsophageal musculature to overcome it results in hypertrophy, but the dilatation and hypertrophy are comparatively slight except in cancer of the lower end, as when the obstruction is higher up, vomiting occurs so quickly that very little food can accumulate.

**Symptoms.**—Dysphagia is almost always present, and is the first symptom in a large majority of cases. Most frequently a patient in perfect health one day experiences a slight discomfort on swallowing; soon he notices that his food seems to stick for a moment before passing on into his stomach. The difficulty becomes slowly but steadily more marked, with rare intermissions lasting for a few meals or at most for a few days. The patient often manages to swallow his food by chewing more thoroughly, by taking smaller mouthfuls and by drinking after each mouthful. More and more effort is required, until after a period, which is generally between 1 to 4 months but may be as long as a year and a half, solid food ceases to pass at all and is regurgitated into the mouth a few seconds later. After an average of 8 months there is complete obstruction to the passage of fluids as well as solids. The patient generally localises the position of obstruction correctly, but he occasionally thinks that it is in the upper end when it is really in the lower third.

Pain is not an early symptom and occurs in only about 50 per cent. of cases; it is most frequently absent when the growth is in the lowest third of the œsophagus. It occasionally begins a few days before or simultaneously with the dysphagia, but more commonly it is not noticed until the latter has been present for 1 or 2 months. The pain may be present only during deglutition, disappearing as soon as the food passes the obstruction. It is situated at the level of the obstruction and often passes through to the back.

Regurgitation of food almost always occurs sooner or later. It generally begins between 1 and 2 months after the onset of symptoms and is rarely delayed as long as 6 months. When the growth is situated in the upper third of the œsophagus the food is violently ejected out of the mouth or even from the nose after a coughing effort. When the middle or lower third is involved, the food regurgitates without effort into the mouth, often immediately after meals. If the œsophagus is dilated,

food may be regurgitated any time up to 2 hours after being swallowed. The food is completely undigested and always contains mucous saliva, often in considerable quantity, as continuous salivation is common. Regurgitation of saliva alone occurs when the obstruction is sufficient to interfere with the swallowing of fluid. The regurgitation of the contents of the dilated œsophagus gives relief to any discomfort or pain which is present. The regurgitated material sometimes contains blood and pus, and in exceptional cases is very foul; occasionally several ounces and, in rare cases, a large quantity of blood is vomited.

Progressive emaciation occurs owing to the small amount of food which is taken, and when obstruction is complete the loss of weight is very rapid. The appetite may remain good, and hunger may be very distressing in the early stages, but this becomes less marked as the disease progresses. Severe thirst with dryness of the mouth is sometimes present, and fetid breath is common when there is extensive ulceration. In the late stages small hard glands are often felt in the neck, especially just above the inner end of the clavicle and beneath the lower jaw.

The vagus or recurrent laryngeal nerves, especially of the left side, may be involved, and one, or rarely, both vocal cords may consequently be paralysed. Pressure on the cervical sympathetic may cause contraction of the pupil with slight enophthalmos and narrowing of the palpebral fissure on the affected side. Compression of the trachea or the main bronchi by the tumour or by secondary glands may cause hoarseness, coughing and dyspnoea. Perforation into the trachea or a bronchus gives rise to a paroxysm of coughing and dyspnoea whenever food is swallowed, and death from broncho-pneumonia or gangrene of the lung is likely to occur. Perforation into the pleural cavity may produce an empyema, but a serous pleural effusion may develop without perforation.

**Diagnosis.**—In a large proportion of cases it is possible to make a definite diagnosis from the history and from the information obtained by radiography, which should always be used without delay in cases of dysphagia. Before giving the opaque meal the thorax should be examined from every direction in order to exclude an aneurysm, although in the very rare cases in which this causes dysphagia, other more characteristic symptoms generally make the diagnosis clear. Occasionally a growth of the œsophagus or secondary glands throw a shadow in the radiogram, but this is rarely obvious until the symptoms have been present for a considerable time. With an opaque meal the radiograms show the position and length of any narrowing of the lumen of the œsophagus, the degree of dilatation above the obstruction and the amount of obstruction, but the latter may be in part caused by spasm. In the earliest stages, when the lumen is not much reduced, the semi-fluid opaque meal may pass down without revealing any abnormality. Some ordinary food which is known to cause pain or difficulty should then be swallowed with the opaque fluid; spasm is induced and the position and extent of the growth can be clearly recognised.

The diagnosis of a growth from achalasia of the cardia has already been considered (p. 545). The presence of hard glands in the neck makes the diagnosis of cancer extremely probable. In those cases in which the history and the radiographs leave the diagnosis in doubt, and especially in early cases, an examination should be made with the œsophagoscope, by means of which the nature of the obstruction can generally be recognised, and a fragment removed for biopsy, though failure to detect malignant disease in the excised fragment does not exclude the possibility of cancer.

There may be considerable difficulty in diagnosing between an epithelioma of the lower end of the œsophagus, which spreads upwards, but very rarely downwards into the stomach, and a primary carcinoma of the fundus of the stomach, which almost invariably involves the cardiac orifice sooner or later. With the former the dysphagia is the first symptom; with the latter anorexia, pain after food, loss of weight and

strength, vomiting and increasing pallor may appear before the dysphagia, but this is not always the case, as dysphagia may be the only symptom. When the tumour is gastric in origin the radiographs show a filling defect, together with irregularity of the folds of mucous membrane and encroachment on the transparent arc which is normally formed by the gas in the fundus, and sooner or later a mass can be felt high up under the left costal margin.

**Prognosis.**—Growths of the œsophagus are of high malignancy and tend to metastasise early; death usually occurs between  $2\frac{1}{2}$  months and  $2\frac{1}{2}$  years after the onset of symptoms, the most common period being between 6 and 12 months. It is most frequently due to broncho-pneumonia, exhaustion from starvation, or the effects of metastases.

**Treatment.**—The radical treatment of cancer of the œsophagus by excision of the growth has until recently rarely been successful. Improvements in the technique of thoracic surgery have however resulted in the successful removal of a steadily increasing number of growths in the middle and lower end of the œsophagus. Various forms of gut or skin tubes to unite pharynx and stomach outside the thorax have been adopted, mostly using a loop of jejunum as an artificial œsophagus. Œsophago-gastrostomy may be possible but in inoperable cases gastrostomy may be the only means of maintaining nutrition when obstruction is complete.

As the diagnosis of carcinoma of the œsophagus in the early stages is not difficult, the prospects of radical surgery may well improve in the future, but at present the mortality rate is high.

Radiotherapy may be given either by massive dosage of deep X-rays or by direct application of radium, but holds out less hope of cure than surgery. The most successful method has been by direct irradiation of the growth at open operation, so partly avoiding the damage to other tissues which adequate irradiation may otherwise cause. Unfortunately growths of the œsophagus spread locally and by lymphatics early and make radical excision or irradiation extremely difficult. The operative mortality of suitably selected cases lies between 20 and 30 per cent.

With modern surgery and the modern forms of radiotherapy, it is now rarely necessary to insert tubes, but if obstruction in the middle of the œsophagus cannot be overcome, a spiral metal tube should be introduced through an œsophagoscope, if necessary after preliminary dilatation of the stricture by bougies. Its lower end reaches beyond the growth, whilst the upper funnel-shaped end rests on its proximal margin. The tube can be left *in situ* until the end, but it sometimes leads to so much dilatation that it passes through the obstruction and is expelled *per anum*.

So long as any obstruction is present the food should be semi-fluid or fluid, and should be taken in small quantities at frequent intervals. As large a dose of atropine as possible, short of producing unpleasant symptoms, given half an hour before each feed and a dessertspoonful of olive oil just before, often help its passage through the stricture.

THOMAS HUNT.

## DISEASES OF THE STOMACH

### INTRODUCTION

#### GASTRIC SECRETION

The healthy stomach secretes gastric juice continuously day and night in varying amounts under varying circumstances, the resting volume being normally about 10

to 15 ml. per hour. It is made up of hydrochloric acid secreted by the parietal (or oxyntic) cells, found in the body of the stomach, alkaline mucus secreted by the mucoid cells, and pepsin, secreted by the chief cells situated mainly at the pylorus. In addition to these specific secretions, the gastric juice contains water, neutral salts (mainly chlorides) and small amounts of urea, amines and ammonia. It is probable that these various constituents of the gastric juice may be independently affected by different stimuli so that it may vary considerably in composition from time to time, and is not uniformly the same under all conditions in the same individual. The parietal cells secrete, however, a relatively constant strength of almost pure hydrochloric acid which is constant in each individual—being approximately 0.154 to 0.2 normal concentration. The volume of juice secreted varies greatly under different circumstances, and the acidity and peptic activity also alter, both as regards the amounts actually secreted and through the effects of dilution with other gastric secretions, saliva, ingested food and the regurgitation of alkaline duodenal contents. In addition, the acidity may differ somewhat in different parts of the stomach, the cardiac end being more acid than the pyloric, especially at the beginning of digestion.

Variations in gastric secretion may also be constitutional, varying from individual to individual, so that different personalities and different physical builds may be associated with different types of gastric secretion. Constitutional variations in gastric secretion may sometimes be familial, and may undoubtedly play a part in the predisposition to certain types of gastric diseases or dysfunction (*vide infra*). At the same time it is important to emphasise that terms such as hypersecretion, hyperchlorhydria, hyperacidity and their opposites hypo- or achlorhydria do not themselves represent diseases but are merely names for secretory variations which are quite compatible with perfect health, good digestion and a normal expectation of life except for the possible development of certain diseases to which they may predispose. These secretory variations are often associated with characteristic temperaments and personalities—the hypersecretory for instance being often found in the ambitious, restless, energetic individual, and the normal or low secretory in the more phlegmatic, resigned and apathetic type.

In a hypersecretory stomach the resting secretion of juice is usually highly acid and of large volume whilst the mucus secretion is generally low, so that when this is associated with a rapidly emptying stomach the duodenum is likely to receive large amounts of acid juice, and the risk of duodenal erosions or ulcer developing is increased.

*Achlorhydria.*—The incidence of achlorhydria among healthy people rises from 4 per cent. at the age of 20, to 8 per cent. in the 30 to 39 period and 12 per cent. in the 40 to 49 period, but above this age only a small increase is found. With achlorhydria there is usually an excess of mucus. The absence of acid allows organisms to reach the small intestine, and the gastric emptying time is usually rapid so that diarrhoea may occur. Flushing of the face during meals is also common in achlorhydria, which is frequently found in acne rosacea.

*Effects on hæmatopoiesis and the nutrition of the central nervous system.*—The absence of free acid from the gastric contents in achlorhydric chronic gastritis, and the enteritis with which it is often associated may interfere with the assimilation of the iron in food, so that in individuals who take a diet in which there is only just enough iron for the needs of the body under the most favourable conditions, a simple achlorhydric anæmia develops, which differs from pernicious anæmia in occurring almost exclusively in women and in being curable by large doses of iron, whilst liver is without effect.

Achlorhydria is found in about 99 per cent. of cases of pernicious anæmia and of subacute combined degeneration of the spinal cord, though it is not the actual cause of it (see p. 734). There is often a history of chronic diarrhoea or other symptoms to which the achlorhydria has given rise, dating from months or years before the onset



of anæmia or nervous symptoms. The occurrence of pernicious anæmia and subacute combined degeneration of the cord in more than one member of the family is due to the familial occurrence of constitutional achylia gastrica and hypochlorhydria, which may depend upon a primary atrophy of the gastric mucosa. Moreover, achylia is often present without any abnormality of the blood or central nervous system, in relatives of patients with these diseases.

*Regulation of gastric secretion.*—The secretory cells of the stomach are influenced by both excitatory and inhibitory stimuli, which may be either nervous or chemical. The main nervous pathway is through the vagus, a psychic stimulation of secretion being set on foot via this nerve by the sight, smell or even thought of food. This psychic phase of secretion begins before food enters the stomach and is markedly affected by emotions, being greatly inhibited by feelings such as fear and sadness and accelerated by feelings such as anger, resentment and anxiety. Prolonged periods of emotional tension may thus lead to engorgement and hypersecretion in the stomach, both the continuous fasting secretion and the psychic secretion being affected. Surgical section of the vagus nerves has in consequence been recommended in treatment of gastric diseases (see p. 587).

*Chemical stimuli.*—The most powerful chemical stimulus to gastric secretion is histamine, which acts mainly upon the parietal cells, and much less powerfully, if at all, upon the pepsin and mucus secreting cells. Meat, meat extracts, peptones, liver extract, coffee and tea (containing caffeine), alcohol and most highly flavoured or irritant foods also act locally as excitors of the gastric secretion—some also if given parenterally. Besides this gastric phase of secretion regulated by chemical substances within the stomach, there are important regulating mechanisms acting through the intestine. The presence of acid in the duodenum, for example, produces an inhibitory effect as does the entrance of fats into the intestine, particularly upon the pepsin-secreting cells in the stomach. These effects are mainly produced through the blood-stream, and extracts of intestinal mucosa which have been in contact with fat have been shown to contain chemical agents which inhibit the gastric secretory response to a test-meal in the absence of any nervous mechanism. The name enterogastrone has been given to one such agent, which has been purified and studied extensively by Ivy, and others, and used in therapeutics with some success. The inhibitory effects of fats has also been made use of in treatment, by the giving of olive oil, milk, cream, etc., to reduce gastric secretion.

#### GASTRIC MOTILITY

Gastric movements have been studied both by radiography and by the use of balloons introduced into the stomach on the end of a Ryle's tube and connected to recording tambours on a revolving drum. By these methods gastric contractions are found to be of two types—short vigorous peristaltic contractions lasting about 30 seconds each, and smaller rhythmic contractions—tonus rhythm—occurring (during rest) from 1 to 3 times a minute. These movements mix up the gastric contents, and intermittently carry small amounts through the pylorus, which normally only opens for momentary periods at a time. Both types of gastric movements may be markedly increased by emotions such as resentment, and inhibited by others such as fear. They are also inhibited for a time by the ingestion of cold water and by fatty foods, and accelerated by the intake of proteins, broths and chemical irritants. Both types of gastric contraction may be increased during hunger, whilst tonus rhythm is lessened when the stomach is full. The emptying time of the stomach varies widely in different individuals, depending partly upon constitution and partly upon the above factors. In general each individual has throughout life a constant type of gastric emptying, either slower or faster, the average normal time lying between  $1\frac{1}{2}$  and  $4\frac{1}{2}$  hours. Emptying is slowest with dry solid mixed meals containing fat, and is quickest with fluid meals containing sugar but no fats.

## GASTRIC SENSATION

If the abdominal wall is properly anæsthetised, no pain is felt when the stomach is cut, pinched or cauterised. Acute mucosal ulcers are also quite painless unless they perforate the peritoneum, and carcinomatous infiltration of the stomach may occur with practically no abnormal gastric sensation at all.

At the same time severe pain may undoubtedly arise from the walls of the stomach and is carried centrally by special pain nerves which may be stimulated either by tension or by chemical agents. The pain of peptic ulcer for instance is related both to increased muscular activity and spasm, and to the acid contents of the stomach as shown both clinically and by many carefully controlled experiments. The threshold of pain, both to muscular spasm and to acid stimulation, probably varies considerably in different individuals and in the same individual at different times. Feelings of gastric distension are related to the degree of tone with which the stomach holds its contents as well as to the actual volume of the contents themselves; in pyloric obstruction, for example, with extreme gastric distension tone and peristalsis may both be lost, pain be absent, and the sensation of stomach fullness directly related to the volume of the contents. On the other hand even a small meal in a nervous subject may cause a great feeling of fullness if the gastric tone fails to relax adequately to hold the food ingested. Many feelings such as appetite, hunger, nausea are excited centrally rather than locally, even though changes in gastric motility, vascularity and secretion occur with them; hunger does not necessarily result from an empty stomach.

## FUNCTIONS OF THE STOMACH

1. *Digestion.*—Foods are softened and mixed in the stomach, whilst the pepsin of the gastric juice converts proteins to peptones in the presence of free hydrochloric acid. Its activity rapidly falls when the amount of free acid present sinks below 0.08 per cent. until it finally ceases in complete achlorhydria. In spite of this, digestion of proteins remains almost unimpaired in achlorhydria, as the trypsin of the pancreatic juice is capable by itself of digesting all the proteins consumed in ordinary meals. An increase in the free hydrochloric acid above the average normal does not lead to any increase in peptic activity. Sugars and starches are little affected during gastric digestion, whilst there is practically no absorption of foods or fluids other than alcohol and water. The gastric enzyme rennin converts the insoluble caseinogen of milk to the soluble casein.

2. *Protection of the small intestine from injury.*—An important function of the stomach is to protect the small intestine from thermal, chemical and mechanical irritants. Very hot and very cold food and drink are brought to the body temperature; the gastric juice dilutes chemical irritants, such as alcohol, and softens hard particles, and the churning movements in the prepyloric region break up lumps of insufficiently chewed food. At the same time the stomach attempts to protect its own mucous membrane from damage by secreting mucus in response to stimulation by chemical and mechanical irritants.

3. *The antiseptic acid barrier of the stomach.*—The free hydrochloric acid of the gastric juice is a very efficient germicide and rapidly destroys streptococci swallowed from the mouth, throat and nose, as well as many organisms present in contaminated food and drink. It also helps to keep the reaction of the small intestine at a level which prevents its invasion by *Bact. coli* from the lower ileum and colon.

4. *Influence on the blood and spinal cord.*—The gastric juice contains the "intrinsic factor" of Castle, which acts on the "extrinsic factor", which is present in protein

food, thereby facilitating its absorption. The intrinsic factor is produced by the glands of the body of the stomach.

The presence of free hydrochloric acid helps the conversion of the iron contained in food into a form in which it is easily absorbed, so as to become available for the production of hæmoglobin.

## CAUSES OF GASTRIC DISORDERS

### A. ORGANIC

(i) *Mechanical, chemical and thermal irritants.*—The mouth acts as the first line of defence in protecting the alimentary tract from damage by swallowed irritants. Food and drink are brought to the body temperature, chemical irritants are diluted, lumps of food are broken up by chewing and are intimately mixed with saliva, which softens hard particles and coats insoluble ones with mucus. Many people, however, bolt their food before it has been thoroughly masticated, and others have insufficient teeth and inadequate dentures, with the result that the stomach is daily subjected to mechanical, chemical and thermal irritants. It is also often damaged by excessive indulgence in alcohol, especially whilst fasting, or by strong tea and coffee, mustard, pepper, curry, pickles, raw or insufficiently cooked coarse vegetables, or tough meat. The stomach is frequently irritated, especially when empty, by the unconscious swallowing of the "juice" of tobacco smoked in excess. Many people injure their gastric mucous membrane by taking drugs often quite needlessly, for supposed constipation, rheumatism and other self-diagnosed complaints, quite apart from those used in the treatment of definite chronic maladies—such are aspirin, bromides, iodides, digitalis, mercury, creosote and quinine. The contents of the duodenum act as irritants when introduced into the stomach; gastritis is consequently a frequent sequel of gastro-jejunoscopy and partial gastrectomy.

(ii) *Infection.*—Infected material is constantly swallowed by people with pyorrhœa alveolaris, infected tonsils, chronic pharyngitis and sinusitis, and by children with adenoids: also by those suffering from chronic cough as in bronchiectasis or pulmonary tuberculosis. In achlorhydria the antiseptic acid barrier of the stomach is lost, but when gastric juice is secreted in normal or excessive quantities, and even when it is deficient (in hypochlorhydria) such swallowed bacteria, with the exception of the tubercle bacillus, are rapidly destroyed. Tubercle bacilli, on the other hand, are completely resistant to gastric acid.

(iii) *Hæmatogenous irritants.*—Many acute infections may be accompanied by acute gastritis, which is often followed by chronic gastritis. The gastritis is due mainly to the direct action of bacterial toxins conveyed in the blood to the gastric mucous membrane, which perhaps makes an attempt to excrete them. Possibly the toxins produced in the body tissues themselves in acute infections may be in part responsible, just as the toxins of uræmia and substances produced in the skin in extensive burns may cause gastro-duodenitis and acute ulcers. The abdominal symptoms in gastric influenza are the result of acute gastritis, and acute ulcers and erosions are common in the stomach and duodenum in fatal cases of a great variety of infections.

### B. NERVOUS (PSYCHOSOMATIC)

The long-recognised effects of nervous influences upon the stomach have been greatly clarified by the work of Wolf and Wolff (1944) upon their patient, Tom. This man had a gastric fistula surgically produced at the age of 9 after he had completely occluded his œsophagus by drinking scalding hot clam chowder. The authors showed how intense was the effect of changes of emotion and mood occurring normally during ordinary life situations upon the secretion, vascularity and motility of the stomach.

Both the degree and the duration of these psychological factors influence the gastric changes. During periods of emotional conflict with anxiety, hostility and resentment, the gastric mucous membrane becomes red, engorged and turgid, and the folds become thicker and succulent so that a picture exactly resembling that formerly described as hypertrophic gastritis is produced. During this hyperæmic period the tissues of the stomach seem to become more sensitive to pain, and symptoms of indigestion may readily be aroused. Similarly, at this time the mucosa is more vulnerable to injury so that small erosions and bleeding may be produced. Such findings clearly demonstrate how easily nervous dyspepsia may arise through worry, anger, resentment and similar feelings, and how secondary organic changes, particularly ulcer, may follow from the same causes. Anxiety is a frequent cause of recurrence of peptic ulcer, and of the sudden increased activity of ulceration which may result in hæmorrhage or perforation. In the opposite direction feelings of well-being, contentment, joy, happiness, etc., are favourable to normal gastric digestion, whilst fear or depression, which involve feelings of withdrawal or defence rather than aggression, are associated with pallor of the gastric mucosa and inhibition of acid secretion and contractions.

Exhaustion from physical or mental overwork, insufficient sleep, malnutrition or from the toxæmia of chronic infections such as phthisis, and acute infections such as influenza, has a depressing effect on bodily functions as a whole and may increase any liability to gastric symptoms which an individual may have. At the same time the stomach preserves its normal activity remarkably efficiently in many serious organic diseases and gastric studies of chronic invalids have shown that most of them are in fact able to digest a normal diet as well as healthy people, provided their psychological state and appetite are good. The sensation of pain from any part of the body, or any strong feeling of disgust or distaste may violently affect gastric motility so as to cause either temporary inhibition or even antiperistalsis and vomiting. The vomiting of coronary infarction, renal colic and other painful conditions belong to this group.

### C. REFLEX

Disorders of other abdominal organs may give rise to reflex gastric symptoms. Thus chronic cholecystitis, recurrent subacute appendicitis and diseases of the colon and urinary tract may all be associated with indigestion, and pyloric spasm in particular is apt to occur in these conditions.

Reflex stimuli from heart, pleura and other organs in the body may also set up gastric symptoms, as may reflexes from eyes or labyrinth as in Ménière's disease.

## EXAMINATION OF THE STOMACH

### 1. CLINICAL

(a) *Size, shape and position.*—Inspection of the abdomen may reveal the outline of the stomach in thin patients, especially if pyloric obstruction has led to excessive peristalsis. By palpation under similar circumstances the lower border of the stomach can sometimes be felt. Palpation may also reveal the presence of a tumour, the size, shape, position and mobility of which should be estimated. Percussion may give some idea as to the quantity of gas in the stomach, but it cannot help in the determination of its size, shape or position. Auscultatory percussion and friction have been shown by means of radiograms to be quite valueless for examining the stomach.

(b) *Tone.*—Gastric splashing can be obtained in an individual with relaxed abdominal muscles and a stomach with normal tone, and gives little information as to the presence of deficient tone. Owing to the adaptation of the normal stomach to the

volume of its contents the upper level of these contents remains constant whether the volume is 4 oz. or 40 oz.; when the stomach is hypotonic this adaptation is less complete and the greater curvature tends to become more dependent with a greater air bubble and an increased area of gastric resonance on percussion at the cardiac end.

(c) *Peristalsis*.—In thin women normal peristalsis is occasionally visible, but in the majority of cases the presence of visible peristalsis indicates organic pyloric obstruction. The patient should be examined with a strong side-light soon after a meal or drinking half a pint of fluid. In doubtful cases peristalsis can be rendered more obvious by massage.

(d) *Rate of evacuation*.—If gastric splashing can be produced by palpation over the stomach at a time when it should be empty—i.e. more than a few hours after the last food or fluid has been taken, gastric stasis is probably present but there are so many fallacies that this finding is of little diagnostic value.

## 2. RADIOLOGICAL

Plain radiography and screening of the stomach enables the upper level and amounts of its contents and the size of the air bubble in the cardia to be determined. For any complete study, however, a barium meal is required, and for this the patient should have at least 8 hours preliminary fasting. A small amount of barium emulsion is then swallowed and the gastric rugæ can first be outlined by palpation under screen control. When more of the opaque meal is drunk, the size, shape and movements of the stomach can be seen on the screen and radiographs taken. The patient should be photographed in the standing and prone positions, and also when bending well forward, in order to demonstrate any gastric herniation through or alongside the oesophageal opening. The shape and position of the stomach varies greatly and the greater curvature may lie vertically or almost completely transversely. The barium falls rapidly to the bottom of the body of the stomach, which may normally reach down as low as the pelvis. Peristaltic waves can be observed or any persistent spasm or incisura. A niche or constant crater may be seen indicating an ulcer or its irregular outline may suggest a carcinoma. A filling defect in the barium shadow which remains unchanged during the examination point to a growth, as do rigid unchanging rugæ or a tube-like fixity of the barium outline. Normally the stomach is empty of barium in 1 to 4 hours, the average time being  $2\frac{1}{2}$  hours. In cases of pyloric obstruction of whatever type, there is still barium present at 6, 8, 12 or more hours, and in some conditions such as migraine or states of fear and anxiety, nervous inhibition of peristalsis may cause much delayed gastric emptying time.

The value of radiological investigation in gastric and duodenal diagnosis depends greatly upon skilled screening by an expert radiologist, who is able to detect areas of tenderness, deformity or rigidity which may not be shown in the radiogram.

## 3. BIOCHEMICAL

The Ewald Carbohydrate Fractional Test-Meal provides a simple method of investigating certain gastric functions; and providing its limitations are appreciated, some useful information can be obtained. The test is performed by passing a Ryle's tube into the stomach of a patient who has been fasting since the previous evening. The total gastric contents are aspirated and measured, after which a meal consisting of either 1 pint of thin oatmeal gruel, or 2 slices of toast and a cup of weak tea is taken. Thereafter 10 ml. of gastric contents are aspirated every quarter of an hour for 3 hours, or until no further samples can be obtained. The total and free acidity of each sample is determined, using Töpfer's reagent and phenolphthalein as indicators, and they are also examined for the presence of starch and bile. Electrometric estima-

tion of the hydrogen-ion concentration of the samples allows the acidity of the unfiltered aspirate to be accurately determined: a pH of 3.5 is taken as the arbitrary level, above which free acid is assumed not to be present in any sample. If no free acid is found in any sample the test is repeated on the following morning, this time using 50 ml. of a 7 per cent. solution of alcohol instead of the carbohydrate meal, and giving a subcutaneous injection of either 0.5 mg. of histamine or 7 units of insulin 1 hour after the alcohol is drunk. If free acid still fails to appear in any of the samples, an achlorhydria is assumed to be present, although a high proportion of subjects who exhibit an histamine-fast achlorhydria to the test-meal, will show secretion of free acid in one or more samples if a 24-hour titration is undertaken.

The normal amount of resting juice found in man is subject to much variation, but if the fluid exceeds 40 ml. in volume and contains food residues, some degree of pyloric obstruction is probably present. Gross contamination of the resting fluid with blood may be due to gastric carcinoma or ulceration, but can also be due to epistaxis, œsophageal varices, acute gastric erosions or a friable hypertrophic gastric mucous membrane.

In gastric ulceration the amount of free acid found does not vary from normal, but in duodenal ulceration a high resting juice acidity is often found, and that of the remaining samples is usually raised. These findings are, however, often demonstrated in normal subjects with no clinical or radiological evidence of peptic ulceration.

Hypochlorhydria is often associated with microcytic anæmia, lenteric diarrhoea and post-prandial epigastric discomfort, but the symptoms are usually relieved by iron, and unrelieved by giving hydrochloric acid by mouth. Most patients with a gastric carcinoma show an achlorhydria at some stage during their illness, but the fact has little value in diagnosis. Almost all cases of pernicious anæmia have a histamine-fast achlorhydria.

A rough estimation of the emptying time of the stomach can be arrived at by testing the samples for starch, which should not be present after 2½ hours.

In 24-hour studies of gastric acidity it has been shown that most cases of duodenal ulceration secrete a large volume of highly acid juice all through the night, whereas normal subjects and patients with gastric ulcers only secrete intermittently during the night, and the juice is of low acidity.

Attempts to detect the presence of gastric carcinoma by microscopic examination of cellular fragments withdrawn with the gastric juice at a test-meal have not yet proved of consistent value in diagnosis.

#### 4. GASTROSCOPIC

Gastroscopic examination of the stomach may provide useful information in certain cases. The procedure requires considerable experience both in the passing of the instrument and in interpreting results. There is a minimal risk of injuring the patient and the mortality risk is less than 0.1 per cent. The pharynx is first thoroughly anaesthetised and after passing the instrument most of the stomach may be visualised except the cardiac antrum, and the lesser curvature of the pyloric vestibule. In very anxious or elderly patients a general anaesthetic may be employed. The main value of gastroscopy lies in the demonstration of a gastric ulcer which has not been recognised by radiography and in a very few cases also of early carcinomata. In patients, therefore, who have gastric symptoms with negative clinical and radiological findings gastroscopy is of special value even if only in ruling out organic disease. It may be used to control the healing of a gastric ulcer, and indeed affords the only really certain evidence of complete healing, since both symptoms and radiographic examination may suggest that this has occurred though in fact an ulcer is still actively present.

Gastroscopy is helpful in the recognition of different forms of gastritis and of

erosions and acute or subacute ulcers, but the interpretation of the findings is not easy. It may be of value after hæmatemesis in excluding ulcer or demonstrating a hypertrophic gastric mucosa, and in diagnosing the cause of post-operative symptoms when radiology has failed to show anything abnormal.

It is possible by a special technique to remove small fragments of gastric mucosa at gastroscopy for biopsy and valuable evidence has been obtained in this way. Careful correlation, however, of gastroscopic findings with symptoms, biopsy and post-mortem examinations have shown that some of the appearances which were regarded as the result of acute or chronic gastritis were in fact only due to temporary changes in the mucosa induced by fear of the examination or other causes. Thus, the congested or reddened state of the mucosa, due to anger or frustration, was thought to be due to hypertrophic gastritis, whilst the pallor often seen in states of disgust or fear was thought to indicate an atrophic gastritis.

## FUNCTIONAL DISORDERS OF THE STOMACH

### VOMITING

**Ætiology.**—(1) **CENTRAL VOMITING.**—(a) Many organic nervous diseases, such as cerebral tumour and meningitis, are accompanied by vomiting, which may also occur in compression caused by injury. This is generally due to increased intracranial pressure, and in cerebral tumour relief of such pressure often leads to cessation of vomiting. A mid-cerebellar tumour may give rise to vomiting as a result of direct pressure on the vomiting centre on the floor of the fourth ventricle long before other symptoms develop.

The vomiting of migraine is also of central origin. The cyclical vomiting of children is generally associated with a family history of migraine, and is often followed by true migraine in adult life. Such attacks may often rapidly lead to ketonuria and may, therefore, be wrongly regarded as caused by "acidosis". Though glucose may help in the prevention of such attacks, their true biochemical nature is not understood.

(b) Various emotions, particularly those of disgust or fear, may result in vomiting, especially in neurotic individuals. It may occur as a result of incidents which subconsciously revive the memory of an emotion which on some particular occasion caused vomiting. Thus, a woman who on one occasion vomited as a result of terror in a railway carriage, subsequently vomited whenever she travelled in a train, and after a time in any vehicle, and even in closed places, such as a church, from which she could not readily escape. The vomiting was associated with vague feelings of fear, *but not consciously with the incident which was the primary cause.*

(c) Hysterical vomiting represents a physical defence against some intolerable situation and usually occurs during or immediately after meals. It is effortless and generally unaccompanied by nausea, so that a patient may vomit meat and vegetables and immediately afterwards be ready to eat a sweet which he retains without difficulty. The stomach is, as a rule, only partially emptied, so that nutrition is preserved, but in rare cases nothing is retained, and severe emaciation, together with the changes in the urine which follow starvation and have erroneously been ascribed to toxæmia, result. The diet has little or no effect, vomiting being as frequent with milk alone as with a full diet.

(d) Habit vomiting. Vomiting is only rarely under the control of the will, but a person who has vomited a number of times may suggest to himself that certain circumstances will invariably cause him to vomit again. Similarly the habit of vomiting may persist after organic causes, such as whooping-cough.

(2) **REFLEX VOMITING.**—Painful stimulation of any afferent nerves, but particularly those of abdominal viscera, such as occurs in gastric ulcer, biliary and renal

colic, Dietl's crises and appendicitis, often causes reflex vomiting. Tickling the fauces is an easy means of inducing vomiting.

Sea-sickness and air-sickness are caused by a reflex arising from excessive stimulation of the semi-circular canals. The vomiting in diseases of the ear in which the semi-circular canals are involved as in Ménière's syndrome, is of similar origin. The vomiting of early pregnancy is probably reflex; when persistent it is almost always hysterical, though other factors may also be concerned. This condition must be distinguished from the vomiting which begins in the later stages of pregnancy and is a symptom of pregnancy toxæmia (pre-eclampsia).

(3) **TOXIC VOMITING.**—Substances produced in the body, as in uræmia, hyperthyroidism and cirrhosis of the liver, may irritate the vomiting centre. In uræmia the action is partly reflex, owing to the excretion into the stomach of toxins which should be excreted by the kidneys, and partly a result of increased intracranial pressure. Toxins formed in acute infections such as scarlet fever, pneumonia, hepatitis and influenza excite vomiting by their irritant action on the gastric mucous membrane, and on the vomiting centre. Toxic vomiting differs from central vomiting, and some cases of reflex vomiting, in being almost invariably preceded by nausea. It is a frequent symptom in active pulmonary tuberculosis (see, p. 1023).

(4) **LOCAL GASTRIC IRRITATION.**—Vomiting occurs when the gastric mucous membrane is irritated by decomposing or contaminated food, and by various inorganic and organic poisons. Thus, strong alcoholic drinks, or the consumption of foods to which an individual is sensitive such as shell-fish (gastro-intestinal allergy), may cause vomiting. Over-distension with food, especially if it occurs rapidly, as when a big meal is bolted, or if it continues for an abnormally long period as a result of pyloric obstruction, has the same effect. In all these cases more or less relief to the local symptoms follows the vomiting. Many drugs, particularly expectorants, given medicinally in normal dosage may cause vomiting in sensitive individuals (idiosyncrasy) or in non-sensitive patients if the dosage is high. Morphine is particularly liable to do so, as is quinine, whilst the vomiting caused by digitalis over-dosage is especially important. Emetics, such as strong salt water, and copper and zinc sulphate act directly upon the stomach, but others, such as apomorphine, cause vomiting by direct stimulation of the vomiting centre. The former are, of course, only effective when swallowed, whilst some such as tartar emetic, ipecacuanha and general anæsthetics act both locally and centrally. In the case of apomorphine the action may be rapid and violent and associated with considerable depression of the vasomotor and respiratory centres, and it must be used with caution.

(5) **OBSTRUCTIVE VOMITING.**—The projectile vomiting of pyloric stenosis and that due to intestinal obstruction are described under their respective organic causes (see pp. 594 and 651).

**Treatment.**—The proper treatment of vomiting is to remove the cause. When it is the result of direct irritation of the stomach, complete evacuation gives relief. This can often be effected by tickling the pharynx or drinking a large quantity of warm water containing sodium bicarbonate. When these methods fail a stomach tube may be used. Sea-sickness and air-sickness can often be prevented by taking gr. 2½ each of phenacetin and soluble barbitone half an hour before and again shortly after starting on the journey, or gr. ⅙ of hyoscine if the vomiting is severe. The antihistamine drugs are also effective in sea-sickness, and in some other conditions such as the vomiting of pregnancy.

## REGURGITATION, HEARTBURN AND WATERBRASH

**REGURGITATION.**—Regurgitation of unaltered food, mixed with more or less saliva, occurs with pharyngeal diverticula, and in œsophageal obstruction resulting from



achalasia of the cardia, and simple and malignant stricture. Regurgitation of small quantities of partially digested food into the pharynx and less often into the mouth, without effort and without nausea, occurs in various forms of dyspepsia; its acidity produces a scalding sensation in the pharynx. Regurgitation is frequently associated with flatulence due to air swallowing, the unsuccessful efforts to bring up wind when no excess is present in the stomach, resulting in regurgitation of some of its fluid contents. The regurgitation may later give place to vomiting, both the regurgitation and vomiting being to a great extent under voluntary control.

**HEARTBURN.**—When the indigestion which gives rise to regurgitation is a result of some swallowed irritant such as excess of condiments, alcohol, tobacco or drugs, the gastritis, which is the cause of the indigestion, is likely to be associated with œsophagitis. Apart from this, frequent regurgitation of acid food through the œsophagus leads to œsophagitis. In whichever way the œsophagitis is caused, the œsophageal mucous membrane, which is normally insensitive to dilute hydrochloric acid, becomes sensitive, so that the gastric contents produce a sensation of burning behind the sternum when regurgitation occurs. This burning sensation is known as heartburn, and may occur with or without regurgitation into the pharynx and mouth; it is not closely related to the degree of gastric acidity, and may in fact occur in cases of gastric carcinoma with achlorhydria. It is particularly frequent in cases of hiatus hernia (*q.v.*).

**WATERBRASH.**—Waterbrash may occur in any of the conditions which give rise to pyalism (p. 530), but most commonly with duodenal ulcer. At a certain interval after a meal, which varies in different cases, but is fairly constant for each individual, an uncomfortable sensation of constriction, which may amount to severe pain, is felt deeply beneath the lower end of the sternum. This is accompanied by profuse salivation, and even sometimes by pain in the jaws from the rapid swelling of the parotid glands. Relief occurs on bringing up a few mouthfuls of clear fluid, which is generally described by the patient as being like water, though it sometimes contains a good deal of mucus. *The fluid rises into the mouth with little or no effort and without nausea: it is sometimes so profuse that the patient may have to keep his mouth open to let the fluid pour out. It comes from the mouth and œsophagus and not from the stomach, as even when the previous meal was large and finished less than an hour before, no food is present in the regurgitated material, which is alkaline in reaction and has all the characters of pure saliva. When the flow of saliva is excessive, it runs down the œsophagus without the patient's knowledge and without the aid of actual swallowing; the cardiac sphincter being closed, the fluid collects in the lower end of the œsophagus.*

The morning vomiting of alcoholic individuals is the result of a similar process, though it is accompanied by more violent vomiting efforts. In this case the fluid consists of saliva with a considerable proportion of pharyngeal and œsophageal mucus, secreted as a result of chronic pharyngitis and œsophagitis.

**Treatment.**—No special treatment is required for regurgitation, heartburn and waterbrash beyond that of the primary condition. The discomfort caused by regurgitation and heartburn may often be overcome by drinking water or sodium bicarbonate solution, or by chewing and then swallowing an alkaline tablet.

## ANOREXIA

Anorexia, or loss of appetite, occurs in a small proportion of cases of chronic gastritis and in the majority of cancer of the stomach, in which it may be the first symptom. It does not occur in uncomplicated gastric or duodenal ulcer. It is common in toxic conditions, such as acute fevers and tuberculosis, and is often present when for any reason the tongue is dry or furred. It is frequently due to psychological causes, in particular, anxiety and states of depression.

## ANOREXIA NERVOSA

**Ætiology.**—Anorexia nervosa occurs in adolescents and young adults of both sexes, but much more commonly in females than males. There may be no family history of psychoneuroses or psychoses. The anorexia is in most cases at first the visceral expression of some emotional disturbance, often an unhappy love affair. Sometimes the diet is voluntarily reduced with the object of overcoming a real or imaginary tendency to get fat, or on account of some fanciful ideas concerning the effect of food in stimulating sexual activity. Whatever the origin of the condition may be, the restriction of food results in the gradual disappearance of the appetite until the patient loses all desire for food. After the anorexia has continued for some time its origin, which is rarely recognised by the patient without explanation, recedes into the background, and it often remains after the psychological difficulties which gave rise to it have disappeared, but recovery usually follows psychotherapy without additional treatment of any kind.

**Diagnosis.**—Anorexia nervosa should not be confused with Simmonds's disease (see p. 487), which is a much less common condition, caused by degeneration of the pituitary gland, generally following childbirth with excessive hæmorrhage, and post-partum necrosis of the gland. This condition is uninfluenced by psychotherapy, and is not necessarily associated with either anorexia or emaciation, but invariably with severe asthenia, loss of axillary and pubic hair, and frequently with premature senility, atrophy of the breasts and low metabolic rate.

In cases of gastric carcinoma the anorexia is particularly felt towards meat, whilst in simple loss of appetite due to anxiety it varies greatly with environment. Anorexia is a very constant symptom at the onset of infective hepatitis, whilst in depressive psychoses it is a part of the general apathy and loss of interest in many things, including food and drink.

**Symptoms.**—The patient shows a complete loss of interest in every kind of food, and as even small quantities have to be forced down, they give rise to a sense of complete repletion, distension and sometimes nausea. She may learn to vomit at will, and as she realises that she can overcome her discomfort by this means, it may occur after every meal. The small intake of food leads to increasingly severe constipation, and the aperients used for its treatment increase the abdominal discomfort.

The patient rapidly loses weight and in time becomes extremely emaciated, almost all the subcutaneous fat disappearing. At first physical and mental activity are unabated, the restless energy and absence of fatigue being in striking contrast with the wasted appearance of the patient, but in the later stages the patient becomes weak and lethargic, and finally may lie in bed unable to move a limb or raise her head. In girls amenorrhœa is a constant symptom; it develops at an early stage and may persist for months after recovery is complete in all other respects. It is probably of psychical origin and not a result of malnutrition, as it develops at an early stage and may persist long after the patient has returned to a normal diet. An abnormal growth of downy hair is a common symptom; this is a direct result of malnutrition, as it is often observed in times of famine. Symptoms of vitamin deficiency only rarely develop even in cases of extreme malnutrition.

The pulse and temperature are normal. Radiographs show no abnormality in the alimentary tract, the constipation being due solely to the insufficient quantity of food residue; gastric secretion is unaffected. The extremities and the nose and ears are cold and blue, the skin dry and scaly. The urine is normal.

If proper treatment is not instituted, death may result from inanition, extreme atrophy without any organic visceral lesion being found post mortem.

**Treatment.**—Except in the earliest stages, it is essential to remove the patient from her home surroundings and to allow only infrequent visits from her relations.

The nature of the symptoms is explained to her, and she is made to understand that she can recover and return to her home and to a normally active life only when, as a result of eating a proper quantity of ordinary food, her weight and strength have returned, and that though this may entail some discomfort at first, her appetite is certain to return when more food is taken. It is essential to be present during the first meal after treatment is begun, and to be prepared to spend a very long time arguing over every mouthful until the meal is at last finished. As resistance almost invariably breaks down under these conditions, the task of supervising subsequent meals can be left to a good nurse, who must at first never leave the patient, as otherwise food is likely to be hidden or thrown away. The patient should from the first day of treatment be given a full diet without restrictions of any kind, and should be induced to eat everything she is given, and with tact, explanation and persuasion this is almost always possible. The psychological origin of the trouble should not be discussed until the patient has greatly improved and often simple psychological explanation without any deep analysis is all that is required. It is essential to interview the parents or relatives, who are often intensely concerned at the patient's refusal of food, and it is important to ensure a sensible and not over-anxious attitude to the patient's illness once she has recovered and returned to her home. Special diets, organotherapy, including gonadotrophic and pituitary hormones, the use of insulin to stimulate the appetite, and the administration of vitamins are of little use in the treatment of anorexia nervosa.

## NAUSEA

Nausea most commonly precedes vomiting, and in this case is relieved when the stomach is emptied. Though primarily a gastric symptom, it is often accompanied by malaise, sweating, salivation and faintness. When associated with headache it is generally a result of migraine. Association with vertigo points to vestibular disease, as in Ménière's syndrome and sea-sickness. It may occur as an independent symptom in chronic gastritis, chronic cholecystitis and in carcinoma of the stomach. It is sometimes the most prominent symptom in early tuberculosis and in the first weeks of pregnancy. It may occur in nephritis and infections of the urinary tract, and in men it may result from prostatic disease; in these conditions it is often an indication of the onset of uræmia, of which it may be the first symptom. All these possibilities should be excluded before regarding it as of nervous origin, but there is no doubt that it is not infrequently an hysterical symptom, and due to the perpetuation by auto-suggestion of nausea which originally resulted from the emotion of disgust, although the actual exciting incident may have been forgotten. In such cases the nausea often serves the subconscious purpose of providing the patient with a means of escape from some difficult situation or uncongenial occupation. Whatever its cause, but especially when it is nervous in origin, nausea is increased by anxiety and depressing emotions, and is less troublesome when the mind is fully occupied.

Nausea may be constant or periodic. It may be specially associated with the consumption of fatty food or less frequently of meat, but it is often quite independent of the kind or nature of the food taken. The patient may wake up with severe nausea, which makes it difficult for him to eat any breakfast. He often thinks it is due to some disease of the stomach, and he consequently reduces the amount of food he takes; severe loss of weight may result.

Experimentally it has been shown that stimuli which cause nausea lead to interruption of peristalsis with diminished muscular tone, diminished secretion of hydrochloric acid, increased secretion of mucus, and pallor of the gastric mucous membrane, together with salivation, sweating and tachycardia followed by bradycardia. The motor changes are not a result of the nausea, as they precede its development, but are an important factor in its production.

## GASTRIC FLATULENCE: AEROPHAGY

Flatulence, or the presence of excess of gas, may occur simultaneously in the stomach and the intestine, but in many cases it is confined to the stomach or to some part of the intestines.

**Ætiology.**—Gastric flatulence may be caused by (a) excessive production of gas by fermentation or putrefaction; (b) the introduction of excess of air by air-swallowing (aerophagy); (c) deficient absorption; (d) deficient elimination.

(a) Achlorhydria may be associated with the formation of a small quantity of gas by bacterial activity, but this is very rarely sufficient to cause discomfort. In pyloric cancer, achlorhydria is associated with severe gastric stasis, and a considerable excess of foul gas may be produced. Offensive belching may occasionally be the first symptom of a gastric growth, but it may also occur in non-malignant pyloric obstruction. A true faecal smell in the gas brought up is found, with faecal vomiting, in the late stages of intestinal obstruction.

(b) Aerophagy is the commonest cause of flatulence. It is often associated with nervous dyspepsia, but it is equally common in organic diseases, especially cholelithiasis and less frequently gastric and duodenal ulcer; the pain in angina pectoris is sometimes caused by it. The patient feels discomfort in the stomach, which he thinks is due to "wind", and which he imagines he can "disperse" by eructation. As there is really no excess of gas present, the attempt proves unsuccessful and results in swallowing of air. After half a dozen or more attempts have been made without success, air being swallowed on each occasion, the stomach becomes distended with gas, which is noisily expelled. The excessive salivation, which often occurs in gastric cancer associated with hyperchlorhydria, and in septic conditions of the mouth and naso-pharynx, also leads to flatulence, as air is swallowed with each mouthful of saliva. The severest cases of aerophagy occur independently of dyspepsia in intensely neurotic women; the symptom is then hysterical. A little saliva with a large quantity of air is swallowed until the stomach is distended, when it is noisily pumped backwards and forwards between the stomach and œsophagus by spasmodic movements of the diaphragm, and is then expelled with loud reports. This may continue periodically for many hours at a time and frequently repeated eructations make the diagnosis of aerophagy certain, as fermentation cannot give rise to so large a quantity of gas. In some cases the patient takes obvious pleasure in the performance. The gas expelled in aerophagy is odourless and may be brought up at any time of day or—very commonly—night. Eructation occurring before breakfast in the absence of pyloric obstruction is always due to swallowed air as there is nothing in the stomach from which gas could be produced. The diagnosis of aerophagy can be confirmed by radiography, whereby it is easy to watch the air being swallowed or expelled.

(c) In portal hypertension with cirrhosis of the liver, congestive heart failure, and chronic bronchitis and asthma, swallowed air and the gases produced by fermentation are insufficiently absorbed and flatulence results. In cardiac failure treatment with digitalis may give complete relief.

(d) In rare cases a valvular mechanism is set up at the cardia, which does not impede swallowing but prevents the passage of gas in the opposite direction. This *œrogastric bloquée* may result from spasm of the lower end of the œsophagus associated with an œsophageal ulcer, or from a kink caused by the dislocation of the stomach from the pressure of a distended splenic flexure in intestinal carbohydrate flatulence or a distended pelvic colon in megacolon. An enormous quantity of gas may collect in the stomach, the distension of which causes great pain, which is relieved by lying down, when the gas passes on into the duodenum, or instantaneously by the passage of a stomach tube.

**Symptoms.**—Gastric flatulence gives rise to a sensation of fullness in the epi-

gastrium, which may extend under the left costal margin. The accumulation of gas in the stomach pushes up the diaphragm; this may cause palpitation and attacks of dyspnoea particularly in those suffering from asthma or heart disease. Flatulence may also be the immediate cause of an attack of true angina pectoris, though more frequently the angina is the cause of the aerophagy.

**Diagnosis.**—When a patient complains of "flatulence", it is first necessary to ascertain whether excess of gas is really present. This can be done most readily and accurately by means of radiography, as it is often difficult to distinguish by percussion whether an accumulation of gas is in the stomach or in the splenic flexure of the colon.

Pseudo-flatulence is generally due to the patient misinterpreting the sensation of fullness which is caused by the increased intragastric pressure produced by sudden distension of the stomach, with excess of food and drink which have been too rapidly consumed. There is no abdominal swelling or increase in gastric resonance, and the patient is unable to bring up any gas, though the condition is often complicated by aerophagy. The eructation of swallowed air may relieve the discomfort which prompted the aerophagy.

Excess of gas in the splenic flexure in intestinal carbohydrate dyspepsia, and in the pelvic colon in megacolon, often gives rise to a feeling of fullness in the left hypochondrium, which is mistaken by the patient for gastric flatulence and may lead to aerophagy.

Pseudo-flatulence may also be caused by *spasm of the diaphragm*. This may occur as an independent condition or as a complication of some organic disorder, such as gastric ulcer or colitis, or after a blow on the abdomen. It is also the cause of the abdominal distension in *pseudocyesis*, in which pregnancy is simulated. The spasm may be continuous and last for weeks or months. More frequently it occurs in attacks; a sensation of great distension is experienced and the abdomen becomes so protuberant that the clothes have to be loosened. The "distension" disappears as suddenly as it comes without eructation or passage of flatus. It may lead to a mistaken diagnosis of intestinal obstruction, and laparotomies have been performed in spite of the fact that the distension disappears under an anæsthetic. The lower ribs are drawn in as a result of the pull of the contracted diaphragm, and firm manipulation of the abdomen causes the abdomen to become flat and the diaphragm to rise. The absence of excess of gas in the stomach and intestines can be recognised by radiography which shows a low position of the diaphragm and shallow respiratory movements. The patient should be taught to breathe properly with his diaphragm, but improvement is often very slow.

**Treatment.**—The treatment of flatulence due to excessive fermentation consists in removing the cause. When flatulence is due to aerophagy, it may be only necessary to explain to the patient the cause of his trouble in order to cure him. He should be told not to eructate, however much he may desire to do so. If he finds it very difficult to restrain himself, he should open his mouth or clench his teeth upon a cork, whenever the desire is very strong, as it is then difficult to swallow air, though any excess of gas in the stomach can be expelled. When aerophagy is secondary to dyspepsia, this requires appropriate treatment. Momentary relief, sufficient to help the patient to forego eructation, can generally be obtained by sipping hot water or chloroform water, or by taking a few drops of a carminative, such as oil of cinnamon or peppermint on a lump of sugar, but the use of spirits for this purpose should be prohibited.

## NERVOUS DYSPEPSIA

**Ætiology.**—Emotional factors may profoundly influence digestion, and the neuroses are often accompanied by visceral symptoms. Anxiety, depression and

is to reduce the Vc and Vp without altering the hæmoglobin percentage. Only after a variable period does the blood take up enough fluid to restore the original Vp, thereby diluting the hæmoglobin sufficiently for its estimation to give a true index of the severity of the hæmorrhage, always provided this has ceased. New blood corpuscles then slowly form, with gradual restoration of Vc and hæmoglobin. The final plasma volume is very constant and in 50 per cent. of cases the plasma is fully diluted by the time the patient is admitted to hospital; in the remainder the period varies, the maximum being 72 hours for full dilution. There are no clinical means of determining that hæmorrhage has ceased, the signs generally regarded as indicative of hæmorrhage being, in fact, the manifestations of hæmorrhagic shock, and in the absence of external evidence of bleeding it may be impossible to be certain whether a falling hæmoglobin percentage indicates continuing hæmorrhage or blood dilution.

**Prognosis.**—The mortality among patients with hæmorrhage from a peptic ulcer is between 3 and 10 per cent. Of Hurst's cases admitted to Guy's Hospital on account of hæmorrhage, 4·8 per cent. died. In recent years the use of drip transfusions and fuller diets have reduced the mortality, which is also closely related to age. Thus, in Avery Jones' series the mortality under 45 years old was 2 per cent.; between 45 and 59, 6 per cent.; between 60 and 69, 12 per cent.; and over 70, 21 per cent.

**Treatment.**—The patient should be kept completely at rest, but since the sheet anchor of treatment is blood transfusion, he should be moved by ambulance to hospital or nursing home, where all facilities for this are available as soon as possible, in spite of the slight added risks of transportation. In order to obtain rest and allay anxiety it is generally advisable to inject morphine, a full dose being given and repeated as necessary. The bed-pan must be used, and the patient should not at first even be allowed up for micturition. Sips of water should be given by mouth from the start, and rectal salines either by drip or in amounts of 8 to 10 oz. 4-hourly are advisable if there is any vomiting or inability to retain fluids easily by mouth. No laxatives should be given, but if the bowels do not open spontaneously on the third or fourth day a simple saline wash-out is generally the only treatment needed.

**Diet.**—The high caloric diet advised by Meulengracht in Denmark in 1934 was based mainly upon the rationale of keeping the stomach full in order to reduce hunger peristalsis and so lessen the tendency for bleeding to continue. Modified feeding similar to that advised by him is generally well tolerated within 24 hours of the bleeding: it avoids any long period of starvation, aids acid neutralisation and gastric rest, and is based upon sound principles of ulcer treatment. Milk feeds with purées, soft puddings, eggs and vegetable soups, as for the Stage 1 ulcer diet may be ordered from the start of treatment, and after this increased as indicated on p. 581. At the same time, especially in older people, large feeds are inadvisable, and it is wiser at first to give only milky foods in frequent small amounts of 3 or 4 oz. rather than insist upon the fuller régime which a young and strong adult can take with advantage.

If the hæmoglobin falls to 40 per cent. or lower, the equivalent of a Vc of 700 ml., the patient should be transfused at the rate of 30 to 40 drops a minute till the hæmoglobin percentage reaches 60, the average volume required being 1500 ml. With slow transfusion (*i.e.* 1 litre in 4 to 8 hours) the blood pressure does not rise nor does the Vp increase above normal; the sole result is the rise in Vc, which is entirely desirable. Transfusion is required to prevent a patient from dying from anæmia; it is not essential for the restoration of the blood to the normal level, as an average gain of 1 or 2 per cent. of hæmoglobin per diem will occur when full doses of iron are given. At the same time there should be no hesitation in giving enough blood to produce a hæmoglobin percentage of 80, especially if surgical treatment is to be undertaken. The use of packed red cells minimises the risks of over-loading the circulation. For surgical treatment, see p. 586.

**Iron.**—Iron and ammonium citrate gr. 30, four times a day in solution is usually

well tolerated, or enteric-coated capsules of ferrous sulphate gr. 6, four times a day may be given. Intravenous injections of iron as the saccharated oxide (Ferrivenin) may be needed at first if oral iron causes vomiting or pain. The daily dose should not exceed 200 mg. Ascorbic acid mg. 200 daily should be given at the same time.

## ORGANIC DISEASES OF THE STOMACH

### ACUTE GASTRITIS

#### (a) ACUTE CATARRHAL GASTRITIS

**Ætiology.**—Acute gastritis is caused by irritation of the mucous membrane of the stomach, varying in degree according to the intensity and duration of the irritation. Most frequently such irritation is due to *exogenous causes of which bad eating habits, the lack of teeth or dentures and the bolting of large indigestible meals, with excesses of alcohol, condiments or badly chewed food are the most important.* The swallowing of infective material from the nose, sinuses, gums, teeth or purulent sputum from the chest are further causes. In many cases the irritant is a toxic product of bacterial activity in food, several individuals being often affected simultaneously; such infection may belong to the *Salmonella* group of organisms or arise from food contaminated by staphylococci during its preparation as, for instance, by a cook with a discharging whitlow on the finger. Chemical irritants in food are less frequent than bacterial, but drugs such as aspirin, salicylates and quinine are common causes. Tobacco chewing is another.

Corrosive poisoning due to the swallowing of violent irritants such as lysol, carbolic acid, arsenic or corrosive sublimate either accidentally or suicidally causes an intense (phlegmonous) gastritis (*q.v.*).

Endogenous causes of acute gastritis include the toxic products of uræmia, and those of acute infections such as influenza, pneumonia, measles, diphtheria, scarlet fever and acute tuberculosis.

**Symptoms.**—The symptoms start acutely soon after the entrance of the irritant into the stomach. A sensation of fullness and discomfort is felt in the epigastrium; heartburn is common, and in severe cases there is acute pain. Tenderness is diffuse and generally only moderate in degree, but in serious cases it may be extreme. The abdomen may be distended. The appetite is completely lost, but thirst is excessive. The tongue is covered with a thick dirty fur, and there is an unpleasant bitter taste in the mouth. The patient constantly belches, and the gas brought up may be foul-smelling. Vomiting, preceded by nausea, almost always occurs, and gives more or less relief to the discomfort and pain. The food eaten at the previous meal, mixed with mucus but with little or no gastric juice, is first rejected; subsequently mucus with saliva, which is generally secreted in excess, bile and occasionally small quantities of blood are vomited. Severe constipation is present unless the irritant also acts upon the bowels and causes diarrhœa. The vomited matter may contain no free hydrochloric acid, but is generally acid in reaction owing to the presence of lactic, butyric and other fatty acids; the saliva and mucus present may, however, give it an alkaline reaction.

The patient is pale and prostrated and complains of headache. These symptoms are most marked in infective cases, when the patient may also be drowsy and even delirious. The temperature is generally slightly raised, but it may be high, especially in children, and the pulse is rapid. Leucocytosis is common, even in the absence of pyrexia. The urine is concentrated and may contain a trace of albumin. Herpes labialis is sometimes present.

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The patient is pale and prostrated and complains of headache. These symptoms are most marked in infective cases, when the patient may also be drowsy and even delirious. The temperature is generally slightly raised, but it may be high, especially in children, and the pulse is rapid. Leucocytosis is common, even in the absence of pyrexia. The urine is concentrated and may contain a trace of albumin. Herpes labialis is sometimes present.

**Diagnosis.**—In severe pyrexial cases the symptoms may simulate the onset of an acute infection, such as typhoid fever, but the rapid improvement soon makes the diagnosis clear. Cases occur in which the pain, tenderness and rigidity are so severe that considerable doubt may be felt at first whether a gastric ulcer may not have perforated.

**Prognosis.**—Recovery generally takes place within 24 or 48 hours, but in toxic and infective cases the acute symptoms may persist for several days, at the end of which they may suddenly disappear. The condition often passes into chronic gastritis, which may remain completely latent, though the stomach is often abnormally irritable for a considerable time.

**Treatment.**—The patient should be kept warm in bed with hot applications to the abdomen. If the stomach is not spontaneously emptied, vomiting should be induced by drinking half a pint of warm water, in which a teaspoonful of sodium bicarbonate has been dissolved; when this fails, the stomach should be washed out.

A saline aperient should be administered if there is constipation. No other drugs should be given except in the rare cases in which very severe pain persists after the stomach is empty, when an injection of morphine may be required. Nothing but water, which may be flavoured with tea, should be taken until all the acute symptoms have disappeared. Sweetened arrowroot made with water may then be given, and, as the appetite returns and the tongue cleans, dilute citrated milk, farinaceous food, eggs, and lastly, fish, chicken and meat can be added to the diet.

#### (b) ACUTE SUPPURATIVE GASTRITIS

**Ætiology.**—This very rare disease is due to the invasion by streptococci or less frequently pneumococci, staphylococci or *Bact. coli*, of the submucous tissue through a carcinomatous ulcer, or still more rarely through a chronic ulcer or the wound left after an operation on the stomach. In exceptional cases the point of invasion cannot be recognised. The condition may also occur in pyæmia, anthrax and smallpox.

**Symptoms.**—Epigastric pain and tenderness are severe. Vomiting is always present. The vomitus may contain pus owing to the rupture of a localised abscess into the lumen of the stomach. Peritonitis generally supervenes in the course of 2 or 3 days. The general symptoms present are those common to severe infections.

**Prognosis.**—A local submucous abscess may burst inwards and spontaneous recovery follows, but more commonly it ruptures outwards, producing general peritonitis. Diffuse suppurative gastritis always ends in peritonitis.

**Treatment.**—In very rare cases a localised abscess has been treated successfully by operation.

#### (c) ACUTE PHLEGMONOUS GASTRITIS

**Ætiology.**—Phlegmonous gastritis results from the ingestion of irritant poisons, such as concentrated acids and alkalis, arsenic and antimony.

**Symptoms.**—The local symptoms are similar to those of acute suppurative gastritis, except that the vomited matter frequently contains blood and sometimes sloughs. The patient is collapsed and may become comatose, the symptoms depending upon the nature of the poison.

**Prognosis.**—Death frequently occurs from shock, general peritonitis or the effect of the poison on other parts of the body. If the patient recovers, achylia gastrica is almost always present as a result of atrophy of the mucous membrane, and pyloric obstruction frequently develops.

**Treatment.**—An attempt should be made to dilute and neutralise the poison. When this is impossible the stomach should be washed out. Morphine should be injected to relieve pain and to keep the patient quiet.

## CHRONIC GASTRITIS

**Ætiology and Pathology.**—Chronic gastritis was formerly believed to be a very common condition, largely owing to the work of Professor Knud Faber on gastric secretion, and later of Schindler and his collaborators with the gastroscope. In recent years greater experience of gastroscopic studies together with a fuller knowledge of the secretory activity of the stomach have greatly altered our conception of this condition. Many changes in the gastric mucosa previously regarded as due to chronic hypertrophic or atrophic gastritis have now been shown to be merely temporary variations from the normal, caused by everyday emotions or by the normal stimuli of food or drink. The observations of Wolf and Wolff (see p. 557) showed conclusively that the gastric mucous membrane normally became hyperæmic, turgid and engorged, with an increase in mucus and acid secretion, under emotional stimuli such as resentment or anxiety, whilst that of fear caused pallor of the mucosa and diminished secretion.

It is probable that the three pathological types of gastritis—superficial, hypertrophic and atrophic—described by Schindler and others are in fact only stages of one process which may have a number of causes. Some cases, probably quite uncommon, have no specific cause that we can determine. In others the same causes are at work as in acute gastritis, either repeated or of longer duration, with in addition an important group of cases due to mechanical pyloric obstruction. Any cause of pyloric stenosis, whether due to cicatrisation of an ulcer, to simple pyloric spasm, to a carcinoma or to congenital stenosis, may equally lead to chronic gastritis. Some gastritis is present around all gastric ulcers, and it is an almost constant finding at the site of a gastro-enterostomy. Full correlation of gastroscopic, histological and clinical findings in cases of gastritis is not yet possible, but pathologically a hypertrophic and an atrophic gastritis may be distinguished, the former showing increased vascularity, œdema, a thickened mucous membrane with very rarely polypoid hyperplasia, the latter avascularity and a thin aplastic mucosa.

**Symptoms.**—Changes in the gastric mucous membrane or in the secretions of the stomach may exist with no demonstrable symptoms whatsoever, and detailed descriptions of the symptomatology of various types of gastritis are quite without accurate clinical foundation. The symptoms of hypertrophic (acid) gastritis if they occur at all are similar to those of chronic peptic ulcer, but it is rare for any symptoms to arise unless an ulcer is in fact present. In the exceptional cases in which symptoms occur in the absence of a chronic ulcer they are indistinguishable from those of duodenal ulcer, and a diagnosis can be made only when a radiographic examination shows that there is no constant gastric or duodenal deformity in spite of the presence of typical symptoms, tenderness and rigidity, associated with hyperchlorhydria and sometimes occult blood in the stools. Rigidity, thickening and coarseness of the mucosal folds as demonstrated by radiological study of the mucosal relief pattern on examination with a thin layer of contrast medium may, in expert hands, give useful confirmatory evidence of gastritis. Hæmatemesis may occur from an acute ulcer or erosion, which gives no radiological signs of its presence but can be clearly demonstrated by gastroscopy, but many hæmorrhages of this kind prove on careful inquiry to be caused by aspirin.

The treatment is that of ulcer, but the period of bed and strict dieting need not be prolonged more than a week unless occult blood continues to be present in the stools. It is, however, essential that the patient should follow the "post-ulcer régime" (p. 585), as otherwise an ulcer will probably develop sooner or later.

**Atrophic gastritis.**—Atrophic gastritis is often symptomless, but may be associated with nausea, especially early in the morning, with in many cases loss of appetite. In alcoholic gastritis morning nausea with inability to eat any breakfast in spite of a good appetite for lunch and dinner is a characteristic symptom.

Pain never occurs in uncomplicated atrophic gastritis, but slight epigastric discomfort, generally described as fullness, pressure or heaviness, is common. It follows immediately after meals, and may last several hours in the small group of cases in which evacuation is slow. It is often partially relieved by belching, but frequent attempts to eructate may result in aerophagy. In spite of the presence of achlorhydria, heartburn and sour regurgitation, which are relieved by sodium bicarbonate, may occur. Tenderness is slight and ill-defined, and there is no rigidity.

Vomiting occurs if nausea is severe, or if the epigastric discomfort is unusually prolonged. It is often to a large extent voluntary, the patient having discovered that it gives relief. The vomited material generally consists of undigested food mixed with mucus and often with bile, but the morning vomit of alcoholics is an alkaline, mucous fluid, composed of swallowed saliva and secretion from the inflamed pharynx and œsophagus.

Constipation is generally present, but in one group of cases chronic or intermittent attacks of diarrhoea occur, and may persist for many years with little or no gastric symptoms to suggest its gastrogenous origin (see p. 610).

The tongue is generally clean, but in alcoholic gastritis it is often furred and the patient complains of an unpleasant taste in his mouth. When achlorhydric gastritis is associated with anaemia, whether simple or Addisonian, atrophy of the filiform papillae is often present, sometimes accompanied by recurrent attacks of sub-acute glossitis, in which the patient complains of soreness of the tongue.

The size and tone of the stomach are generally normal, but evacuation is usually rapid. In the achlorhydria following the gastritis of an acute infection it may be slow owing to the rapid exhaustion of peristalsis, the radiogram showing periods of complete inertia alternating with periods of normal activity, but there are no characteristic findings which enable the radiologist to diagnose the condition. The test-meal may give some indication of the presence, type and degree of gastritis. In most cases mucus is present in the resting juice and in each fraction, and the curve of total acidity remains moderately high above the base line. In advanced cases, in which atrophy of the mucous membrane has occurred and involved the superficial mucus-secreting cells as well as the tubules, mucus is absent and the total acidity is much reduced. So long as mucus is present, treatment is likely to result in recovery of the power of secreting free acid, but this very rarely occurs in the absence of mucus. In the former case, but not in the latter, an injection of histamine when fasting or at the end of the test-meal is generally followed by the secretion of free acid.

**Treatment.**—All possible causes of gastritis should be removed as far as possible. The teeth should be put into good condition and artificial ones supplied when necessary. Septic tonsils should be enucleated, and nasal infections treated. If the tongue is furred it should be frequently scraped, and sufficient dry food should be given to promote an adequate secretion of saliva. The food should be thoroughly chewed and eaten at regular times, the last meal at least 2 hours before going to bed. The patient should rest for half an hour after meals, and, if he is tired, for a short time before meals also.

Alcohol should be entirely prohibited, and smoking strictly limited. Tea must be weak and freshly brewed, and coffee only drunk if mixed with at least an equal quantity of milk. Meat should be allowed at only one meal a day and should be very tender. Ripe cheese, coarse bread substitutes and oatmeal, skins and pips of fruit, salads, pickles and green vegetables, except as purées, should be prohibited. A purée of spinach is particularly useful, as it contains a histamine-like substance which is a stimulant of gastric secretion, even when taken by mouth. In severe cases, especially if the stools contain occult blood, it is best to give the strict ulcer diet (p. 583) for the first week or two, but with 2-hourly instead of hourly feeds.

If much mucus is present in the test-meal, Hurst recommended that the stomach should be washed out every morning with dilute hydrogen peroxide, beginning with

a teaspoonful and increasing gradually to a tablespoonful to the pint. The nascent oxygen given off dislodges the mucus from the surface of the mucous membrane, and at the same time acts as an antiseptic and perhaps stimulates the secretion of gastric juice.

In old and debilitated patients, for whom lavage is too strenuous a treatment, a teaspoonful of sodium bicarbonate in a glass of soda water, drunk whilst fasting first thing in the morning, has a similar though less powerful action.

Hydrochloric acid may be helpful, and a teaspoonful of the dilute acid (B.P.) in about 5 oz. of water to which sugar and the juice of an orange or of any other fresh, bottled or stewed fruit have been added, may be drunk before breakfast and as a beverage with lunch and dinner; gr. 5 of pepsin may be added to the two latter doses.

The bowels should be kept regular by taking honey, fruit from which pips and skins have been separated, and green vegetable purées. If necessary, liquid paraffin can be given, but irritating aperients should be avoided.

## GASTRIC AND DUODENAL ULCER

**Ætiology.**—Gastric and duodenal ulcer, though similar both pathologically and clinically, must be regarded as essentially different in several important aspects. Chronic gastric ulcer occurs with equal frequency in males and females, but duodenal ulcer is about four times more common in males. Duodenal ulcer occurs between three or four times as frequently as gastric ulcer in the higher social grades, and between three and eight times as frequently in most British hospitals. The mortality from gastric ulcer is some two to three times greater in the lower social classes than the higher, whilst from duodenal ulcer there is little difference between the various social levels. Duodenal ulcer is increasing in incidence, whilst gastric ulcer is not; *ambitious, energetic professional or business men tend to develop the former, whilst poorer, badly fed and less active people, women or men, develop the latter.* Hæmorrhage and perforation are frequent in duodenal ulcer, but less frequent in gastric ulcer. The main causes of duodenal ulcer lie essentially in the make-up and temperament of the individual and his over-active stomach, whilst in gastric ulcer the most important causes lie in local mucosal irritation, associated with nutritional factors and environmental conditions.

A chronic gastric ulcer was found by Stewart in 2.2 per cent. and a chronic duodenal ulcer in 3.8 per cent. of 4000 consecutive necropsies. The scars of healed ulcers were found in the stomach in 2.3 per cent. and in the duodenum in 3 per cent. of the series. Chronic ulcers or scars were found in the stomach and duodenum of the same individual in 0.5 per cent. Thus, a chronic ulcer, healed or unhealed, was found in 9.5 per cent. of post mortems, and it may therefore be assumed that about 10 per cent. of all individuals suffer at some time in their lives from a chronic gastric or duodenal ulcer.

Though chronic ulcer is rarely diagnosed in children, the symptoms date from the age of 12 to 18 in some 20 per cent. of cases recognised later in life, and an onset during early school age is by no means rare. It is uncommon for a duodenal ulcer to develop after the age of 50 in women, but in men the first symptoms not infrequently appear between 50 and 60 and occasionally even later.

Hurst gives the average age of onset of gastric ulcer in women as 26 and in men 45, with that of duodenal ulcer as 38 in both sexes, but in my experience the average age for duodenal ulcer has been lower.

Chronic ulcer frequently occurs in several members of a family in one or more generations. The ulcer is generally either gastric or duodenal in all the affected members, but a familial incidence is relatively more common in duodenal than in gastric ulcer. In familial cases the symptoms tend to begin at an

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a teaspoonful and increasing gradually to a tablespoonful to the pint. The nascent oxygen given off dislodges the mucus from the surface of the mucous membrane, and at the same time acts as an antiseptic and perhaps stimulates the secretion of gastric juice.

In old and debilitated patients, for whom lavage is too strenuous a treatment, a teaspoonful of sodium bicarbonate in a glass of soda water, drunk whilst fasting first thing in the morning, has a similar though less powerful action.

Hydrochloric acid may be helpful, and a teaspoonful of the dilute acid (B.P.) in about 5 oz. of water to which sugar and the juice of an orange or of any other fresh, bottled or stewed fruit have been added, may be drunk before breakfast and as a beverage with lunch and dinner; gr. 5 of pepsin may be added to the two latter doses.

The bowels should be kept regular by taking honey, fruit from which pips and skins have been separated, and green vegetable purées. If necessary, liquid paraffin can be given, but irritating aperients should be avoided.

## GASTRIC AND DUODENAL ULCER

**Ætiology.**—Gastric and duodenal ulcer, though similar both pathologically and clinically, must be regarded as essentially different in several important aspects. Chronic gastric ulcer occurs with equal frequency in males and females, but duodenal ulcer is about four times more common in males. Duodenal ulcer occurs between three or four times as frequently as gastric ulcer in the higher social grades, and between three and eight times as frequently in most British hospitals. The mortality from gastric ulcer is some two to three times greater in the lower social classes than the higher, whilst from duodenal ulcer there is little difference between the various social levels. Duodenal ulcer is increasing in incidence, whilst gastric ulcer is not; ambitious, energetic professional or business men tend to develop the former, whilst poorer, badly fed and less active people, women or men, develop the latter. Hemorrhage and perforation are frequent in duodenal ulcer, but less frequent in gastric ulcer. The main causes of duodenal ulcer lie essentially in the make-up and temperament of the individual and his over-active stomach, whilst in gastric ulcer the most important causes lie in local mucosal irritation, associated with nutritional factors and environmental conditions.

A chronic gastric ulcer was found by Stewart in 2.2 per cent. and a chronic duodenal ulcer in 3.8 per cent. of 4000 consecutive necropsies. The scars of healed ulcers were found in the stomach in 2.3 per cent. and in the duodenum in 3 per cent. of the series. Chronic ulcers or scars were found in the stomach and duodenum of the same individual in 0.5 per cent. Thus, a chronic ulcer, healed or unhealed, was found in 9.5 per cent. of post mortems, and it may therefore be assumed that about 10 per cent. of all individuals suffer at some time in their lives from a chronic gastric or duodenal ulcer.

Though chronic ulcer is rarely diagnosed in children, the symptoms date from the age of 12 to 18 in some 20 per cent. of cases recognised later in life, and an onset during early school age is by no means rare. It is uncommon for a duodenal ulcer to develop after the age of 50 in women, but in men the first symptoms not infrequently appear between 50 and 60 and occasionally even later.

Hurst gives the average age of onset of gastric ulcer in women as 26 and in men 45, with that of duodenal ulcer as 38 in both sexes, but in my experience the average age for duodenal ulcer has been lower.

Chronic ulcer frequently occurs in several members of a family in one or more generations. The ulcer is generally either gastric or duodenal in all the affected members, but a familial incidence is relatively more common in duodenal than in gastric ulcer. In familial cases the symptoms tend to begin at an earlier age than

usual, and there is a great tendency for anastomotic ulcers to form after operation. There is also a special tendency in some families for the ulcers to be complicated by hæmorrhage.

**Pathogenesis.**—The peculiar type of ulcer found in the stomach and duodenal bulb occurs nowhere else except in the part of the jejunum immediately distal to the anastomosis after gastro-jejunostomy and partial gastrectomy, in the lower end of the œsophagus when relaxation of the cardiac sphincter allows gastric juice to regurgitate, and also in association with heterotopic gastric mucosa in the lower extremity of the œsophagus and in Meckel's diverticulum. The one common feature of these situations is the presence of acid gastric juice, and owing to the fact that gastric pepsin plays some part in their causation by digesting dead or ischæmic mucous membrane such ulcers are termed peptic.

Acute and chronic gastritis are frequently associated with localised loss of the superficial tissue, which varies in size from minute erosions only recognisable on microscopical examination to acute ulcers easily recognisable with the naked eye. Acute ulcers occur in any part of the stomach, in the duodenal bulb, and in the region of the anastomosis after gastro-jejunostomy or partial gastrectomy. The majority of erosions and acute ulcers heal rapidly, but in certain individuals and under certain circumstances they may become chronic. The various conditions already described which give rise to gastritis can thus be regarded as factors in the development of chronic ulcers.

Long hours without food, especially during periods of nervous strain and fatigue, or hastily eaten meals taken without mental relaxation, are particularly frequent antecedents in cases of duodenal ulcer. Though all occupations are liable to peptic ulcer, transport and lorry drivers, doctors, waiters and business men are amongst those especially affected. Frequent changes of shifts from day to night work and the irregular hours of meals sometimes necessary in certain industries may also be predisposing factors. Some evidence suggests that excessive smoking increases the tendency to develop a chronic ulcer, perhaps partly by the frequent tendency for heavy smokers to substitute a cigarette for a meal. As indicated on p. 557, the mucous membrane of the stomach becomes thick and hyperæmic, and muscular activity and the secretion of gastric juice are increased during periods of anxiety and with frustration and annoyance. This congested mucous membrane is more vulnerable to slight injury and, if the protective mucus is wiped away, an ulcer may develop, which explains why emotional upsets frequently give rise to recurrence of ulceration. Chills and acute upper respiratory infections may also bring on relapses, which are particularly liable to occur at the change of the season in spring and autumn. In rare cases duodenal ulceration follows extensive burns (Curling's ulcer), possibly as a result of the histamine substances produced in the skin stimulating excessive gastric acid secretion.

#### ACUTE GASTRIC AND DUODENAL ULCER

**Symptoms.**—An acute ulcer gives rise to no symptoms unless it causes hæmorrhage, which is often profuse but very rarely fatal, or, in very exceptional cases, perforation. Hæmorrhage or perforation occurring without any previous indigestion is thus frequently due to an acute ulcer. The gastritis, of which it is a complication, is often completely latent, but it may give rise to any of the symptoms described on p. 573.

Acute duodenal ulcer is the most common cause of *melæna neonatorum*. Less frequently it causes hæmatemesis in infants, and it may also give rise to vomiting and marasmus without obvious hæmorrhage during the first 4 months of life.

**Prognosis.**—Acute ulcers can develop into chronic ulcers, but the majority heal rapidly, leaving no trace of their presence. There is a great tendency to relapse, but the patient is able to take a full diet without discomfort between the attacks.



**Treatment.**—For the treatment of the hæmorrhage, see Hæmatemesis. All possible causes of gastric irritation should be dealt with, the after-treatment being that of chronic ulcer. The patient should be kept in bed on a strict ulcer diet until no occult blood has been present in three consecutive stools. The diet can then be rapidly increased.

#### CHRONIC GASTRIC ULCER

**Symptoms.**—The onset is generally insidious, the symptoms first appearing after big or indigestible meals. The pain, which is often burning in character and may be very severe, is situated in the middle or slightly to the left of the epigastrium and may radiate upwards and to the back; it is much increased by indigestible food and generally disappears with a milk diet. In ulcers situated near the cardia it begins almost immediately after meals, and in prepyloric ulcers 2 or 3 hours after, intermediate intervals often indicating an ulcer on the lesser curvature. The pain generally disappears spontaneously after about an hour. It is completely relieved by vomiting and by alkalis, but, as a rule, only partially by food. Some relief may follow lying down and the application of warmth to the epigastrium.

A small area of tenderness, the position of which is constant for each case, may be present in the epigastrium. It is more severe than in any other gastric disease; it is most marked in the presence of spontaneous pain. It is often associated with rigidity of the left rectus.

With increasing pain vomiting appears; it occurs at the height of the pain, a small quantity of acid fluid with a little well-digested food being brought up. When the pain is severe, vomiting is often induced by the patient and may eventually develop into a voluntary act.

Occult blood is almost always found in the stools and vomited material, but disappears slowly when the patient is dieted. In about 25 per cent. of cases obvious hæmatemesis occurs at some period of the illness. When the blood is abundant it is bright in colour and the stools are tarry; when less abundant it is coffee-coloured and mixed with food, and is recognisable in the stools only by chemical and spectroscopic examination. Melæna may also occur without hæmatemesis, but much less frequently than in duodenal ulcer.

The appetite is good at first and the tongue is clean, but fear of pain may lead to diminished intake of food with consequent loss of weight and weakness. In some cases, however, the relief given by food encourages the patient to eat heartily. Constipation is commonly present.

In uncomplicated cases there may be some delay in evacuation owing to reflex spasm of the pyloric sphincter; this is especially frequent with ulcers near the pylorus, but occasionally with those on the lesser curvature also gastric stasis up to 12 or even 24 hours may occur. A spasmodic narrowing is sometimes observed radiographically in the centre of the stomach when the ulcer is situated on the lesser curvature (see p. 559). Conclusive evidence as to its size and position is almost always obtainable by the discovery of a "niche" formed by the crater of a chronic ulcer, which is filled with the opaque salt and is the site of the maximum tenderness. If the examination is postponed for 2 or 3 weeks on account of hæmorrhage, it is often impossible to recognise a niche, though the ulcer has not yet healed.

A test-meal gives no constant result, but in long-standing cases hypochlorhydria and even achlorhydria may be present; these are caused by the associated chronic gastritis, and a test-meal given after the ulcer has healed shows an increase in acidity and even hyperchlorhydria, the treatment having led to disappearance of the gastritis.

**Diagnosis.**—A presumptive diagnosis of gastric ulcer may generally be made from the symptoms, especially if hæmatemesis has occurred, but in its absence it is impossible to be certain without the aid of radiography. If the latter does not reveal

the presence of a niche, a chronic ulcer can, as a rule, be excluded, but gastroscopy occasionally reveals a small chronic ulcer which has escaped recognition with the radiograph. In carcinoma of the stomach anorexia is likely to be present and a palpable tumour may be found, which is far less frequent in ulcer. Anæmia may occur in both. The discomfort of gastric cancer, even in its early stages, usually begins directly after meals and is more persistent than the pain of ulcer, as may be that of chronic gastritis. Free hydrochloric acid is absent in the test-meal in about 50 per cent. of cases of cancer, and occult blood is usually present in the stools continuously. The gastric symptoms associated with cholecystitis may simulate ulcer, but the relation of the pain to the nature and time of meals is less regular, and less relief is given by alkalis; tenderness is present over the gall-bladder in addition to the epigastrium. For the differential diagnosis of other conditions causing hæmatemesis, see page 569, and for the distinctions between œsophageal and duodenal from gastric ulcer, see pp. 549 and 579.

**Complications.**—Perforation of an anterior ulcer leads to general peritonitis (*vide* p. 712). It is rare for a gastric ulcer to be situated sufficiently near the pylorus to cause obstruction on healing, but the swelling and œdema round a prepyloric ulcer together with reflex interference with the normal relaxation of the sphincter often result in temporary pyloric obstruction, which disappears when the ulcer heals as a result of treatment. Recurrent cicatrization over a period of many years of a large and very chronic ulcer in the body of the stomach in women may cause hour-glass constriction. Very chronic gastric ulcers, especially in the prepyloric region, may rarely become carcinomatous (p. 590), but such ulcers may form definite tumours without being malignant. The earlier onset and absence of remission of pain, with the occurrence of anorexia and progressive loss of weight in the absence of alkalosis, should suggest the possibility of malignant degeneration.

#### CHRONIC DUODENAL ULCER

**Symptoms.**—The earliest symptom of duodenal ulcer is generally a sense of discomfort or fullness 3 hours after the largest meals. This is gradually replaced by pain, which occurs between 1 and 4 hours after every meal, the interval being longer the larger the meal. In the early stages, however, it is likely to occur only after the heaviest meal. It frequently wakes the patient in the early part of the night, particularly if the last meal was finished less than 3 hours before going to sleep. It is generally situated in the middle line rather nearer the umbilicus than the ensiform cartilage; it may radiate to the right or be situated on the right side only; less often it is on the left. The pain is at first associated with a feeling of hunger and is relieved by taking food; it is therefore commonly known as "hunger pain". It is also relieved by alkalis and when the stomach is emptied by vomiting, which is, however, rare in uncomplicated cases, though regurgitation of mouthfuls of scalding, very acid, fluid may occur when the pain is at its height.

Constipation is almost always present. The appetite remains good, and the patient does not lose weight or strength.

Periods of hunger pain lasting some weeks or months alternate with periods of more or less complete freedom from symptoms. The attacks are more common in cold weather than in hot, but the autumn and early spring are generally more trying than winter. Attacks are liable to be brought on suddenly by worry, exposure to cold, acute naso-pharyngeal or bronchial infections, indigestible meals and excessive smoking or drinking.

In the majority of cases occult blood is found in the stools. Severe hæmorrhage occurs in about 25 per cent. of cases: it always results in mælena and may also give rise to hæmatemesis.

In early cases radiography shows that the stomach is often of the short high type

and empties itself with unusual rapidity. In more chronic cases reflex spasm of the pyloric sphincter may lead to delayed evacuation and consequent increase in size of the stomach, the greater curvature of which then reaches below the umbilicus. Irregularity in the outline of the duodenal bulb, due partly to the deformity caused by the ulcer itself and partly to spasm, is always found. It affords evidence that an ulcer has been present, but unless it is tender or a definite niche is seen, may only indicate the scar of a healed ulcer. The niche formed by an ulcer on the lesser curvature of the duodenal bulb can be recognised in the silhouette of the bulb; one on the anterior or posterior wall can only be recognised when a radiograph is taken whilst the bulb is being compressed. A test-meal generally shows hyperchlorhydria with a climbing curve, and excess of acid juice in the fasting stomach and after all the starch has left indicates that this is associated with hypersecretion. The nocturnal fasting secretion shows a continuously high acid level.

**Diagnosis.**—When the symptoms have been present for a short time only, an actual ulcer may not be present, but there is a pre-ulcerative duodenitis, which may be associated with a rapidly emptying duodenal bulb, no constant radiographic deformity and no occult blood in the stools. It is likely to result in ulcer if not adequately treated. Excessive smoking, over-fatigue and anxiety may give rise to almost identical symptoms in individuals with hypersecretion.

The diagnosis from gastric ulcer depends upon the later onset of pain, the greater relief on taking food, the rarity of vomiting, the greater frequency of a climbing hyperchlorhydric curve obtained with a fractional test-meal, the frequent situation of pain and tenderness to the right of the middle line, the more frequent periods of complete freedom from symptoms, and the results of radiogram examination, which occasionally, however, reveals the presence of an ulcer in the stomach as well as in the duodenum. Haematemesis without melæna is much more common in gastric than in duodenal ulcer, and melæna alone is more common in duodenal ulcer. The symptoms may closely resemble those of cholecystitis, but in the latter condition the pain is much less regular in its time relations, the tenderness is over the gall-bladder, and evidence of gall-bladder disease is obtained by cholecystography and duodenal intubation.

Carcinoma of the pylorus may closely simulate duodenal ulcer, but the symptoms are more continuous, there is often more local tenderness on palpation, and there is much less relief with food. Recurring attacks of chronic relapsing pancreatitis are also difficult to distinguish from ulcer (p. 705), but there is usually more vomiting, and loss of weight with pain severe enough to require morphine, usually radiating to the left side and often to the back.

**Complications.**—The inflammatory swelling and spasm around a large ulcer may lead to *obstruction*, the first symptom of which is generally vomiting. This may rapidly clear up with medical treatment, but after a number of relapses an ulcer may heal with much scarring causing a cicatricial pyloric stenosis which can only be treated by surgical operation. *Perforation* may occur, and lead to general peritonitis, or less commonly to a localised abscess. Sub-phrenic abscesses due to duodenal ulcer are always to the right of the *suspensory ligament* and may contain gas, unlike those secondary to appendicitis. *Penetration* of the ulcer into neighbouring organs—chronic perforation—is a common complication particularly involving the pancreas. Dense adhesions may form and the surrounding mass of fibrous tissue may become so hard and dense that it is difficult to distinguish it from malignant disease. Duodenal ulcers, however, never are and never become malignant. *Hæmorrhage* is a serious complication and may occur at any period of an ulcer history. It is often followed by a temporary relief of symptoms, but may in a few cases arise without any previous pain at all.

The long-continued use of alkalis and loss of chloride by persistent vomiting may give rise to alkalosis, the first symptoms of which are anorexia, irritabi-

treatment is properly carried out and to provide the mental and physical rest and atmosphere of confidence and calm which it may be impossible to obtain at home.

For the first 2 to 3 weeks of treatment the patient should be kept warm in bed, but he should be allowed up to have a bath and open his bowels, the difficulties of which are much reduced if the use of the bed-pan is avoided. As a rule, no smoking is to be permitted during the period of strict treatment, but exceptions may be necessary in special cases. Mental relaxation is essential, and freedom from business or family worries must be achieved if possible. Judicious regulation of any work done, visitors allowed, etc., must be adopted according to the individual, and relapse during treatment may readily follow bad news or an unpleasant interview.

The less irksome the treatment and the diet can be made the more successful is it likely to be, and many ulcer patients have proved to their physicians that they are able to heal their ulcers and remain well when eating items of food which they like and enjoy, even though they cannot do so on diets which nauseate and disgust them. When and how food is eaten is at least as important as exactly what sort of food it is. It is now recognised that it is unnecessary to adopt any "ladder" system of daily graduated increases in diet, as originally advised by Lenhartz, Sippy and others, and at all stages of treatment hunger is to be avoided, and extra milk given if it is required.

Frequent feeding is the essential factor and at the start hourly feeds (Stage 1) are often advisable or essential. In these cases 5 oz. of milk, which can be flavoured with tea, cocoa or chocolate are given every even hour from waking until the patient settles for the night, an equal quantity of custard, junket or other milky food or white vegetable purée being given at the odd hours. An additional feed should be given each time the patient wakes during the night. Thin bread and butter, rusks and one or two lightly boiled or raw eggs can be added to the diet; they should be thoroughly chewed, and the fluid feeds should be slowly sipped. Apple or other fruit jelly may be used to flavour some of the feeds, and an ounce of strained orange juice should be given three times a day; 50 mg. of ascorbic acid should be given twice a day. Immediately before three of the feeds half an ounce of olive oil is taken, and cream may be added to three of the other feeds if available. The oil inhibits the secretion of gastric juice; at the same time it supplies a digestible and unirritating food of high nutritive value in a concentrated form.

Not all cases require, however, such frequent feeds and many patients may be treated successfully from the beginning by 2-hourly feeds (Stage 2) in which solid meals are given at 8 a.m., 12 noon and 6 p.m., and feeds as in Stage 1 at 6 a.m. (if awake), 10 a.m., 2 p.m., 4 p.m., 8 p.m. and 10 p.m. The solid meals may consist of boiled or steamed fish, or chicken, mashed potatoes and puréed vegetables, steamed or milky puddings, toast, and pip-less jam or honey, plain cake, biscuits and cream cheese. In the third stage (Stage 3) of treatment lamb, tongue, rabbit, sweetbreads and liver are added, the intervals between feeds being lengthened to 8 a.m., 10.30 a.m., 1 p.m., 3 p.m., 4.30 p.m., 7 p.m., 9 p.m., and 11 p.m.

Strict treatment should be continued until the patient has no spontaneous pain and no tenderness or rigidity on examination. Rate of progress must be judged for each case, but no treatment should last less than 6 weeks and in large and chronic ulcers it may need to be 8 or 12 weeks or more. Healing will be quicker in young patients with recent ulceration, and slower in older patients or in those with a long history of relapses. In many cases Stage 2 may be adopted from the start of treatment but in others Stage 1 must be ordered for the first week or 10 days. In general, Stage 2 is to be continued for a period of 3 to 4 weeks or more. On this treatment pain generally disappears within 48 hours; occult blood in the stools may persist for 1 or 2 weeks, but if it continues longer without interruption in the case of a gastric ulcer it suggests a possible malignant lesion. Radiographic control of healing is advisable, particularly in the case of gastric ulcers, but with duodenal ulcers it

is far less satisfactory as deformity of the duodenal cap due to scarring may make interpretation of the appearances very deceptive. There is no fixed rule which can decide exactly when an ulcer has fully healed, as the crater may become filled with granulation tissue so that no niche is seen with the radiographs a fortnight or more before it is replaced by mucous membrane. With gastric ulcers the gastroscopist can determine exactly the stage of healing, but with duodenal ulcers this is of course impossible.

Any ulcer which fails to improve symptomatically within 4 weeks on the above régime demands a full review of the case, as it is either complicated by neurosis or other disorder (e.g. cholecystitis) or it must be considered as probably requiring surgical treatment.

**ALKALIS.**—The use of alkalis during the period of strict treatment is probably unnecessary, and in large dosage may be actually dangerous. With hourly feeding it is better to avoid them, but with the later stages of treatment an alkaline powder given between feeds three or four times a day and last thing at night is often useful, especially if any abdominal discomfort or flatulence persists. Magnesia and sodium bicarbonate have the disadvantage of causing a change in the reaction of the body fluids to the alkaline side—alkalosis—if given in overdosage, and they may also cause some reactionary increase in gastric secretion immediately after their ingestion. Aluminium hydroxide preparations (Aludrox, Lactalumina and others) and mag. trisilicate do not affect the blood reaction at all, so may be given in almost unlimited doses if desired without any danger of alkalosis. Bismuth salts and alumin. silicate (kaolin) may have some beneficial action by forming an insoluble coating to the surface of an open ulcer. None of these preparations given in ordinary dosage, however, appreciably depress gastric acidity for more than a very short time indeed after their administration. The usual dosage of mag. trisilicate is  $\frac{1}{4}$  to 1 drachm and that of alumin. hydroxide preparations 5 or 10 per cent. solutions in doses of 1 to 3 teaspoonfuls. The latter tends to be constipating and the former laxative so that a combination of the two together is often very satisfactory.

**ANTISPASMODICS.**—During strict treatment full doses of atropine, hyoscyamine or belladonna are valuable in reducing gastric motility and spasm. Atropine sulphate gr.  $\frac{1}{16}$  is given in 60 minims of water before the 8 a.m. and 8 p.m. feeds, and a double dose may be given last thing at night. The dose should be increased by 10 minims every day up to the maximum the patient can take without unpleasant dryness of the mouth or paralysis of accommodation, as dosage short of this has no inhibitory effect at all on the stomach.

**SEDATIVES.**—Both mental and physical rest are vitally important factors in the healing of an ulcer. To assist the former some sedative is advisable and phenobarbitone should be given in a dose of gr.  $\frac{1}{4}$  four times a day from the start of the treatment, unless it causes undue depression or any toxic symptoms. Bromides and chloral are unsuitable owing to their irritating action upon the stomach, and opium is not advisable owing to the danger of habit formation.

**GASTRIC LAVAGE.**—An ulcer in the neighbourhood of the pylorus may give rise to obstruction owing to surrounding œdema and inflammatory swelling with pyloric spasm. In such cases continuous hypersecretion of gastric juice often occurs and the ulcer is unable to heal, so that a cicatricial obstruction is often suspected. If, however, the ulcer can be made to heal the "functional" obstruction may be relieved and any scarring produced may be insufficient to cause lasting obstruction. In such cases gastric lavage, either by stomach tube and funnel or by Senoran's evacuator, with complete removal of all gastric contents may be of great value. This should be done each night at 10 p.m., no feed having been given after 6 p.m. After the stomach has been emptied a full dose of alkali with a maximal dose of atropine is given, and as soon as not more than 3 or 4 oz. of fluid are found to be present on two consecutive nights, the lavage may be discontinued.

**After-care.**—When healing is complete, usually at the end of 6 to 8 weeks, the patient must be advised regarding the prevention of recurrence. It is not difficult to cause an ulcer to heal, but the predisposing causes are still present, and the exciting causes may still be operative unless special precautions are taken to control them. It is essential to give instructions in writing for the patient to follow (*vide infra*). In addition help must be given him as far as possible as regards his mode of life, hours of work, domestic and family problems and any environmental factors which may produce anxiety, conflict or resentment. In hospital practice the Lady Almoner may often greatly help these patients, and elaborate dietary instructions are usually a waste of time.

From the beginning of treatment the swallowing of infective material should be kept in check as far as possible by careful dental hygiene, and as soon as the patient is convalescent thorough treatment of the teeth should be undertaken, and he should subsequently have his teeth put into good order at least twice a year. Any infective foci in the throat and nose should also be treated.

The patient should eat slowly and masticate thoroughly; he should acquire this habit during the period of observation and strict treatment. It should be impressed upon busy men that when they have no time to sit down to a proper meal it is better to drink milk or eat plain chocolate than to bolt some less digestible solid food. Tough meat, new bread and other articles of diet which cannot easily be chewed to a pulpy consistence should be prohibited. The patient should avoid the pips and skins of fruit, whether raw, cooked or in jam, cake or puddings, and pickles, salads and uncooked vegetables, such as celery; green vegetables are best given as purées with butter, but spinach, which is a powerful stimulant of gastric secretion, should be avoided. Condiments, vinegar, and unripe and acid fruit, high game, sausages and curry should be prohibited. The patient should be allowed to smoke only in strict moderation. He should remain on this régime until he has been free from symptoms for 2 years, and should follow it in a modified form for the rest of his life.

During periods of overwork and especially of mental stress, the patient should, if possible, spend 1 day or half a day a week resting and should be kept on a 2-hourly diet even in the absence of digestive symptoms. If he is much worried or sleeping badly he should be given gr.  $\frac{1}{4}$  to  $\frac{1}{2}$  phenobarbitone three times a day and sufficient at night to secure sound sleep. Special care should be taken to avoid infections. If he gets a cold, sore throat, influenza or other infection, he should remain in bed on a very light diet until he has completely recovered.

The bowels should be kept regular with liquid paraffin. If this is insufficient, fluid preparations of magnesia may be given with it, but other aperients should be avoided. No strong tea or coffee should be allowed or any alcohol on an empty stomach: a little diluted whisky, light wine or beer may be permitted with meals for those who especially desire it.

The patient should for a time take a teaspoonful of magnesium trisilicate or aluminium hydroxide after meals and subsequently have some always available so as to be able to take enough to keep himself comfortable at the slightest suspicion of heart-burn or gastric discomfort. He must be urged to carry an alkaline tablet always with him and suck one at any time if pain occurs and before this has had time to "get a grip". He should be warned of the danger of recurrence, and should be told to have a day or two off work on a strict diet at the first indication of a return of symptoms. If he does so this may be sufficient to ward off an attack, but if he waits until the symptoms become fully developed, a prolonged stay in bed is likely to be required.

The strict ulcer treatment and the post-ulcer régime can be summarised as follows:

#### *Strict Ulcer Treatment*

##### *Stage I*

Every even hour whilst awake 5 oz. of milk. This can be warm or cold and may be flavoured with tea.

Every odd hour a 5-oz. feed which may be made of any of the following :

- (a) Arrowroot, Farola, Benger's, Horlicks, junket, custard. These can be made more appetising by the addition of red currant, apple or other fruit jelly, and the junket may be flavoured with chocolate.
- (b) At least two should consist of a thick soup or semi-solid purée of potato, peas, artichoke, cauliflower or parsnip.

During the night the patient should have milk by his bedside, so that whenever he wakes he can take a feed.

A rusk, plain biscuit or thin bread with butter or honey may be eaten with any of the feeds. A lightly boiled egg may be taken once or twice a day.

Water may be drunk between feeds. An ounce of strained orange, tomato or other fruit juice should be taken with three of the drinks, and 100 mg. of ascorbic acid dissolved in milk should be given daily.

A teaspoonful of atropine mixture (atropine sulphate, gr.  $\frac{1}{100}$  in 1 dr. water) is given before the last feed, and before two or three other feeds if the acidity is high. The dose should be increased by 10 minims every day until an unpleasant degree of dryness of the mouth or paralysis of accommodation occurs : the dose should then be reduced to that of the previous day.

Half a teaspoonful of magnesium trisilicate in a little water with a teaspoonful of 10 per cent. aluminium hydroxide may be given three or four times a day between feeds and last thing at night.

No smoking during the strict treatment.

## Stage II

2-hourly feeds.

On waking.	Milk, or weak, milky tea.
Breakfast.	Weak, milky tea, or milk flavoured with coffee. One egg—scrambled, poached or soft boiled ; or steamed finnan or white fish, or strained porridge, cornflakes, groats or Bemax with black currant purée, with milk and sugar. Toast, or bread with butter or margarine. Jelly marmalade, honey, syrup or jelly jam.
Mid-morning.	Milk, flavoured with Marmite or Ovaltine. Plain biscuit, bread and butter, or Madeira cake.
Midday.	Steamed fish or chicken, rabbit, tripe or sweetbreads, liver, minced beef or mutton, or tender beef or mutton. Mashed or creamed potato. Sieved vegetable or cauliflower tops. Milk pudding, baked custard, milk jelly, junket or clear jelly with fruit purée or light plain sponge. Or cream cheese, butter, cream crackers.
2 p.m.	Milk, flavoured, if desired.
Tea.	Weak, milky tea. Bread, butter or margarine. Jelly, jam, honey, syrup or Marmite. Plain biscuits, Madeira or sponge cake.
Evening Meal.	Steamed fish, etc., as at midday, or cheese custard, cheese spaghetti, cauliflower au gratin, or cheese potato. Bread, butter or margarine. Milk pudding, etc., or ice cream or fruit purée, with milk and sugar.
Bed-time.	Weak, milky tea, if desired. Milk, flavoured as desired. Bread and butter or plain biscuits.

Night. Milk must be left at the bedside with an alkaline powder, but patients need not, as a rule, be wakened for regular feeds. If night pain occurs, however, he should be wakened at a time *before* this usually occurs and given a feed. If the pain is not prevented in this way, a continuous milk drip throughout the night is usually advisable (p. 587).

*Post-Ulcer Régime*  
*To be followed permanently*

1. A meal or feed (milk, plain biscuits or chocolate) should be taken at intervals of not more than 2½ hours from waking to retiring, and again if awake during the night.

2. Eat slowly and chew very thoroughly. Adequate time should be allowed for meals, which must be punctual. Avoid taking a meal when tired, but rest for a short time beforehand if possible. When there is no time for a proper meal, it is better to drink some milk or eat some plain chocolate or biscuits than to bolt some less digestible solid food.

3. Do not smoke on an empty stomach and not at all if you have any indigestion; it is best to avoid it altogether.

4. During periods of overwork, and especially of mental stress, at least one clear day a week should be spent resting, on a strict 2-hourly diet, even in the absence of digestive symptoms. If you are much worried or sleeping badly, ask your doctor for a sedative.

5. Special care should be taken to avoid chills. If you get a cold, sore throat, influenza or other infection, remain in bed on a very light diet until you have completely recovered.

6. Avoid alcohol, except (if desired) a small quantity of beer, light wine or diluted whisky with (but never before) meals. Avoid pips and skins of fruit (raw, cooked or in jam) and raisins, currants, figs, ginger and lemon-peel in puddings and cakes, nuts and unripe fruit.

Avoid radishes, cucumber, raw celery, tomato skins; stringy French beans; hard peas and beans. Coarse green vegetables (cabbage, etc.) should be passed through a sieve.

Avoid porridge made with coarse oatmeal and cereals and biscuits made with much coarse husk.

Avoid tough or twice-cooked meat, pork, strong meat soups and extracts and highly seasoned foods.

Avoid most fried foods, especially if fried for a long time; avoid sausages and fried (chip) potatoes.

Avoid mustard, pepper, vinegar, curry, pickles and chutney. If in doubt about any food, remember you must not eat anything which cannot be chewed into a mush.

7. One or two tablets of magnesium trisilicate and aluminium hydroxide should be chewed twice a day between meals and also whenever the slightest indigestion or heartburn is felt. Noon and 4 to 6 p.m. are the times at which alkalis are most often required.

8. Liquid paraffin or magnesia may be taken for the bowels if necessary, but no other aperient should be used without the doctor's advice.

9. Visit your dentist regularly every 6 months.

10. Take no drugs in tablet form. Take no aspirin or Veganin but, if necessary, powdered calcium aspirin may be taken instead.

11. If you have a return of symptoms, go to bed on a strict diet at once. Consult your doctor and do not wait for the symptoms to get serious.



### *Surgical Treatment*

An operation should be advised under the following circumstances :

1. At the earliest moment after a perforation.
2. For pyloric obstruction without active ulceration.
3. For pyloric obstruction with active ulceration, if it persists after 3 weeks of strict treatment by rest and diet, with evacuation of the stomach every night.
4. For a gastric ulcer causing organic hour-glass contraction sufficiently severe to produce 3-hour stasis in the proximal segment. This is very rare.
5. When the symptoms recur after one or more courses of thorough medical treatment followed by adequate after-treatment. The number of such courses which may be tried depends upon such circumstances as the social position, occupation and place of residence of the patient. Thus the better the social position of the patient, the less strenuous his occupation and the less important are occasional absences from business, and the warmer and more equable the climate, the less urgent is the necessity for operation. The results of surgery are least satisfactory when evacuation is rapid, acidity is high, and the patient is young, and are best when the stomach empties slowly, acidity is normal or low, and the patient is over 50. Surgery on the whole becomes progressively more urgent in gastric ulcer the longer the condition has remained unhealed, whatever the age of the patient, whilst in duodenal ulcer longer perseverance with medical treatment is usually advisable.

6. *Hæmorrhage*.—Surgery is very rarely advisable in young patients suffering from their first hæmatemesis. Recurrent bleeding, however, from a proved chronic ulcer is usually best treated by operation, and in patients over 40 the need for this is greatly increased. In most cases the acute hæmorrhage can be successfully treated medically (see p. 570) and operation postponed till the patient is better able to stand it. In others, however, in which bleeding appears to be continuing, especially in older patients with sclerotic vessels, it is urgent to consider operation early as an emergency and not wait too long before asking for surgical help. If operation is decided upon the patient must be given a blood transfusion in sufficient quantity to bring his hæmoglobin to 70 per cent., and dehydration and shock must be overcome by the use of adequate fluids and salt, given either orally or intravenously: the blood urea and blood chlorides should be estimated before operation if facilities for these are available.

At operation an attempt should be made to resect the ulcer, or if this is impossible, to ligate the bleeding-point: failing this, a series of sutures should be tied round the ulcer so as to cut off as much as possible of its blood supply. Gastro-jejunostomy alone is, of course, quite useless unless pyloric obstruction is present.

7. When for any reason it appears possible that a gastric ulcer is malignant and not benign (p. 589) partial gastrectomy should be performed, even if naked-eye appearance shows no evidence of malignancy.

8. Though malignant degeneration of a simple gastric ulcer is rare, this change occurs more frequently in the pre-pyloric than in the more commonly situated lesser curvature ulcers, and as it is often impossible with radiography to distinguish a simple ulcer from an early malignant ulcer in the prepyloric region, partial gastrectomy should be performed in all cases of prepyloric ulcer which do not rapidly respond to medical treatment; gastro-jejunostomy is not advisable as it is impossible to exclude early malignant changes even by inspection and palpation during the operation. Ulcers on the greater curvature are most often malignant and these should be resected; the size of an ulcer is no safe guide as to its nature.

Partial gastrectomy is the only satisfactory operation for a gastric ulcer wherever it is situated. Gastro-jejunostomy was previously thought to be the best operation for cases of duodenal ulcer with obstruction, but at the present time most physicians agree in advising some form of gastro-duodenal resection if the condition at operation

permits. Technical difficulties, however, may be very great and if so the risk of the larger operation may not be justified as compared to that of simple short-circuit. If the gastric resection can be made high up and includes the pylorus the reduction in acidity is very considerable. In the case of gastric ulcer the results of gastrectomy are extremely good and the operative risk not high.

Complete achlorhydria only rarely results, and anastomotic ulcer may follow the operation in a small percentage of cases. The mortality of gastrectomy is higher than that of gastro-jejunostomy, but the risk of recurrence of symptoms following gastro-jejunostomy is not less than 30 to 40 per cent., whilst that following partial gastrectomy is certainly not greater than 10 to 15 per cent.

*Post-gastrectomy syndrome.*—After gastrectomy in some 10 to 20 per cent. of patients attacks of great weakness, nausea and sweating may occur soon after eating, due probably to the rapid entry of food into the jejunum causing sudden distension. The symptoms are usually first noticed when the patient begins a normal life after the operation and are most likely to come on in the standing position. As a rule they disappear spontaneously within 1 or 2 years. They should be treated by giving dry solid meals with, if possible, a rest lying down for a short time after eating; as there is often much distress concerning the symptoms and the patients are usually of the anxious type, a sedative is also advisable in treatment. In a few patients bouts of diarrhoea and steatorrhoea, with loss of weight, anaemia and signs of vitamin deficiency occur and in a small percentage of cases hypoglycaemic attacks 2 or 3 hours after eating have been shown to occur.

In spite of these occasional sequelæ, the results of partial gastrectomy are good, and patients should return after operation to a normal mode of life and diet, except for somewhat restricting the size of their meals and the rate at which they eat.

**SUBSIDIARY METHODS OF TREATMENT.**—(a) *Continuous milk drip: duodenal feeding.*—The use of a Ryle's tube, with a continuous milk drip aimed at neutralising without intermission gastric acidity, is particularly useful in cases that are resistant to orthodox treatment. The tube is passed through the nose and retained for 2 or 3 weeks, often with very little discomfort to the patient. Additional solid feeds may be given by mouth as required.

(b) *Parenteral treatment.*—Many attempts at ambulant treatment of peptic ulcer by injection treatment have been made, but it is unnecessary to mention these in detail. All act either by suggestion or through some mild non-specific protein-shock effect which perhaps aids slightly the healing of inflammatory processes in general. Gastric and duodenal extracts (entero-gastrone) and histidine (an amino acid) are two preparations which have been widely advocated. Non-specific injection treatment should never be given in place of thorough treatment on orthodox lines.

(c) *Vagotomy.*—Section of both vagus nerves was originally suggested by Dragstedt and has been fairly extensively performed either through the thorax or the abdomen and, as mentioned previously, leads to reduction in quantity and acidity of the gastric juice, diminished motility of the stomach and possibly abolition of duodenal spasm. The operation is simple and safe, but its results have not confirmed its original hopes. It is now limited to patients who have developed jejunal ulcer after previous operations, or as a primary procedure only when combined with some short circuit operation or pyloroplasty to prevent subsequent gastric atony, stasis and vomiting.

#### POST-OPERATIVE GASTRO-JEJUNITIS AND ACUTE AND CHRONIC GASTRO-JEJUNAL AND JEJUNAL ULCER; GASTRO-COLIC FISTULA

**Ætiology.**—The incidence of gastro-jejunal ulcer and jejunal ulcer after gastric operations depends upon the acidity of the gastric contents following the operation. It is consequently much more common after gastro-jejunostomy performed for

duodenal ulcer, occurring in between 20 to 40 per cent. of cases, than when performed for gastric ulcer, and it never follows operations for carcinoma. It is very rare in women. It may occur after partial gastrectomy, especially when performed for duodenal ulcer or gastro-jejunal ulcer, as hyperchlorhydria persists in about 50 per cent. of cases. In 20 per cent. of cases the anastomotic ulcer develops immediately after the operation and in the majority within 2 years, though they may develop after as long as 20 years of freedom from symptoms.

The condition begins with inflammation of the anastomotic area—the neighbouring gastric mucous membrane and the first inch of the distal limb of jejunum. Acute ulcers, which may cause severe hæmorrhage or perforate, follow. These may heal spontaneously or develop into chronic ulcers. Gastro-jejunal and jejunal ulcers are of equal frequency.

**Symptoms.**—The indigestion which follows gastro-jejunostomy is due in a large proportion of cases to an anastomotic ulcer. The commonest symptom is pain, which comes on soon after meals in contrast with its comparatively late onset before the operation, and it is generally situated to the left of the umbilicus instead of at a higher level and in the middle line or to the right. It is usually less relieved by alkalis or food than is that of duodenal ulcer, and may radiate severely to the back and persist, particularly during the night. Hæmatemesis, which is sometimes the only symptom, occurs in about 50 per cent. of cases, and occult blood is usually present in the stools. Perforation may also occur without warning. In about 5 per cent. of cases the ulcer becomes adherent to the colon, and a gastro-colic, gastro-jejuno-colic or jejuno-colic fistula develops. This may at first cause little or no change in the symptoms, but sooner or later diarrhœa, which is occasionally fatty, and vomiting of fæculent material or eructation of foul gas occur. In rare cases the proximal part of the colon becomes obstructed and severe pain and distension from accumulated fæces results.

A "niche", corresponding with an ulcer crater, can generally be recognised by radiographic examination when a chronic ulcer is present, but in the frequent cases in which recurrent acute ulcers develop nothing abnormal can be seen. Gastroscopy has demonstrated the frequency of acute inflammation with or without erosions in the mucous membrane on the gastric side of the anastomosis in cases in which nothing abnormal is revealed with the radiograph, especially when hæmorrhage is the only symptom. Direct pressure over the stoma or the jejunum just beyond it often gives rise to pain. Free acid is invariably found after a fractional test-meal if care is taken not to allow the tube to pass through the stoma; in many cases there is hyperchlorhydria. An opaque meal can sometimes be seen to pass direct into the colon if a fistula has developed. In other cases the fistula can be recognised only after an opaque enema, when some of the barium is seen to pass direct from the colon into the stomach.

**Treatment.**—Prolonged treatment of exactly the same kind as that described for gastric and duodenal ulcer may lead to healing and the hypertrophic gastritis, which often occurs around the stoma in the absence of a chronic ulcer and which is a common cause of recurrent hæmorrhage, may also recover. Medical treatment, however, often fails and when the symptoms recur in spite of following a careful régime, the whole of the anastomotic area should be excised and a partial gastrectomy performed. It should be remembered that no sign of the ulcer may be visible on external examination, and that it is useless merely to divide any adhesions which may be found, as they are never responsible for the symptoms.

## TUBERCULOSIS OF THE STOMACH

Tuberculosis of the stomach is very rare. In miliary tuberculosis the mucous membrane may be involved, but no symptoms are produced. In advanced pulmonary

tuberculosis a tuberculous ulcer may form, generally near the pylorus. The symptoms are indistinguishable from the dyspepsia common in such cases, unless hæmatemesis occurs; this may, however, be due to the presence of a simple ulcer. Hurst recorded one case of chronic gastric ulcer and one of carcinoma, in which microscopical examination of the specimen removed at operation showed that secondary tuberculous infection had taken place. Both were associated with achlorhydria and had no distinctive symptoms, and the primary infection which was presumably present in the lungs was completely latent.

## SYPHILIS OF THE STOMACH

**Ætiology.**—Syphilis of the stomach is apparently not uncommon in America and some Continental countries, but it is certainly very rare in England. It occurs in males twice as frequently as in females. Its incidence is greatest between the ages of 30 and 40, and it may develop any time between 4 and 40 years after infection.

**Pathology.**—Characteristic gummatous infiltration of the walls of the stomach, especially the pyloric end, has been found in specimens excised at operation and much less frequently at necropsy. In at least two post-mortem specimens spirochætes were discovered.

**Symptoms.**—Epigastric pain generally occurs immediately after meals; less frequently it is delayed as in ulcer. Fluids and small meals give some relief. Vomiting is common, but nausea, anorexia and anæmia are rare. The symptoms become steadily worse with increasing loss of weight and strength. Hæmorrhage is very rare, and occult blood is only occasionally found in the stools. Achlorhydria is present in 85 per cent. of cases and hypochlorhydria in most of the remainder. The lesion is most frequently prepyloric, but pyloric incompetence owing to rigidity of the outlet of the stomach is as common as pyloric obstruction, and less frequently an hour-glass contraction is present. A tumour is only occasionally palpable. In 25 per cent. of cases other clinical signs of syphilis are found.

The radiograph generally reveals a local or diffuse involvement of the walls, which lead to stiffening, diminished mobility and abnormal peristalsis. The stomach is generally small. Less frequently there is a filling defect and very rarely a niche.

**Diagnosis.**—The possibility of syphilis should be considered when symptoms suggestive of cancer are present; even if there is no history or other evidence of syphilis the Wassermann reaction should be tested. The diagnosis would be confirmed by the rapid improvement with anti-syphilitic treatment in spite of the failure of other measures.

**Treatment.**—The usual treatment for syphilis should be given; it is generally very successful. In late cases a short-circuiting operation may be required for pyloric obstruction caused by cicatricial contraction if anti-syphilitic treatment has failed to give relief.

## CARCINOMA OF THE STOMACH

**Ætiology and Pathogenesis.**—Carcinoma of the stomach is the most frequent type of cancer found in the male sex, and is commonest between the ages of 45 and 65. When allowance is made for the number of people living at each age, however, it is seen that there is a steady rise in incidence throughout adult life. This incidence has increased during recent years and the ratio of men to women amongst people over 40 is approximately 3 to 1.

Hurst and others believed that carcinoma never developed in a normal stomach, and it is certainly true that evidence of chronic gastritis can be found pathologically in the neighbourhood of the growth in many cases. Chronic gastric irritation, in

the form of repeated dietetic or other insults (see chronic gastritis) may perhaps be one factor in causation, but other susceptibilities are certainly also involved. Some positive hereditary history can be found in approximately 20 per cent. of cases, but no occupation is especially involved. Clinical and post-mortem statistics show that the stomach accounts for only 30 per cent. of deaths from carcinoma of the alimentary tract in England compared with 65 per cent. in Holland and Sweden, and cancer of the stomach occurs in England with greater frequency in the poor than in the well-to-do, although the relative frequency of cancer in other organs is approximately the same in all countries and in all classes. The urban incidence is higher at all ages than the rural, but especially so in younger people.

In a proportion of cases cancer develops upon a chronic peptic ulcer—ulcer cancer. This happens much more frequently in the relatively rare prepyloric ulcer than in the common lesser curvature ulcer. In about 6 per cent. of chronic ulcers excised by operation, which appear innocent to the naked eye, small areas are found in the margin which show microscopical evidence of malignant degeneration, and in about 16 per cent. of cases of obvious carcinoma there is pathological or clinical evidence that the disease followed a simple chronic ulcer.

Carcinoma accounts for 99 per cent. of all primary malignant growths of the stomach. Almost all arise from glands, and are adenomatous, but they may be of various types. The most frequent type is that of an irregular infiltrating ulcer with a hard raised edge, but soft fungating, polypoid or hard scirrhous (leather-bottle) growths also occur. The latter take the form of a diffuse rigid fibrous thickening of the stomach sometimes described as *linitis plastica*. As a rule carcinomatous ulcers are of large size when first diagnosed and any ulcer in the stomach with a diameter greater than 2.5 cm. radiographically should raise the suspicion of a growth.

**Symptoms.**—When an individual above the age of 40, who has hitherto had a good digestion, suddenly begins to suffer from gastric symptoms, the possibility of cancer should always be considered, and with increasing age this possibility steadily increases. The nature of these symptoms depends partly upon the site of the stomach involved, but the most common one is epigastric discomfort or pain immediately or soon after meals. After a time the pain, which is generally dull and distressing, but not very acute, becomes continuous, but it is still aggravated by meals. In a small proportion of cases the pain begins 2 or 3 hours after meals and is relieved by food, thus simulating duodenal ulcer, but there are never spontaneous remissions of symptoms, and in these cases achlorhydria is usually present. At an early stage the appetite diminishes, the patient having a special repugnance for meat. This is often the first symptom, though in ulcer-cancer the appetite may be maintained for some time. The anorexia may be associated with nausea, which can also occur independently, occasionally as the earliest symptom. In about one-fifth of the cases there is a long history of symptoms suggestive of gastric ulcer, the pain having recently become more severe and continuous instead of intermittent.

Though anæmia is often present, the blood picture may remain normal even in very extensive and inoperable growths with occult blood present in the stools. The anæmia is partly due to constant oozing from the ulcerated growth, but this has comparatively little effect unless actual hæmatemesis or mælena occurs; anæmia of this kind can be overcome by treatment with iron and, in severe cases, repeated transfusions. It is often of the simple achlorhydric type, which responds rapidly to treatment with large doses of iron, but occasionally it is Addisonian and responds to treatment with liver in spite of the presence of a growth. Flatulence is commonly present, the gas brought up being as a rule odourless, but occasionally foul. Vomiting is generally present sooner or later. In cancer of the cardiac end of the stomach dysphagia with regurgitation of food immediately after swallowing occurs, and the symptoms may be indistinguishable from those of a growth of the lower end of the œsophagus. Vomiting is commonly preceded by pain and nausea, both of which it temporarily

relieves, but less completely than in gastric ulcer. The vomited matter contains blood more often than in gastric ulcer; it often has the appearance of "coffee grounds". Hæmatemesis is rare, but in exceptional cases may be the earliest symptom. In a large proportion of cases blood constantly oozes from the surface of the growth, so that one or more of the specimens obtained with a fractional test-meal may be obviously blood-stained, and all are likely to contain occult blood. The oozing is unaffected by diet, so that occult blood is present in every stool examined, however carefully the patient is dieted. The growth sooner or later involves the pylorus in two-thirds of all cases; the special symptoms then present are described under pyloric obstruction (p. 594).

The patient rapidly loses strength and weight, the emaciation being more than can be accounted for by the vomiting and diminished intake of food. In the late stages the disappearance of subcutaneous fat, loss of elasticity of the skin, œdema and anæmia give the patient a characteristic cachectic appearance. A low pyrexia is not uncommon and is almost constant if metastases are present in the liver.

In the earlier stages nothing abnormal is found on abdominal palpation; but sooner or later a hard, moderately tender tumour is generally felt. It is often most easily palpable when the stomach is empty, but occasionally only becomes obvious after meals. When the fundus or body is involved the tumour is felt descending from under the left costal margin, when it may sometimes be mistaken for an enlarged spleen. In carcinoma of the lesser curvature and pylorus the tumour lies across the upper part of the epigastrium.

Radiography often shows an irregular filling defect in the outline of the stomach, which coincides with the tumour if one is palpable, and often involves the greater curvature. The normal progress of the peristaltic waves is interrupted, sometimes before any obvious deformity is present. The first radiological sign may be irregularity in the arrangement of the folds of mucous membrane seen in a radiograph taken after swallowing one or two mouthfuls of a suspension of barium sulphate. In carcinoma of the fundus, the arc formed by the gas under the diaphragm is irregular in shape and reduced in size, and the growth itself may be faintly visible through the gas bubble.

If there is the slightest reason to suspect cancer a fractional test-meal should be given. The resting-juice often contains pus cells in excess of the leucocytes present in a specimen of saliva obtained at the same time, and even if the specimen is not obviously blood-stained, red corpuscles are often found on microscopical examination. In 60 per cent. of cases complete achlorhydria is present, and in at least another 20 per cent. there is hypochlorhydria; in most cases secondary to ulcer free acid is present, sometimes actually in excess. If pyloric obstruction and achlorhydria are present, but not otherwise, the resting-juice generally contains lactic acid. It is, however, absent if the stomach is washed out thoroughly the previous evening. It is thus a product of the decomposition of stagnating food and is not a secretion of the growth. Moreover, the lactic acid is the inactive variety, and therefore of fermentative and not animal origin: it may also be present in other conditions, such as migraine, if achlorhydria and gastric stasis are present together; occasionally it is possible to detect fragments of tumour tissue in the test-meal sediment.

Secondary deposits frequently occur in the liver and in 5 per cent. of cases in both ovaries (Krukenberg's tumour) and the symptoms they give rise to may be the most prominent clinical manifestation. Direct spread to the peritoneum and omentum is common, and irregular abdominal masses are often palpable; ascites may occur as a result of the malignant peritonitis, and jaundice as a result of deposits in the liver or portal fissure causing biliary obstruction. A small gland just beneath the insertion of the left sterno-mastoid muscle is generally attacked before any other cervical glands, and less frequently deposits occur in the inguinal glands. The growth may spread along the urachus to involve the umbilicus, where a hard nodular mass

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**Symptoms.**—When an individual above the age of 40, who has hitherto had a good digestion, suddenly begins to suffer from gastric symptoms, the possibility of cancer should always be considered, and with increasing age this possibility steadily increases. The nature of these symptoms depends partly upon the site of the stomach involved, but the most common one is epigastric discomfort or pain immediately or soon after meals. After a time the pain, which is generally dull and distressing, but not very acute, becomes continuous, but it is still aggravated by meals. In a small proportion of cases the pain begins 2 or 3 hours after meals and is relieved by food, thus simulating duodenal ulcer, but there are never spontaneous remissions of symptoms, and in these cases achlorhydria is usually present. At an early stage the appetite diminishes, the patient having a special repugnance for meat. This is often the first symptom, though in ulcer-cancer the appetite may be maintained for some time. The anorexia may be associated with nausea, which can also occur independently, occasionally as the earliest symptom. In about one-fifth of the cases there is a long history of symptoms suggestive of gastric ulcer, the pain having recently become more severe and continuous instead of intermittent.

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can be felt. A rectal examination should always be made, as a deposit is not infrequently present in the recto-vesical or recto-vaginal pouch at a comparatively early stage.

Perforation may occur, general peritonitis being usually prevented by the presence of old adhesions, so that a local abscess forms; less frequently the colon becomes involved and a gastro-colic fistula results, the patient then rapidly dying from emaciation due to constant faecal vomiting and severe diarrhoea.

Other terminal complications are suppurative gastritis, pylophlebitis, suppurative parotitis, thrombo-phlebitis migrans, septic pneumonia, empyema and infective endocarditis.

**Diagnosis.**—Apart from the history and the discovery of a tumour, radiological examination is the most important means of distinguishing a growth from other gastric disorders, the most characteristic signs being rigidity and irregularity of the mucosa, an intragastric filling defect, or a definite ulcer crater. The latter may be difficult to distinguish from a benign ulcer, but is often larger, more ragged and irregular and is usually antral or prepyloric. Ulcers on the greater curvature are usually malignant. The leather-bottle stomach is narrow, rigid and tube-like, and shows no peristaltic movements. In gastric ulcer the pain begins only at an interval after meals, and if present when food is taken it is temporarily relieved, whereas in cancer the pain generally begins directly after meals and is rarely relieved by food. In the group of cases in which duodenal ulcer is simulated, the absence of periods of freedom from symptoms, the presence of achlorhydria and the radiogram appearance should prevent a mistake in diagnosis. Pernicious anaemia may closely simulate a growth of the stomach; the megalocytosis and high colour index are characteristic of the former, and the presence of occult blood in the stools is distinctive of the latter. It should, however, be remembered that in rare cases pernicious anaemia may be associated with carcinoma of the stomach. Gastroscopy is, as a rule, only indicated when radiography is indefinite, but may be of great value in demonstrating the nature of an ulcer, whose edges may show the raised nodular indurated appearance characteristic of carcinomatous infiltration. It is especially indicated in any case of gastric ulcer which fails to respond satisfactorily under medical treatment. In late cases the diagnosis may have to be made from cirrhosis of the liver with ascites, from heart failure, or from growths in the pancreas or colon with secondary deposits in the peritoneum.

**Prognosis.**—The average duration of life after the appearance of the first symptom is a year. Temporary improvement and considerable gain in weight may occur as a result of rest and careful dieting. Death is most frequently due to exhaustion; in other cases it results from one of the complications already mentioned. The results of surgery are disappointing, and the operation mortality of total gastrectomy is at least 25 per cent.; some guide to prognosis can be obtained if the tumour after resection can be graded for malignancy by the pathologist. If the patient is still alive 5 years after operation, his expectation of life is then the same as for the normal individual. Of those cases in which resection is possible at operation, not more than 15 to 20 per cent. are likely to be alive after 5 years, but only about one-quarter of all cases are resectable when first diagnosed. The prognosis is better in older patients, whilst in cases occurring in men under 30 it is almost hopeless.

**Treatment.**—Medical treatment is only palliative. In some cases the post-ulcer régime with alkalis may keep the patient comfortable, and small semi-fluid feeds are often all that can be tolerated. Gastric lavage may give relief, and an acid mixture may sometimes help to improve appetite. A sedative mixture or aspirin powders are generally sufficient to control pain for a time, but if morphine is required there should be no hesitation in giving as large a dose as is needed.

An operation should be performed in all cases in which there is no evidence of secondary deposits or involvement of glands beyond those in the immediate neigh-

bourhood of the stomach, unless it is found impossible to improve the patient's condition sufficiently to hold out any hope of success. If anæmia is present it should be treated before operation with large doses of iron, and, if necessary, blood transfusion until the hæmoglobin percentage is 80. When the pylorus is obstructed, the stomach should be washed out every morning and evening for a week before operation and large quantities of saline solution given by rectum. With proper preparation and bold and skilful surgery many apparently inoperable tumours can be completely removed. If secondary deposits make a radical operation impossible in a case of pyloric carcinoma, much relief may follow gastro-jejunostomy. Small nodules in the liver are not a contraindication to partial gastrectomy, as they may grow so slowly that the patient remains quite comfortable for many months after the operation. Total gastrectomy combined with an œsophago-jejunostomy has a mortality of 20 to 30 per cent., but may give remarkably successful results in suitable cases.

## HOURL-GLASS STOMACH

A gastric ulcer situated on the lesser curvature may give rise to spasm of the corresponding segment of circular muscle fibres, which leads to a depression or "incisura" on the greater curvature, like a finger pointing at the "niche" on the lesser curvature. The degree of spasm varies with the activity of the ulcer, but a slight spasm may persist after healing is complete. It never gives rise to sufficient obstruction to cause stasis or increased peristalsis in the proximal segment. It may disappear on vigorous massage or after strongly contracting the abdominal muscles and sometimes, but not always, after the administration of atropine. A less persistent spasm may occur as a reflex result of duodenal ulcer, disease of the gall-bladder and appendicitis.

Cicatrization of a very chronic gastric ulcer may produce an hour-glass constriction. This hardly ever occurs in men, the large majority of cases being in women with such a high threshold of sensibility to pain that, though they may have had an ulcer for 20 or 30 years, they have never complained of indigestion of sufficient severity to raise a suspicion of the presence of organic disease. The frequency of hour-glass stomach has steadily diminished during the last 25 years and the condition is now rare, probably owing to earlier diagnosis and better medical treatment. In 50 per cent. of cases found post mortem the ulcer has healed completely and is replaced by a scar. The comparatively rapid healing of a lesser curvature ulcer by medical treatment, however large the ulcer may be, never results in an hour-glass stomach, a period of many years with alternating periods of activity and spontaneous healing being essential for its development. The obstruction caused by an hour-glass contraction with a still active ulcer is always exaggerated by the presence of spasm, so that the narrowing found at operation is often much less than would be suspected from the radiograph.

One of the two hour-glass stomachs Hurst records in men was caused by a band passing from an ulcer on the lesser curvature to the omentum; the constriction disappeared when this was divided. Hour-glass constrictions caused by cancer and syphilis are extremely rare.

**Symptoms.**—In organic hour-glass stomach a history of comparatively slight indigestion occurring intermittently for many years, possibly with one or more hæmorrhages, can almost always be obtained. The symptoms are similar to those of pyloric obstruction due to ulcer, with the exception that the amount vomited is generally less, and greater relief is obtained on lying down. There is no visible peristalsis unless the proximal segment is unusually large. The diagnosis is impossible without radiographic examination. In contrast with the hour-glass constriction caused by spasm, the neck passes from a point above and to the right of the lowest

part of the proximal segment. If an active ulcer is present, the niche produced by the crater is seen on the lesser curvature.

**Treatment.**—If no niche is present and the upper sac of the stomach is empty within 4 hours, the patient often keeps perfectly well by following the "post-ulcer régime" (p. 585). If the ulcer is still active, surgery is indicated. When the constriction is sufficiently narrow to produce definite stasis in the proximal sac, a gastro-gastrostomy should be performed, or if this is impossible and there is little or no stasis in the proximal sac, a partial gastrectomy. As an hour-glass constriction is occasionally associated with pyloric obstruction, the condition of the pylorus should always be investigated in case a gastro-jejunostomy is required in addition to a gastro-gastrostomy.

## PYLORIC OBSTRUCTION

**Ætiology.**—Pyloric obstruction may be organic and incurable medically or functional and curable. Organic obstruction of the pylorus or duodenal bulb is caused by the contraction of fibrous tissue formed during cicatrisation of an ulcer in its neighbourhood, 85 per cent. being duodenal and 15 per cent. prepyloric. Two-thirds of all cases of carcinoma of the stomach involve the pylorus. Pyloric obstruction is said to result from chronic gastritis as a result of hypertrophy of the mucosa or generalised sclerosis of the mucosa, submucosa and muscular coats. Syphilis is a very rare cause of pyloric obstruction. In infants, obstruction may result from hypertrophy of the pyloric sphincter (p. 596).

External pressure very rarely causes pyloric obstruction, and simple adhesions between the pylorus and the neighbouring viscera do not, as a rule, interfere with the passage of food into the duodenum. In exceptional cases, however, cholecystitis may lead to such strong and extensive adhesions with the pylorus that a certain amount of obstruction results. Gastropexy never causes pyloric obstruction (*see* Visceroptosis, p. 710).

The œdema and congestion round an active duodenal or prepyloric ulcer may cause severe obstruction, which disappears when the ulcer heals as a result of treatment. In such cases the obstruction is exaggerated by the presence of spasm of the sphincter, which may also occur reflexly with an ulcer on the lesser curvature and with cholecystitis. In rare cases a benign pyloric hypertrophy occurs in adults and causes delayed gastric emptying (*see* below).

**Symptoms.**—In the early stages attacks of severe pain may occur at varying intervals after meals owing to the violent peristalsis of the stomach in its attempt to overcome the obstruction. Later, nothing more than an unpleasant sense of fullness is experienced, especially after meals, but if frequent vomiting prevents the stomach from becoming much distended, attacks of pain are likely to persist. With an ordinary diet vomiting occurs regularly every day, but this characteristic symptom is less marked if the patient takes food which leaves little or no solid residue. The vomiting generally occurs at first in the afternoon or evening; but in the later stages, when dilatation has supervened, large quantities are vomited several times a day and often during the night. Articles of food may be brought up which have been eaten many hours or even days before. The odour is sour in non-malignant and foul in malignant cases. Excessive fermentation and putrefaction may give rise to offensive eructation, and in rare cases this is the first symptom noticed by the patient, especially, but not exclusively, in malignant obstruction. Wasting is progressive, and the tissues become abnormally dry and inelastic. The patient has generally little appetite, but complains of great thirst. The urine is scanty, and obstinate constipation occurs.

Pyloric obstruction occasionally gives rise to tetany and to symptoms simulating uræmia, but although there is a considerable rise in the blood urea the condition is caused by chloride deficiency and alkalosis and not renal insufficiency.

In addition to the symptoms already enumerated, others depending upon the cause of the obstruction, such as ulcer or carcinoma, are, of course, also present.

Pyloric obstruction leads to distension of the stomach. The signs of this, together with the distinctions between the malignant and non-malignant cases, are considered in the section on the examination of the stomach.

**Prognosis and Treatment.**—The treatment of organic pyloric obstruction is surgical. It is useless to waste time in well-marked cases with prolonged lavage or other medical treatment, as the improvement which follows operation is rapid and progressive. The immediate mortality is, however, high unless operation is preceded by preliminary medical treatment, which is essential in all cases to overcome dehydration and alkalosis. The stomach should be completely emptied every night and small quantities of custard, junket, vegetable purées and other soft, easily digestible foods with as much salt as possible, but very little fluid, given during the day. As much fluid as possible should be given per rectum, at least 3 to 4 pints of saline being run in either by a drip or as a 15 to 20 oz. injection every 6 hours. The blood urea must be estimated and intravenous fluids given if this is high; the urinary chlorides or, if possible, the plasma chlorides should also be estimated and if below the normal level of 560 mg. per cent., normal or half-normal saline should be given in amounts depending upon the degree of deficiency. The blood protein level may be low from prolonged starvation and vomiting, and a transfusion of plasma is an important help if this is the case. In severe cases potassium deficiency may follow the continued vomiting and is suggested by unduly severe prostration, low blood pressure and changes in the electrocardiograph tracing. Operation must be postponed until dehydration is overcome, the electrolyte balance restored and the urine output and intake are balanced.

When the obstruction is only partial and an active ulcer is present, the effect of medical treatment of the ulcer should be tried, as the obstruction may be largely due to the surrounding inflammation, which disappears when the ulcer heals, and when healing is rapid the scar generally gives rise to no obstruction.

## BENIGN HYPERTROPHY OF THE PYLORUS

**Ætiology and Pathogenesis.**—Pyloric hypertrophy in adults is rarely congenital. In most cases it is associated with recurrent gastric ulceration, but in some it appears to follow prolonged nervous dyspepsia. In a few cases it is associated with chronic cholecystitis or appendicitis. The pyloric muscle is thickened and the pyloric canal elongated but not rigid.

**Symptoms.**—The symptoms resemble those of duodenal ulcer but are usually more closely related to anxiety or excitement than to eating. Pain is not so severe as in ulcer and may be quite absent. The main symptom is vomiting, which is often periodic and may date from childhood. Nausea is marked. The diagnosis can only be made radiographically, when the narrowed and elongated pyloric canal can be seen; no fixed ulcer deformity may be demonstrable, but this does not always mean that an ulcer is not present. Some gastric dilatation may result. The condition must be distinguished from malignant hypertrophy of the pylorus, which is due to an infiltrating carcinoma of the pyloric antrum and which converts the pylorus into a narrow inflexible tube through which no peristaltic waves can be seen to pass.

**Treatment.**—Treatment as for ulcer should be advised, with sedatives such as Amytal, gr.  $\frac{1}{2}$  t.d.s., but if there is any doubt as to the benign nature of the condition, laparotomy must be advised without delay. At operation a partial gastrectomy is usually advisable as the results of gastro-enterostomy are less successful and the exact nature of the condition cannot always be determined with certainty by sight and feel at the operation.

THOMAS HUNT.

## CONGENITAL HYPERTROPHY OF THE PYLORUS

**Synonym.**—Hypertrophic Pyloric Stenosis.

**Definition.**—This is a disease of early life, formerly believed to be a rarity, but now recognised as of not uncommon occurrence. It consists essentially in a great thickening of the pylorus, leading to gastric stasis, with all the symptoms that result from such a condition.

**Ætiology.**—The pathogeny of the disease is still obscure. The theory that it is simply a congenital malformation is not in harmony with the clinical facts, and the most generally accepted view is that it results from an overaction of the pyloric sphincter, the consequence of a lack of co-ordination between the gastric and pyloric mechanisms. There is some reason to suppose that the Anglo-Saxon and Teutonic races are more affected by the disease than the Latin, but it is exceptional to get a history of other cases having occurred in the family. Boys are affected at least four times as often as girls, and in a remarkably high proportion the patient is the first child of the family.

**Pathology.**—The most striking change is an immense thickening of the pylorus, due to overgrowth of its circular muscle-fibres. The stomach is dilated, its muscular coat somewhat hypertrophied, and the mucous membrane in a state of catarrh. The other post-mortem appearances are those usually met with in inanition.

**Symptoms.**—The child has usually been born at full term, after a natural labour, and in the majority of cases has been breast fed. For a week or two or longer all goes well, and then vomiting sets in. The vomiting is "projectile" in character, the stomach contents being violently shot out. The vomit is usually larger in quantity than the last meal, and is often mixed with mucus; the presence of any blood in it is very rare. Meanwhile the child steadily loses weight, but does not look really ill, and maintains his strength and activity. The bowels are obstinately constipated, and the motions small and dark.

The most important diagnostic sign of the disease is the palpation of the *pyloric "tumour"*. With experience many believe that this is always possible although not necessarily at the first attempt. The stomach should be empty, washed out with normal saline if necessary. The examiner sits comfortably at the left side of the baby and with a warm left hand palpates the right upper abdomen. The index finger should be on the liver edge and the next finger dips around the rectus towards the vertebral column. A feed is started and usually the pylorus is found as a round tumour, described as like the end of the nose felt through a blanket. It tends to harden and soften as waves of peristalsis reach it. As the stomach fills with the feed visible gastric peristalsis appears. On inspection of the abdomen, waves of contraction can be seen sweeping across its upper part from left to right. Sometimes three such waves can be seen at once, each being about the size of a golf ball. If they are sluggish in appearing a little gentle stimulation below the left costal margin will often succeed in eliciting them.

**Complications and Sequelæ.**—The complication most to be dreaded is the supervention of an infective diarrhœa, which in these cases is apt to prove fatal. Some degree of biochemical disturbance is also apt to develop in severe cases. There are no sequelæ of the disease; if recovery takes place, it is complete and permanent, and, indeed, many of the patients ultimately attain a degree of health and development beyond the average. The hypertrophy of the pylorus disappears.

is remembered. The vomiting is distinguished from that of indigestion by its projectile character, and the co-existence of constipation is characteristic. Palpation of the thickened pylorus is diagnostic. Visible peristalsis is suggestive but may be present in a wasted infant without true stenosis. Mild cases of pyloric spasm may simulate true stenosis, but in these the symptoms are less severe, and waves of peristalsis are indefinite. The patient is often a girl. Stenosis of the duodenum from congenital malformation may simulate pyloric stenosis, but the symptoms in the duodenal cases date *from birth*, and bile is present in the vomited matter. A radiographic examination sometimes helps in the diagnosis.

**Prognosis.**—It is very difficult to estimate the chances of recovery or the relative merits of different forms of treatment statistically. Much depends upon the severity of the particular case, but in general it may be stated that no case is so severe that recovery is impossible. Cases treated in private do much better than those seen in hospital.

**Treatment.**—There are two methods of treatment—medical and surgical. Medical treatment consists in washing out the stomach once or twice daily with normal saline, and carefully regulating the feeding. If breast milk is not available, a half-cream dried milk with the addition of dextrimaltose is the best substitute, and should be given in quantities of 1 or 2 oz. every 2 or 3 hours, depending upon the degree of vomiting. Atropine methyl nitrate (Eumydrin) (1 to 5 ml. of a freshly prepared 1 in 10,000 solution or by a lamella placed under the tongue) is the best anti-spasmodic. If under this treatment the vomiting ceases, and the weight begins to rise, good and well. If not, or if the symptoms have set in early and with great severity, operation should be had recourse to, Rammstedt's plan of splitting the pylorus longitudinally being the procedure to be preferred.

ALAN MONCRIEFF.

## ACUTE DILATATION OF THE STOMACH

**Ætiology.**—After operations, especially for acute abdominal conditions, and much less frequently in the course of acute infections, especially pneumonia, the stomach suddenly becomes greatly dilated owing to a complete loss of tone. The dilatation, which is often much aggravated by severe aerophagy, leads to obstruction of the duodenum by the mesentery at the point where the latter crosses it, and the dilatation then becomes extreme.

**Symptoms.**—The abdomen is very distended, large quantities of dark but not faecal fluid are vomited but the stomach is never completely emptied. The patient rapidly becomes very collapsed. "Black vomiting" after operations is almost always due to acute dilatation of the stomach, and not to the intestinal paralysis with which it is often associated.

**Treatment.**—The stomach should be kept empty by aspirating through a Ryle's tube kept continuously in position, however ill the patient may be. Nothing should be given by the mouth, but saline solution should be injected continuously by intravenous drip to replace the fluids withdrawn. If recovery does not occur in 3 or 4 days, a jejunostomy should be performed, the patient being fed through the stoma till the stomach contracts to its normal size.

## DUODENAL ILEUS

**Ætiology.**—Minor degrees of duodenal obstruction are not infrequent and may be due to a number of causes. In some cases a congenital or an inflammatory band constricts the duodenum which then becomes hypertrophied and dilated above the

constriction, causing stasis of its contents and later atonic distension. In others the third part of the duodenum becomes occluded by the root of the mesentery carrying the superior mesenteric artery, which compresses it between this and the vertebral column. Such obstruction is usually intermittent, but may become continuous and almost complete in which case an extreme degree of mega-duodenum may result. Where the obstruction is due to an inflammatory band this usually results from a healing ulcer and is dense and thick, in contrast to congenital bands which are thin and translucent.

**Symptoms.**—The symptoms of duodenal ileus may closely resemble those of pyloric stenosis. In severe cases vomiting and pain may be violent, but more usually there is an irregular complaint of central epigastric fullness with feelings of distension and nausea, and increased discomfort 1 to 2 hours after eating. There is often relief of symptoms after vomiting and a striking and characteristic feature is the relationship of the symptoms to position. Patients often discover for themselves that they are more comfortable lying on their face with slight pressure on the abdomen, or in the knee-chest position, and frequently resort to this position to obtain relief. In some cases attacks similar to migraine occur, in which severe headache, nausea and vomiting occur with an abrupt and complete cessation as if something had been released in the abdomen as soon as the vomiting ends. Most patients are worse if they have much standing to do, and in a number the symptoms first arise after a period of worry or anxiety in which loss of weight has occurred. For this reason they are often thought to have an emotional origin and to be hysterical in nature.

**Diagnosis.**—Duodenal ileus must be diagnosed from duodenal ulcer, pyloric stenosis, migraine and from nervous dyspepsia. There are rarely any abnormal signs to be found, but there is sometimes a pendulous abdomen and evidence of recent loss of weight. A barium meal examination must be carried out in the erect position when a dilated duodenum may be seen with an obvious constriction, but this is not always demonstrable, as the condition is intermittent and radiographic examination may be quite normal. A duodenal ulcer is present in association with the ileus in some 20 per cent. of cases.

**Treatment.**—In minor degrees of ileus reassurance as to its nature and the relief which patients feel when they are no longer regarded as "neurotic" may be all that is required. Advice as to position with raising of the foot of the bed at night and some light abdominal massage are useful, but abdominal belts or supports are of no value.

In diet small meals are advisable, but if the patient has lost weight it is important to try and regain this by a high calorie intake. When pain and vomiting are pronounced and radiographic examination shows definite duodenal enlargement, laparotomy is to be advised when adhesions may be severed or, if necessary, a duodeno-duodenostomy or duodenojejunostomy performed according to the exact conditions found.

## DIVERTICULA OF STOMACH AND SMALL INTESTINE

Gastric diverticula are very rare. If present they are usually small and arise close to the œsophageal opening. In a few cases an acquired traction diverticulum may form as a result of adhesions following healing of a gastric ulcer, but other diverticula of the stomach are congenital, and no treatment is, as a rule, required.

Diverticula of the small intestine are found in between 1 and 2 out of every 1,000 necropsies. Except for the duodenum they almost all occur in the jejunum, where they are usually multiple, whereas duodenal diverticula are most often single. The majority are congenital in origin and consist of pouches on the free border of the intestine, which are made up of all the intestinal layers, but in the duodenum they are more often acquired, being found mainly in the second part as the result of a hernial protrusion through a weak spot in the muscularis mucosæ. They occur especially

near the opening of the common bile duct and are often difficult to demonstrate either radiographically or at post mortem. They are most often found in women over the age of 50 and as a rule do not cause any symptoms. In rare cases perforation or hæmorrhage may occur, but more usually any symptoms produced are due to an associated duodenal ulcer. Indeed many cases reported radiographically as diverticula prove at operation to be large ulcer craters.

The symptoms of duodenal diverticula, if they occur, resemble those of duodenal ulcer, but it is important to exclude other causes carefully before attributing such symptoms to the diverticulum. This is most likely to be the case if the diverticulum is large, and if on radiographic examination it retains the barium after the duodenum is empty. It is uncommon for diverticula of the third part of the duodenum to cause symptoms.

Diagnosis is only possible by radiographic examination.

Treatment is surgical, if it can be shown that the diverticulum is causing symptoms of sufficient severity, but the operation may be a difficult one and removal a formidable undertaking.

THOMAS HUNT.

## DISEASES OF THE INTESTINES

### INTRODUCTION

#### I. THE FUNCTIONAL DIVISIONS OF THE INTESTINES

1. *The small intestines.*—In the duodenum the food is mixed with the pancreatic juice, which is essential for the digestion of protein and fat, and with bile, which promotes the absorption of the products of fat digestion. In its passage through the small intestines the chyme is mixed with the succus entericus, which contains enterokinase, which activates the pancreatic ferments, and invertase, maltase and lactase. The chyme passes rapidly through the jejunum and most of the ileum, in the last 12 in. of which it remains for a considerable time. The terminal ileum indeed forms an "ileal stomach", in which the greater part of the digestion of protein, fat and carbohydrate takes place and the products of digestion are absorbed.

2. *The proximal colon.*—Observations on patients with cæcal fistulæ show that about 500 g. of semi-fluid chyme, containing 90 per cent. of water with very small quantities of sugar, fat, salts, coagulable protein and of the soluble products of their digestion pass through the ileo-cæcal sphincter in a day. Water and all the soluble constituents of the chyme which reach the cæcum are absorbed there or in the ascending colon and proximal half of the transverse colon, which may therefore be regarded as the "colonic stomach".

3. *The distal colon.*—The pelvic colon acts as a storehouse for fæces, to which they are conveyed through the transverse colon, the descending colon and the iliac colon when digestion in the colonic stomach is complete. Here they remain until the time for defæcation arrives.

4. *The rectum.*—The rectum has the important function of maintaining the regular evacuation of fæces. It is empty except immediately before defæcation. The distension of its walls when fæces enter it produces the sensation which prompts the individual to perform the voluntary acts which help the efficient performance of the defæcation reflex.

#### II. THE INTESTINAL MOVEMENTS

The movements of the intestines have two main objects: (1) mixing the food with the digestive juices and bringing them into contact with the mucous membrane



which absorbs the products of digestion and water; and (2) propulsion of its contents from the duodenum to the rectum, and of the indigestible residue of the food from the rectum.

1. *The small intestines.*—In the small intestines peristalsis and segmentation take place simultaneously, the former with the object of propelling the chyme into the "ileal stomach", and the latter with the object of mixing the food with the digestive juices and exposing it to as large an area of mucous membrane as possible. In the jejunum and greater part of the ileum peristalsis is the predominating motor activity, but when the ileal stomach is reached it ceases almost completely and segmentation becomes extremely active. After a varying interval peristalsis becomes active again, and as the ileo-cæcal sphincter relaxes with the arrival of each peristaltic wave, the ileal stomach empties its contents into the cæcum.

2. *The colon.*—When the colon is examined after an opaque meal it appears to be completely immobile. In spite of this, both segmentation and peristalsis occur under normal conditions, but their character differs considerably from the corresponding movements in the small intestine. Peristalsis occurs in the form of "mass movements" about three times a day: a single very powerful peristaltic wave travels slowly along a considerable part or even the whole length of the colon, pushing in front of it most of the contents. Deep segmentation movements, which are too slow to be visible with the naked eye, can be recognised by comparing radiographs taken at 3-minute intervals and often in those taken at intervals of a single minute. Segmentation is the result of the ceaseless activity of the muscularis mucosæ, the normal "haustation" of the colon seen in the radiogram being produced by projecting folds of mucous membrane. As a result of the continuous segmentation in the colon much of the water and all of the soluble constituents of the food and the products of their digestion which have escaped the small intestine are absorbed.

The chyme leaves the ileal stomach very slowly except during and immediately after meals, when, as a result of a gastro-ileo-cæcal reflex, frequent peristaltic waves pass down the terminal ileum to the ileo-cæcal sphincter, which opens widely as each wave reaches it. The chief stimulus to mass peristalsis of the colon is a gastro-colic reflex. On comparing these events it becomes clear that the ileal stomach passes its contents into the cæcum when it is necessary that it should be empty for the reception of the food coming down from the stomach after a meal, and that the colonic stomach similarly evacuates itself to leave room for the reception of the contents of the ileal stomach.

### III. DEFÆCATION

During defæcation the contents of the pelvic colon, together with any fæces which may be present in the descending and iliac colon, pass into the rectum. The distension of the rectum causes it to contract as a whole just like the bladder and at the same time causes reflex relaxation of the sphincter ani, so that the contents of the rectum are evacuated. Simultaneously the contents of the cæcum and ascending colon pass into the transverse colon, whilst the contents of the latter pass into the pelvic colon.

Normal defæcation depends upon a conditioned reflex. The infant is taught at an early age to empty his bowels directly he is placed on a chamber. The act quickly becomes a purely reflex one, and it continues to be so when he grows older and the chamber is replaced by the seat in the w.c. Breakfast by itself gives rise to a simple gastro-colic reflex. Sitting down on the familiar seat in the w.c. is, however, the starting-point of the more elaborate conditioned reflex, which produces the most efficient gastro-colic reflex of the day, in which the whole colon from the cæcum to the rectum takes part. In the healthy adult defæcation remains to a great extent a conditioned reflex. It is enough to sit down in the accustomed place, perhaps with a pipe and a

newspaper, for the reflex to begin, often without the "call to defæcate"—the perineal sensation produced by the entry of fæces into the rectum—and without the voluntary stimulus produced by the increased intra-abdominal pressure caused by descent of the diaphragm and contraction of the abdominal muscles; these are, however, with the final contraction of the levator ani muscles, always brought into action to help in the complete expulsion of the fæces.

Failure to open the bowels on the first day of a holiday is not due, as is popularly supposed, to the "hard water" of the locality, deficient exercise in a train or on board ship, but to the unfamiliar w.c. and perhaps the unusual hour of getting up—or the absence of getting up—such small changes being enough to upset for the moment the delicately adjusted conditioned reflex.

## EXAMINATION OF THE INTESTINES

### SIZE, SHAPE AND POSITION OF THE COLON

The cæcum and iliac colon are the only parts of the bowel which are always palpable under normal conditions. In very thin people and in patients with very lax abdominal muscles the whole colon except the splenic flexure and the pelvic colon can often be felt. Apart from these conditions the colon may become palpable when in a state of spasm or when filled with fæces, and tumours involving it can often be recognised by abdominal examination. In all intestinal cases a rectal examination must be made; by this means not only the rectum but also part of the pelvic colon can be palpated. For further investigation of the size, shape and position of the whole colon in the erect as well as the horizontal posture a radiographic examination after a barium meal is essential. The pelvic, descending and iliac colon cannot always be seen satisfactorily, as they may be full only in the early morning, and defæcation empties them completely before it is convenient to make a radiographic examination.

### MOTOR FUNCTIONS

(a) PALPATION.—In every case of intestinal disorder an abdominal and rectal examination should be made. No medicine or enema should be given during the preceding 24 hours. The quantity of fæces present in each part of the colon varies greatly according to the time at which meals are taken and defæcation occurs. In a normal person whose bowels are satisfactorily opened after breakfast, the whole of the colon is empty during the greater part of the morning, though a thin layer of soft fæces may cover the wall of the cæcum and perhaps the ascending colon and so render them partially opaque to the radiograph if a barium meal was taken 24 hours earlier, and a small quantity of semi-solid fæces may be present in the distal part of the transverse colon. Between 3 and 4 hours after breakfast the cæcum begins to fill; the filling becomes much more rapid after lunch, so that in a short time the ascending colon also becomes filled. During the rest of the day palpation shows the cæcum and ascending colon, and often the proximal part of the transverse colon, to be filled with soft fæces, and the resonant note which is generally obtained on percussion over the right half of the colon in the morning is replaced by a dull note in the afternoon.

In the early morning the rectum is empty, but the pelvic colon can be felt through the anterior rectal wall to be filled with solid scybalæ, which sometimes extend upwards into the iliac and the descending colon. On getting up, but often only after breakfast, the pelvic colon empties some of its contents into the rectum, giving rise to the "call to defæcate". From this moment until defæcation has occurred is the

only time in which the rectum of most normal individuals is filled with faeces. At other times it is empty, and a proctoscope shows that there is not even a trace of faeces adherent to the mucous membrane. In defaecation the whole of the colon beyond the splenic flexure empties itself. Consequently the descending iliac and pelvic colon are empty during the whole morning, except that faeces may be conveyed during defaecation from the transverse colon into the lower part of the pelvic colon, and more may arrive from the proximal colon with the mass peristalsis occurring after lunch. Apart from this, the pelvic colon is generally empty or almost empty until after tea or more commonly after dinner, when another wave of mass peristalsis fills it with the contents of the colon from the neighbourhood of the hepatic flexure and the proximal half of the transverse colon.

If the rectum is full of faeces and the patient has no desire to defaecate, dyschezia can be diagnosed (see p. 605). If the faeces are soft it is clear that there can have been no delay in the passage to the rectum, such as is likely to have occurred if it contains hard and dry scybala. When the rectum is empty but the pelvic colon can be felt through the anterior rectal wall to contain scybala, the form of dyschezia which is due to inability of the pelvic colon to empty its contents into the rectum is present. In severe cases hard scybala may also be felt in the iliac and perhaps the descending colon.

(b) **THE CHARCOAL METHOD.**—By giving two or three charcoal lozenges with some food 8 hours after defaecation and observing after what interval black faeces are passed, the total time taken in their passage through the alimentary canal can be ascertained.

(c) **RADIOGRAPHIC EXAMINATION.**—1. *Opaque meal.*—The only reliable means of determining the rate of passage through the various parts of the alimentary canal is a series of examinations with the radiograph. If the bowels have not been spontaneously opened the morning before the opaque meal is to be taken, an enema should be given in the evening. It is important to discontinue the use of all aperients for at least 48 hours before the first examination, as the intestinal functions might otherwise be observed whilst still under their influence instead of under natural conditions. No aperients and no enemata should be used till the examination is finished, but the patient should make an attempt each morning to open his bowels naturally. If the attempt is successful, the stools should be examined to ascertain whether any of the barium has been evacuated. The patient should follow his usual occupations and take his ordinary diet. An examination should be made in the morning and evening of each day until all or most of the barium has been passed in the faeces or has reached the rectum. Normally a barium meal reaches the terminal ileum from  $\frac{1}{2}$  to 5 hours after ingestion, whilst the rate of colon filling is extremely variable, barium continuing to enter the transverse colon intermittently for some 4 to 24 hours after it has first started to do so.

2. *Opaque enema.*—Although an opaque meal is the best means of obtaining information of the motor functions of the colon, an opaque enema generally gives earlier and more exact information concerning the possible presence, degree and position of a stricture, especially in the iliac and pelvic colon, which often cannot be satisfactorily examined by the former method. The patient lies on his back, and the barium sulphate suspension is run in from a container at a pressure of between 2 and 3 feet through a valveless Higginson's syringe connected with a rubber tube introduced just within the rectum, the syringe being used, when necessary, to help the passage of the fluid with light pressure. It often reaches the caecum in 2 minutes and almost invariably within 5 minutes. When the examination is complete, part can be run out through the tube, the rest being evacuated in the ordinary manner. A further radiograph is then made. Additional information, especially as to the presence of polypi, can often be obtained by injecting air into the colon after the greater part of the opaque enema has been evacuated.

An organic stricture of the colon generally obstructs the passage of the fluid, the shadow ending at the seat of the obstruction, which can be overcome only incompletely or not at all by waiting an additional 10 minutes, by increasing and decreasing the pressure of injection, by massage and by changes in posture. The flow of the enema is often prevented in cases of growth before there is any clinical evidence of obstruction: such a hold-up, with or without a marked filling defect in the colon may be present even when there is diarrhoea or the bowels still act normally and an opaque meal passes through the colon without delay. This is probably due to the occurrence of a spasmodic contraction of the bowel, which occurs at the seat of obstruction as soon as the enema reaches and distends the part immediately below it.

A barium enema may be the only way in which the presence of diverticulosis and diverticulitis may be detected, but it must not be forgotten that growths in the rectum low enough to be felt by the finger may not give any sign of their presence by radiography.

## EXAMINATION OF FÆCES

The consistence, smell, colour and reaction of the stools when no aperient is being taken should be noted, abnormal acidity indicating excessive fermentation and abnormal alkalinity excessive putrefaction. The presence of mucus with solid stools is not in itself a sign of disease, but if it is mixed with blood or pus or present with fæces which are unformed though no aperient has been taken, some organic disease is almost certainly present. The presence of mucus with hard scybala or with soft stools obtained after the use of an aperient is due to the normal reaction of the colon to a mechanical and chemical irritant respectively, mucus being secreted in order to protect the mucous membrane. Red blood by itself may come from hæmorrhoids or a rectal polyp; if associated with mucus or pus or both, ulceration or cancer of the colon or rectum must be present. The brighter the colour of the blood the lower is its source. The presence of pus indicates disease of the pelvic colon or rectum unless the stools are very fluid. For the naked-eye appearances of the stool in bacillary and amœbic dysentery, see pp. 114 and 276.

Microscopic examination may reveal the presence of blood corpuscles, pus, amœbæ or their cysts, and the ova of intestinal worms. The investigation of the stools for excess of food residue is described elsewhere (see p. 612).

A bacteriological examination of the stools may show a relative excess of enterococci or *Bact. coli*, the normal inhabitants of the colon, or strains of streptococci or *Bact. coli* which are not normally present, or salmonella, dysentery or tubercle bacilli. If an endoscopic examination is made, a swab should be taken from the mucous membrane, together with any mucus or pus which may be seen, for cytological and bacteriological examination. In doubtful cases the agglutinating power of the patient's blood for abnormal bacteria isolated from the stools may be tested, and special culture media must be employed in the search for dysentery and other organisms.

## OCCULT BLOOD

When blood is swallowed or is derived from an ulcer or growth in the œsophagus or stomach or an ulcer in the duodenum, it is evacuated in the stools partly as acid hæmatin and partly as hæmatoporphyrin. Both also appear in the stools when the blood originates in the colon unless diarrhoea is present, when the blood does not remain in the bowel long enough for the former to be converted into the latter. The chemical tests for "occult blood"—traces of blood insufficient to produce any change in the appearance of the fæces—depend upon the conversion of a substance with little or no colour, such as guaiac or benzidine, into a coloured substance when

oxidised by hydrogen peroxide in the presence of a carrier, such as hæmatin. The guaiac reaction is preferable to the benzidine, as, unlike the latter, it does not give a colour-reaction when iron salts are given by mouth; it can, therefore, be used in patients with ulcer who are receiving iron on account of post-hæmorrhagic anemia. Hæmatoporphyrin, which contains no iron, gives neither reaction. A spectroscopic examination of the stools should also be made, as even considerable quantities of hæmatoporphyrin, which is occasionally present in the absence of acid hæmatin, would otherwise escape recognition. Moreover, a positive spectroscopic finding is valuable confirmation of a positive chemical reaction, as, although it is much less sensitive, there is less chance of error.

Before the stools are examined such foods as liver are excluded from the diet, but otherwise no special restrictions are required and green vegetables need not be excluded. For the guaiac test a small amount of feces is macerated with glacial acetic acid into a thin paste. An equal quantity of ether is then added to extract the pigment and the ethereal extract is poured off, some being kept for the spectroscopic examination. Two or three drops of tincture of guaiac are added to the remainder; a small quantity of ozonic alcohol is then poured in, and a change of colour is looked for at the junction of the two fluids. A "positive" reaction is one in which a deep blue colour rapidly appears; a "feeble-positive" reaction is one in which the colour is faint purple, bluish or greenish. If 1 ml. of blood enters the stomach or intestines, the next day's stool will give a positive reaction.

The benzidine test is carried out by adding some fecal emulsion to a specially prepared powder containing 25 mg. of pure benzidine with 200 mg. of barium peroxide, when a positive result shows a green or deep blue colour developing at once or within 30 seconds.

A positive guaiac reaction signifies the presence of occult blood. A negative guaiac reaction proves its absence, except occasionally at the end of a period of hæmorrhage, when the spectroscopic test may alone be positive, as the traces of blood still present may then be completely converted into hæmatoporphyrin, which gives a characteristic spectrum, but does not give the chemical reaction.

By the spectroscopic test of the stools one can recognise (1) acid hæmatin, which also gives a positive guaiac and benzidine test, and (2) other hæmoglobin derivatives, *i.e.* porphyrins, which do not give a positive colour-reaction. The spectrum of acid hæmatin is so faint that it can be seen only in fairly concentrated solutions: the typical band of acid hæmatin ( $\lambda$  620) is found only when considerable quantities of blood are present in the stools.

In the absence of hæmorrhoids and rectal or colonic polypi (which may be quite latent) and of bleeding from the mouth, throat and nose, the presence of occult blood in the stools is strong evidence that an ulcer or growth is present in the œsophagus, stomach or intestines. It is occasionally found in gastritis, diverticulitis and in such conditions as cirrhosis of the liver.

## PROCTOSCOPIC AND SIGMOIDOSCOPIC EXAMINATION

Wherever there is any possibility of organic disease of the pelvic colon or rectum, a proctoscope and, if necessary, a sigmoidoscope should be passed, after a preliminary digital examination. No special preparation is required but the patient must have had his bowels emptied as completely as possible shortly before the examination. No aperient or enemata are necessary, but if the rectum is found to be full of feces, the examination should be abandoned and repeated later 3 to 4 hours after a simple bicarbonate (1 per cent.) wash-out has been given. The instrument should be passed without an anæsthetic either in the knee-elbow (which is the easiest), or in the left lateral position if the patient is easily exhausted or elderly.

The passage of a proctoscope requires very little experience, and sigmoidoscopy is practically without discomfort or danger to the patient provided the examiner avoids using any force in passing the instrument and has had adequate instruction in the technique required.

Proctoscopy may show the presence of ulcerative colitis, in which the rectum is usually involved from the outset, and is the last part of the bowel to recover; it will also enable growths to be seen as far up as the pelvic-rectal flexure. It is essential to pass a sigmoidoscope in any case of suspected malignant disease if nothing abnormal is seen proctoscopically, and in cases of amœbiasis the fuller examination is also advisable. In these cases swabs may be taken direct from any ulcers seen, and scrapings made with a sharp spoon examined at once under the microscope, may show amœbæ when ordinary stool examinations have failed to do so. This is also true of rectal schistosomiasis in which the ova of the schistosoma may be only found from scrapings of the rectal ulcers, and without which diagnosis is impossible.

## FUNCTIONAL DISORDERS OF THE INTESTINES

### CONSTIPATION

**Definition.**—Constipation may be defined as a condition in which no residue of the food taken during one day is excreted within the next 48 hours.

**Ætiology and Pathology.**—Constipation may be due to (1) the passage through the colon being delayed, whilst defæcation is normal—colonic constipation; (2) the evacuation from the pelvic colon and rectum being inadequately performed, whilst the passage through the colon is normal—dyschezia; and (3) insufficient formation of fæces.

1. **COLONIC CONSTIPATION.**—Delay in the passage of fæces through the intestines is due to their motor activity being deficient, or to the force required to overcome some obstruction being insufficient. The motor activity of the colon may be diminished owing to deficient reflex activity, inhibition or uncontrolled and irregular action. It is rarely if ever due to actual weakness of the muscular coat. The reflexes which maintain intestinal activity may be reduced owing to lack of mechanical and chemical stimulants in the food, or to some endocrine deficiency as in hypothyroidism. The inhibitory sympathetic nerves may be stimulated centrally by depressing emotions, and reflexly in painful diseases and injuries of any part of the body, but particularly of the abdominal and pelvic viscera.

Painful colon spasm may be induced reflexly by the presence of mild irritants in the colon of a patient with an abnormally excitable nervous system—spastic constipation. Such an irritant may be the abnormally hard and dry fæces which result from dyschezia, or from insufficient consumption of water, or its excessive loss in the urine or sweat, such as may occur in Europeans living in the tropics. Spasm may result from irritation by organic acids in intestinal carbohydrate dyspepsia, in which constipation may alternate with diarrhœa. Spastic constipation is a constant symptom of diverticulitis. The reflex may also be excited by disease in other parts of the abdomen, especially the gall-bladder and appendix. Similar spasmodic contraction of the intestines occur as a result of excessive smoking and in lead poisoning.

The work to be done by the intestinal musculature is excessive when an organic obstruction such as stricture, adhesions or volvulus narrows or blocks the intestinal lumen.

2. **DYSCHEZIA.**—Dyschezia may be due to inefficiency of the defæcation reflex, to abnormally hard and bulky fæces requiring excessive force for their evacuation, or an obstacle to efficient defæcation, such as spasm or congenital or acquired strictures

of the anal canal. Dyschezia due to inefficient defæcation is the most common cause of severe constipation. It often originates in neglect to respond to the call to defæcate owing to laziness, insanitary condition of the w.c. or false modesty. The conditioned reflex upon which defæcation normally depends is gradually lost. The rectum dilates so that an increasing quantity of fæces is needed to produce the adequate internal pressure required to give the sensation of fullness which is the natural call to defæcation. Finally the sensation is lost completely. But the patient is still capable of emptying his rectum if he tries. He has, however, by now often convinced himself that he cannot get his bowels to open unless he takes enemata or such enormous doses of aperients that the fluid fæces practically act as enemata. He suggests to himself that his rectum is powerless to act by itself, and soon the dyschezia becomes in part a psychological inhibition.

In many individuals the sensation of a full rectum is ignored because it does not occur at their usual time for defæcation, so that after a while a rectal tolerance is developed; in such patients it is important to instruct them to empty their bowel in accordance with their sensations rather than with the supposed rules of a once-a-day convention.

Dyschezia may be due to various other causes, such as weakness of the voluntary muscles of defæcation, the assumption of an unsuitable position during defæcation and voluntary inhibition from fear of pain in diseases of the anal canal, such as a fissure. But whatever the primary cause, the final result is the same. The conditioned defæcation reflex is lost, and the incomplete evacuation of the rectum results in the accumulation of fæces and consequent dilatation of the rectum.

Careful training is required from earliest infancy in order to develop the defæcation reflex, and neglect of this is the cause of the dyschezia of infants, in whom the slight additional distension produced by the introduction of a finger or a piece of soap into the rectum results in an adequate stimulus.

The rectal muscle-sense is abolished or defective in diseases of the spinal cord in which the defæcation centre itself or the fibres connecting it with the brain are involved.

3. The third great class of constipation is due to the quantity of fæces formed being insufficient to produce an adequate stimulus in the pelvic colon and rectum, and to a less extent in the rest of the colon. The insufficient bulk of fæces is due to an inadequate quantity of food residue reaching the colon as a result of anorexia, or of œsophageal or pyloric obstruction, or to unusually complete digestion and absorption of an abnormally low-residue diet.

**Symptoms.**—Many people regard themselves as ill if they do not have one action of the bowels a day, although this is really nothing more than a convenience, being found to suit the habits and diet of the majority of civilised people. Perfect health may be maintained by individuals who defæcate regularly two or three times a day, and by others who obtain an evacuation once in 2, 3 or more days. The latter, so long as defæcation, when it does occur, is complete, can no more be regarded as diseased than those otherwise normal people whose hearts beat only 40 or 50 times a minute. Many, however, although they may suffer no inconvenience for a considerable time, finally develop symptoms due to fæcal accumulation, gradually increasing quantities of fæces being retained. For practical purposes, therefore, an individual may be considered constipated if his bowels are not opened at least once in every 48 hours. A less frequently recognised variety of constipation is that in which insufficient fæces are excreted, although the bowels may be opened every day, often more than once, a condition analogous to retention of urine with overflow.

It is important to distinguish the symptoms of constipation from those of the conditions which give rise to it. There is little evidence in support of the view that toxic absorption in constipation is a cause of the headache, fatigue, anorexia, furred tongue or mental symptoms which are so often attributed to it. The majority of

such symptoms are without doubt psychoneurotic and attributable largely to the anxiety caused by the supposed dangers of faulty bowel action. Some may be a direct reflex effect due to overloading and distension of the rectum, as is supported by their immediate disappearance after defæcation, and the fact that they may be experimentally simulated to some extent by filling the rectum with tow or distending it with a rubber balloon in normal individuals.

Fæcal retention is a common cause of intestinal flatulence and colic. In rare cases a fæcal tumour may form, generally in the pelvic colon, and give rise to obstruction. A fæcal accumulation in the rectum may cause hæmorrhoids, pruritus ani, catarrhal proctitis and neuralgic pains in the perineum, back and down the legs. Hard fæces make defæcation painful, and their passage may give rise to anal ulcers.

**Diagnosis.**—It is comparatively rare for a patient to consult a doctor on account of constipation without having already attempted to cure himself with aperients. But no accurate diagnosis can be made until it has been ascertained whether he is actually constipated at all. The symptoms generally ascribed to auto-intoxication caused by intestinal stasis are often really produced by purgatives, which lead to the excessive production of toxins by hastening the half-digested contents of the small intestine into the cæcum, where fermentation and putrefaction are consequently increased. Purgatives also cause the contents of the transverse, descending and pelvic colon to be fluid instead of solid, so that absorption of toxins continues throughout the whole length of the bowel instead of in the cæcum and ascending colon alone. In spite of his probable protests the patient is instructed to see what happens if no drugs are taken for 3 days, an effort being made to open the bowels each morning. In many cases he loses his abdominal pain and his so-called toxic symptoms. The bowels are often opened daily, in which case a diagnosis of hysterical pseudo-constipation can be made—hysterical because the patient had suggested to himself, as a result of faulty education aggravated by the reading of pernicious advertisements, that he was constipated and required aperients to keep himself well. In such cases explanation of the physiology of his bowels and the origin of his symptoms with persuasion to try and open his bowels regularly each morning without artificial help results in cure. In some cases, however, the patient does not succeed in opening his bowels, although he may feel more comfortable than when he was taking drugs. A second abdominal and rectal examination should then be made. If no sign of organic disease is present and the rectum is found to be filled with fæces, dyschezia can be diagnosed (*vide supra*).

In severe cases it is advisable to investigate the motor activity of the intestines radiographically, a barium meal being given after the patient has discontinued taking aperients. Great care must be taken, however, in interpreting the wide normal variations in the passage of barium in different individuals. Thus, ileal stasis should be diagnosed only if no trace of barium has reached the cæcum 6 hours after the opaque meal, or if a considerable quantity of barium-containing chyme is still in the end of the ileum 6 hours after evacuation of the stomach is complete. If most of the barium is still in the cæcum and ascending colon at the end of 24 hours, stasis is present, even if a little has passed to the more distal parts of the colon; but a faint shadow of the cæcum is often visible in normal individuals even 3 days after the meal. If the splenic flexure is reached in 24 hours, but barium is still in the colon at 72 hours, there must be stasis in this part of the bowel. In dyschezia most or all of the barium has accumulated in the rectum in 24 hours. In pelvic colon dyschezia a similar accumulation occurs in the pelvic colon, but the rectum remains empty.

**Treatment.**—Under no circumstances should the patient fail to make an effort to open his bowels after breakfast, even if he feels no desire to do so, and a call to defæcation felt at any other hour in the day should be obeyed at once. Sufficient time should be spent over the act of defæcation, and it is often advisable to pay two visits to the w.c. at short intervals, perhaps before and after breakfast. In order to



prevent the temptation to hurry over defæcation, the closet should be clean, devoid of smell and sufficiently warm in winter. In dyschezia with weak abdominal muscles a footstool, 9 in. lower than the seat, should be provided. In many cases of dyschezia no treatment is required beyond explaining to the patient the nature and cause of his condition, and persuading him to give up aperients and to make an effort to empty his rectum, which he must realise is quite capable of doing its work. By perseverance it is very often possible to re-develop the lost conditioned reflex upon which normal defæcation depends.

It is most important to see that sufficient food is taken, as constipation is often as much due to its insufficient quantity as to its unsuitable quality. The diet should contain an increased proportion of vegetable foods, especially those which contain much cellulose and organic acids. Fresh or dried fruit should be taken three times a day, and green vegetables or salad should be eaten at lunch and dinner. Stewed prunes taken at breakfast are especially valuable. Porridge and cream and wholemeal brown bread are also useful. Sufficient fluid should be drunk; a glass of water taken on rising in the morning often helps the bowels to act after breakfast.

The majority of cases of constipation can be cured without drugs if proper treatment is instituted at a sufficiently early stage. In dyschezia purgatives act only when fluid stools are produced, colic and toxic symptoms often resulting and a considerable quantity of fluid and nutritive material being wasted. In the treatment of diseases which are aggravated by coexisting constipation, purgatives should be regularly given. They are also useful for making the stools soft when straining at stool is accompanied by danger, as in patients with heart disease. In colonic constipation, when advice and dietary treatment prove insufficient, purgatives must also be used, but an effort should be made to dispense with them at the earliest possible moment. The stool produced by an aperient should be normal in size and consistence, and the dose should be so regulated that one stool is passed every day. It should cause no pain or discomfort, and should not irritate the intestinal mucous membrane sufficiently to lead to the appearance of mucus in the stools. An infusion of senna pods in cold water is particularly useful, as senna acts on the colon alone, and the dose can be regulated from day to day by the patient. An attempt should be made at intervals to reduce the number of pods by one at a time, until finally none may be required. Accurately standardised extracts of senna are also useful and simpler to regulate.

The bulk of the fæces may be increased by the administration of an unirritating vegetable mucilage, such as Isogel or coreine derived from psyllium seeds which pass through the intestines without undergoing decomposition or absorption. These preparations are valuable when the fæces are hard and dry, and in dyschezia the soft stools which result from their use are expelled with less difficulty than ordinary fæces. From a teaspoonful to a tablespoonful of paraffin or double the dose of a plain 50 per cent. paraffin emulsion may be taken immediately after one, two or three meals every day, to act as an intestinal lubricant, or a teaspoonful of Isogel or coreine, which absorbs water to form a bulky gelatinous mass which becomes intimately mixed with the fæces, may be taken with one or more meals in addition to or as a substitute for paraffin. Half a tumblerful of water must be taken after each dose of Isogel, otherwise it may cause severe pain in the chest or epigastrium.

The majority of cases of moderately severe constipation are more or less cumulative, excess of fæces being always present in the large intestines. It is therefore necessary that the colon should be completely evacuated before other methods of treatment are adopted. This can best be done by washing the colon out with 1½ or 2 pints of warm water run into it from a douche-can or funnel at low pressure through a soft catheter inserted just beyond the anal canal. The regular use of enemata, Plombières douches and of continuous intestinal lavage with many pints of fluid are harmful both from a physical and psychological point of view.

It is essential in treating dyschezia to keep the rectum and pelvic colon empty, so that they may in time regain their normal tone and contractile power. This can be accomplished by the use of glycerin suppositories or of a 1-oz. enema consisting of equal parts of glycerin and water every morning, if a prolonged attempt to defæcate naturally has proved unsuccessful. The strength of the enemata should be gradually reduced by replacing a drachm of the glycerin by water every other day until only water is used. As a rule the normal defæcation reflex and with it the tone and contractile power of the rectum slowly return.

When dyschezia is due to inability of the pelvic colon to empty its contents into the rectum, 6 oz. of paraffin should be injected on going to bed and retained during the night; the bowels are then generally opened without difficulty in the morning. If, however, they fail to act, a plain water enema should be given.

When the sphincter ani is in a condition of spasm as a result of inflamed hæmorrhoids or an anal ulcer, or when the anal canal is congenitally too narrow or a stricture has followed an operation for hæmorrhoids, relief can be obtained by dilating the passage by means of diathermy applied locally through a conical electrode.

Regular exercise in the open air is a useful means of preventing constipation, especially in individuals who follow a sedentary occupation. When any of the voluntary muscles of defæcation are weak, considerable benefit can be gained by the performance of remedial exercises every morning and evening. Special attention should be devoted to the levator ani muscles, especially in women in whom the pelvic floor has been injured during parturition, and in cases in which there is any tendency to prolapse on straining at stool. Stasis in the proximal part of the colon may be benefited by massage applied directly to the affected part.

## DIARRHŒA

**Definition.**—Diarrhœa is a condition in which unformed stools are passed. Defæcation generally occurs several times in the day, but mere frequency of defæcation is not diarrhœa, for this may even be associated with constipation. The bulk of fæces excreted in 24 hours is generally excessive, but this again may occur without diarrhœa, as excessive fæces are occasionally formed when the passage through the alimentary canal is not abnormally rapid. The one essential factor in diarrhœa is the abnormally rapid passage of the food residue through the alimentary canal.

**Ætiology.**—1. **EXCESSIVE STIMULATION OF MOTOR ACTIVITY.**—The most common cause of diarrhœa is the presence in the food of excess of the mechanical and chemical stimulants of intestinal activity. Thus over-indulgence in green vegetables, salads and especially unripe fruit is a familiar cause. Chemical irritants may also be swallowed in decomposing food, as in some cases of fish and meat poisoning, but food may also cause diarrhœa by giving rise to a bacterial infection of the intestine (see p. 119). Diarrhœa very frequently results from the habit of taking aperients, either in excess of what is required for the correction of chronic constipation, or even when the bowels left to themselves would act quite normally.

Chronic diarrhœa is a common sequel of the acute diarrhœa following infection with a pathogenic organism which gains access to the intestines in contaminated food or water, and it may follow acute general infections such as influenza. In some cases the infection is derived from a septic focus in the mouth, nose or pharynx, and in rare cases recurrent subacute appendicitis is the source of a chronic infection of the colon. Some infective bacteria, such as those of the *Salmonella* group, act chiefly on carbohydrates and may lead to excessive fermentation. Others, such as streptococci and various anaerobes, act on proteins and lead to putrefactive diarrhœa. Severe intestinal carbohydrate dyspepsia (p. 629) may give rise to chronic diarrhœa or

alternating constipation and diarrhœa, and deficient digestion of proteins, resulting from either gastric or pancreatic insufficiency, may lead to a non-infective putrefactive diarrhœa. Deficient digestion of fat and deficient absorption of fatty acids and soaps give rise to fatty diarrhœa (steatorrhœa) (see p. 620).

Diarrhœa is sometimes gastric in origin. This *gastrogenous diarrhœa* may occur when the gastric juice is deficient or absent, or the stomach empties unduly rapidly. An abnormal number of organisms reaches the intestines in these circumstances, as the partial protection afforded by the bactericidal action of the hydrochloric acid in the stomach is lost. As in addition to the digestion of meat in the stomach the connective tissue of meat and the cellulose of vegetables are normally softened by the hydrochloric acid of the gastric juice, undigested lumps of meat and fragments of vegetable leave the stomach and pass through the small intestine to the colon, where they are liable to undergo bacterial decomposition. The irritation of the mucous membrane of the intestines by the insufficiently divided fragments of food and by the products of bacterial decomposition leads to diarrhœa, which may become aggravated by secondary enteritis or entero-colitis if the irritation is sufficiently intense or prolonged. Similar *gastrogenous diarrhœa* may occur after the performance of a gastro-jejunostomy or partial gastrectomy, the food leaving the stomach with such rapidity that the intestines are overwhelmed with undigested and irritating food.

Lastly, stimulation of intestinal activity may occur in general diseases and cause diarrhœa such as is found in uræmia, hyperthyroidism and septicæmia.

2. OVER-EXCITABILITY OF THE NEURO-MUSCULAR MECHANISM WHICH CONTROLS THE INTESTINAL MOVEMENTS.—(a) *Post-prandial diarrhœa*.—Under normal conditions the entry of food into the empty stomach gives rise to a gastro-colic reflex, which is the chief stimulus to the movements of the colon. In most individuals this is followed by defæcation only after breakfast, as the pelvic colon is then full, and the sudden passage of fæces from it into the rectum gives rise to the call to defæcation. Sometimes the gastro-colic reflex is abnormally active. This may manifest itself after breakfast; a formed stool is passed first, but in the course of the next half-hour or hour one or more loose stools are passed in addition. In severer cases the bowels are also opened after dinner and less frequently after lunch, the stools again being often soft or fluid.

(b) *Nervous diarrhœa*.—It is not uncommon for a fright to result in the immediate passage of a semi-fluid stool. In some patients, attacks of diarrhœa occur whenever they are in any place where it would be awkward for them to relieve themselves. When this has once happened, it is likely to recur under similar circumstances, largely owing to fear that it will do so. In such cases there are almost always other phobias and evidence of psychoneurosis. At the same time it must be remembered that diarrhœa, whatever the cause, tends to be worse after meals, especially breakfast, and is also frequently influenced by nervous factors, so that it is important to exclude any other primary causes before diagnosing a case as one of purely nervous diarrhœa. The diarrhœa, for instance, of such conditions as ulcerative colitis is markedly affected by the emotions, and many individuals who have lived in the tropics and suffered from repeated attacks of bacillary dysentery or from amœbiasis often continue to be liable to diarrhœa for many years after their return to a temperate climate, a condition sometimes described as irritable bowel.

3. ORGANIC INTESTINAL DISEASE.—(a) *Enteritis*.—The profuse, watery diarrhœa of acute food poisoning and infections such as the enteric fevers is a result of acute enteritis, which is generally accompanied by acute gastritis, though the colon is often spared. The irritating products of the excessive bacterial activity resulting from the stasis in organic obstruction of the small intestine give rise to enteritis; consequently diarrhœa and not constipation is almost always present in chronic small intestine obstruction.

In these conditions the chyme from the stomach passes rapidly through the

small intestine and the bulky fluid contents are evacuated by the colon almost at once, even though this may remain quite healthy.

(b) *Colitis*.—Diarrhœa is a constant symptom of acute inflammation of the colon, except in the rare cases in which this is confined to the cæcum and ascending colon. Thus it is always present in ulcerative colitis and bacillary dysentery, in which the disease begins and remains longest in the pelvic colon and rectum, but it may be absent in some cases of chronic amœbic dysentery in which the cæcum is mainly involved. Diarrhœa may occur in carcinoma of the colon, especially the distal part, before the lumen has been narrowed sufficiently to lead to fæcal retention. The diarrhœa in these conditions is due to irritation of the bowel by the products of bacterial decomposition of the albuminous exudate of the diseased parts, and in colitis also to deficient absorption of fluid by the inflamed mucous membrane.

**Symptoms.**—The chief and sometimes the only symptom of diarrhœa is the abnormally frequent passage of abnormal stools. In small intestine diarrhœa discomfort and colicky pain are often felt round the umbilicus. In severe cases of diarrhœa, whatever its origin, discomfort or pain is felt over the whole of the lower part of the abdomen for a short time before the bowels are opened. It may be followed by a sensation of soreness, but the abdomen is neither tender nor rigid, and warm applications generally relieve it. At times severe colic occurs, which may be temporarily relieved each time the bowels are opened or flatus is passed. The passage of a large and watery stool is often followed by a feeling of exhaustion and faintness, which may be accompanied by sweating and coldness of the extremities and occasionally even by syncope.

In severe cases of acute diarrhœa and in persistent cases of chronic diarrhœa the nutrition suffers and the patient loses weight; sometimes an extreme degree of emaciation results. Dehydration may be an urgent symptom. Loss of fluid, mineral salts and protein in the stools lead to a dry tongue, sunken eyes and an inelastic skin. Salt depletion may be a cause of coma and death if there is vomiting also, and the blood proteins may fall with the subsequent appearance of œdema in severe cases. These symptoms are especially dangerous in children in whom "summer diarrhœa" may be a medical emergency of great seriousness. Prostration is often profound and the blood pressure may fall to 70 or less and the pulse rate rise to 130 or higher.

**Diagnosis.**—When a patient complains of diarrhœa, it is first necessary to ascertain whether the passage of fæces through the intestines is really taking place with abnormal rapidity. Many people think that frequent defæcation, particularly if the stools are in part fluid, is sufficient evidence that diarrhœa is present, whereas this is by no means necessarily the case. The stools of every patient supposed to be suffering from diarrhœa should be examined; if they are of a uniform semi-solid or fluid consistence, true diarrhœa is probably present, whereas numerous stools, if they are small and solid, or fluid stools containing small solid fragments are against a true diarrhœa. In a doubtful case, 2 or 3 charcoal lozenges should be given with some food immediately after the bowels have been opened in the morning; each stool is now examined and the time which elapses before black fæces are passed is noted. If charcoal is seen in the stools within 12 hours, true diarrhœa is present; if in less than 4 hours, the small intestine must be involved as well as the colon. If no charcoal appears within 48 hours, constipation and not diarrhœa is present. A series of radiographic examinations after a barium meal affords a more accurate method of determining the rate of passage through the alimentary canal, and it has the advantage of showing in what part of the bowel the rate is excessive. In small intestine diarrhœa the head of the opaque meal may reach the cæcum within an hour or two; when the colon alone is involved, it arrives after the usual interval of 3 or 4 hours.

The most common cause of false diarrhœa is dyschezia. Although the rectum is never properly emptied, the patient feels a constant desire to open his bowels, and as a result of his efforts a very small quantity of hard fæces may be passed. The

constant presence of faeces in the rectum calls forth the secretion of clear mucus. In slight cases there may be nothing more than a thin layer of mucus over the hard lumps of faeces; in severer cases a larger quantity of fluid mucus, which is often stained brown, is passed either alone or with hard particles of faeces. In all such cases the discovery of solid faeces in the rectum immediately after the bowels have been opened should remove doubt as to the diagnosis. A growth of the rectum or pelvic colon, and less frequently a growth in other parts of the colon, though rarely on the proximal side of the splenic flexure, may lead to false diarrhoea, faeces being retained above the growth, whilst the serous and often blood-stained exudation from its surface, mixed with mucus produced by the irritant action of the exudation on the mucous membrane below it, are passed at more or less frequent intervals, so that the patient regards himself as suffering from diarrhoea. The character of the stools should at once make it obvious that endoscopic and radiological examinations are required, even if nothing abnormal is felt on abdominal or rectal examination. In all cases of diarrhoea the history is of great importance in diagnosis. An acute onset suggests an infective cause, but emotional factors must be carefully considered, as must any residence abroad or particular dietary indiscretions or idiosyncrasies. A more gradual onset of intermittent diarrhoea in a middle-aged individual, who has hitherto been regular or constipated, suggests the possibility of a growth. A careful abdominal and rectal examination should be made in every case. The former may reveal the presence of a tumour or an abnormally dilated or contracted condition of the colon. In any doubtful case a sigmoidoscopy should always be done, as the mucous membrane of the accessible part of the colon is almost invariably involved when diarrhoea is due to some form of colitis, and very frequently when due to growth.

The examination of the stools is of the greatest importance, as it gives valuable indications for treatment as well as helping in diagnosis. In small intestine diarrhoea the stools are watery, at any rate in the early stages, whereas in colonic diarrhoea they are unformed but not fluid. In acute enteritis there may be flakes of mucus floating in fluid faeces, which is often blood-stained, and microscopical examination shows the presence of red corpuscles, degenerated epithelial cells and pus cells; as the inflammation subsides the mucus becomes cell-free and finally disappears. Similarly the unformed, but not watery faeces of an irritable colon can be distinguished from the faeces of colitis by the presence of mucus, pus and blood in the latter. In amœbic dysentery the stools are usually semi-solid and very foul smelling with dirty brown mucus and dark blood, whilst in acute bacillary dysentery they often consist of blood and mucus only, the latter being tenacious, sticking to the bedpan and odourless.

The presence of excess of starch, meat fibres or fat indicates a small intestine diarrhoea. Excess of undigested starch is found on microscopical examination in fermentative diarrhoea, and of striated muscle fibres in putrefactive diarrhoea. The faeces are often frothy and have an acid smell and reaction when fermentation is excessive; they are alkaline and have a putrefactive odour when excessive putrefaction is present.

*Steatorrhœa.*—The stools passed when fat is insufficiently digested or absorbed may usually be recognised by their pale colour and increased bulk, but it must be remembered that a high stool fat content may be present in spite of a normally coloured stool. Faecal fat analysis is therefore necessary, but simple percentage estimations may be misleading unless the diet is known, since a high residue and low fat diet will lead to a low fat percentage in the dried stool. The pale colour of sprue stools is generally attributed to reduction of the normal stercobilin to colourless stercobilinogen and on exposure to light such stools darken markedly in colour; it must also be remembered that pale stools may sometimes follow an attack of dysentery or other infection, even without any excess of fat being present. If the excess is in the form of neutral fat, the stools are oily (*fatty diarrhoea*), and pancreatic insufficiency can be

diagnosed; striated meat fibres are also likely to be present. This condition is, however, rare in the absence of jaundice caused by obstruction of the common bile duct. More frequently most of the fat is present as fatty acid and soaps (*soap diarrhœa*), showing that pancreatic digestion is normal, but that absorption is deficient. This may result from absence of bile salts in obstructive jaundice, and from the sprue-syndrome (*cœliac disease in children and sprue and non-tropical sprue in adults*). Soap diarrhœa is also caused by obstruction of the lacteals by tuberculous, simple inflammatory or secondary malignant disease of the mesenteric glands. In the latter case the stools become perfectly normal on a fat-free diet, the digestion of meat and vegetable food being unaffected. In soap diarrhœa almost all the calcium in the food combines with fatty acid to form calcium soap and the blood calcium is consequently diminished, so that tetany may result. In children growth is greatly impaired, and deformities result from the softness of the long bones. The inability of the intestines to absorb fat may be associated with deficient absorption of sugar, iron, protein and vitamins A, B, D, E and K, causing anæmia, neuritis and severe malnutrition (malabsorption syndrome).

*Additional investigations.*—A bacteriological examination should always be made in the hope that the nature of any infection which is present may be discovered, but except in the early stages this is often negative, even in infective cases.

The blood sedimentation rate should be measured in doubtful cases, as in nervous diarrhœa it is likely to be within normal limits, whereas if it is raised organic disease is more likely to be present.

A barium enema should never be allowed to replace careful clinical and especially rectal examination, but is a valuable means of diagnosis in diarrhœa, especially in cases of suspected carcinoma of the colon, even though a rectal growth may be missed by this method. A barium enema will also indicate the degree and extent of an ulcerative colitis, and the presence of diverticula. Radiography after a barium meal may also indicate typical changes in sprue, regional ileitis and other small intestine disorders.

*Prognosis.*—The prognosis of diarrhœa depends upon the cause. The liability to nervous diarrhœa often remains throughout life, but considerable improvement and even a cure can result from treatment. Unlike other forms of diarrhœa, it rarely affects the general health and is chiefly troublesome on account of the inconvenience it causes.

*Treatment.*—The specific treatment of diarrhœa must depend upon its cause, but much may be done symptomatically for the relief of the patient.

*Acute stage.*—The patient should be kept warm and at rest in bed until the attack has subsided. If it is due to food poisoning and he is seen within 12 hours of the onset, he may be given hourly doses of mag. sulph. (1 drachm) for 3 or 4 doses, to clear the irritant material out of the small as well as the large intestine, unless the diarrhœa is so severe that it appears probable that this has already occurred. No food should be given for 24 hours or even longer in severe cases, but the patient may drink as much water as he likes. Sweetened arrowroot made with water should then be given, but nothing else until the diarrhœa has ceased. Milk, junket, bread and butter, eggs and milk puddings are next allowed, after which a gradual return should be made to an ordinary diet, the speed with which this is done depending on the severity of the case. The only symptomatic drugs which are of real use in acute diarrhœa are kaolin and opium and its alkaloids. Two tablespoonfuls of kaolin should be given three times a day or more. If the diarrhœa shows no signs of abating after 24 hours, codeine should be given, the dose being regulated according to the severity of the diarrhœa and the general condition of the patient. The treatment of acute bacillary dysentery is described on p. 117, but many mild cases, particularly of Sonne dysentery, may closely resemble an acute enteritis and respond at once to sulphonamide drugs. The oral use of streptomycin in enteritis is also of value. If there is severe

dehydration from loss of fluid intravenous saline may be necessary, in which case approximately 3 to 4 litres of water containing 3 to 4 g. of sodium and 2 to 4 g. of potassium will represent an average minimal requirement for 24 hours.

**Chronic diarrhœa.**—In all cases of chronic diarrhœa recovery occurs most rapidly if the patient remains in bed during the first few days of treatment. In many instances the diarrhœa, which may have been present for months, disappears in a few days, and the patient may even become constipated. Unless, however, other treatment is instituted, the diarrhœa is very likely to return as soon as he gets up again. As the improvement which results from staying in bed is due in part to the rest and in part to warmth, it is important for the patient to avoid over-exertion and to avoid exposure to cold for a considerable period after the symptoms have disappeared. Patients who have recently suffered from chronic diarrhœa should not go to the tropics, as a slight intestinal attack from bad food is likely to have much more serious results with them than in an individual who has not before suffered from any intestinal disorder.

The successful treatment of chronic diarrhœa depends upon the recognition of its cause, and cases secondary to organic disease of the intestines, such as colitis and cancer, are considered elsewhere.

Whatever the actual cause of the diarrhœa, it is important to avoid anything which could produce mechanical irritation in the colon. The food should be thoroughly chewed, and the patient should avoid such things as tough meat, nuts, pips and skins of fruit, whether raw, cooked or in jam, currants, raisins and lemon peel in puddings and cakes, and all raw vegetables in salads or pickles; cooked green vegetables should be allowed as purées; meat extracts are often stimulating to bowel peristalsis; and alcohol should only be taken with food and in small amount if at all.

For the treatment of *fermentative diarrhœa*, vide *Intestinal Carbohydrate Dyspepsia* (p. 630).

For the treatment of *steatorrhœa*, see pp. 619, 622.

In some cases of diarrhœa in which *fæcal streptococci* are greatly in excess of coliform organisms in the stools, a teaspoonful of a culture of *B. acidophilus* taken fasting every morning, or a quarter pint of Yoghurt (sour milk) daily may be successful. Nervous diarrhœa is often completely uninfluenced by diet, but drugs which diminish the activity of the gastro-colic reflex, either peripherally or centrally, are sometimes effective. A mixture containing gr. 5 of sodium bromide and 15 minims of tincture of belladonna taken immediately before meals is all that is required in mild cases. In severer cases a small dose of codeine should be added. The exact dose of each drug should be varied to suit each patient, as different individuals react very differently to these drugs, especially to belladonna. Phenobarbitone gr.  $\frac{1}{2}$ , taken half an hour before each main meal is also useful; when the diarrhœa has been completely controlled, the quantity of each drug should be gradually reduced and finally discontinued. In some cases it is advisable to allow the patient to have a pill containing belladonna and codeine always with him, so that he can take one before going to a dinner-party or on any other occasion when he fears that he will have diarrhœa. He soon learns to trust so thoroughly in his pill that it probably acts more by suggestion than in any other way, and the dose can accordingly be progressively reduced until it is infinitesimal.

THOMAS HUNT.

## EPIDEMIC DIARRHŒA IN CHILDREN

**Synonyms.**—Summer Diarrhœa; Infective or Infectious Diarrhœa; Acute Gastro-Intestinal Infection; Acute Ileo-Colitis; Cholera Infantum.

The form of diarrhœa here spoken of used to be one of the chief scourges of infant life, but is certainly much less common now than formerly. It prevails epidemically in institutions, although sporadic cases may be met with at any time. The

association of epidemics with hot weather is no longer a feature. It chiefly affects children below the age of 5, but is most fatal in the first year. Boys are more susceptible than girls. Epidemics among the newborn have been described.

**Ætiology.**—It is generally agreed that the disease is caused by infection with micro-organisms; but in spite of much research the bacteriology is by no means clear. It would appear that not all cases are due to the same organisms, and various members of the coli-typhoid-dysentery group have been blamed at different times.

Next in importance as an ætiological factor must be put the influence of unhygienic surroundings, such as dirt, overcrowding, a contaminated milk supply and want of cleanliness in feeding utensils. The infection is probably often conveyed by dust, and flies may act as carriers.

Any digestive derangement in the child may predispose to infection, and bottle-fed infants are specially liable. The disease appears to be to some degree contagious, and if introduced into a ward is apt to spread to unaffected infants. The influence of age and sex have already been referred to.

**Pathology.**—The changes found after death may be surprisingly slight, considering the severity of the disease, and vary materially in different cases and epidemics. As a rule the mucous membrane of the stomach and intestines is in a condition of "mucous catarrh". There may also be areas of congestion, with here and there small petechial hæmorrhages. The lymphoid tissue of the alimentary canal is often swollen, and in severe and protracted cases the solitary follicles in the colon and lower ileum may exhibit superficial ulceration.

Other organs, such as the liver and kidneys, show fatty or parenchymatous degeneration, whilst the lungs are often congested and œdematous, with, in protracted cases, patches of broncho-pneumonia in the lower lobes.

**Symptoms.**—The clinical picture is often very complicated, and if it is to be understood it is essential to realise that the disease causes a profound disturbance of metabolism and is not merely a disorder of the alimentary canal. The supervention of dehydration, acidosis and disturbances of tissue and cell metabolism, with their own clinical manifestations, tend still further to perplex the observer and make it impossible for him to decide to what extent the symptoms are due to the primary infection or to these secondary developments.

The disease may start insidiously, with a gradually increasing diarrhœa; or the onset may be abrupt, with a rapid rise of temperature and early prostration. The diarrhœa is not necessarily a pronounced feature, and the worst cases are often those with fewest stools. The character of the motions varies; but in the early stage they are usually green, slimy and ill-digested, becoming dark and watery later. In the choleraic cases they are of the profuse "rice-water" type. When the colon is affected, visible mucus and blood may be passed with much straining. The discharges are usually attended by colicky pain and the passage of flatus. Vomiting is generally present at the onset, but varies greatly in amount. The temperature is always elevated at some period of the disease, but the height, duration and course of the pyrexia are very inconstant. Hyperpyrexia may supervene towards the close in fatal cases. Prostration and circulatory failure are early features, and are shown by depression of the fontanelle, pallor, pinched features, an inelastic skin due to dehydration and coldness of the extremities. When "intoxication" is a factor, consciousness becomes impaired, and the infant passes into a state of stupor, with intervals of restlessness, which may result in complete coma, sometimes terminating in convulsions. If acidosis is present, the respiration may show the characters of "air-hunger".

The urine is scanty, highly acid and contains a little albumin and a few hyaline casts. Acetone bodies may be present.

**Course.**—The course of the disease varies greatly. In the severest cases, especially those of the choleraic type, death may ensue within a few hours of the first onset of symptoms. In the milder forms the acute symptoms last for 2 or 3 days, and then



gradually the prostration passes off and the stools assume a normal character. Only too often, however, the improvement is but partial, and the child lapses into a marasmic condition, with continued looseness of the bowels, from which recovery may only take place gradually. In all cases relapses, brought on either by reinfection or by injudicious feeding, are extremely common and apt to prove fatal.

In children above the age of 2 the disease usually assumes a milder form—prostration is not so severe and the range of temperature lower. Vomiting, also, is a less prominent symptom than in infants. Complete recovery is more frequent, and relapses and the continuance of the disease in a chronic form are rare.

In the special type of the disease commonly spoken of as “cholera infantum” the invasion is always abrupt, with a rise of temperature, followed by profuse vomiting and purging. Death usually ensues in a few hours, and is commonly attended by hyperpyrexia.

**Diagnosis.**—The diagnosis has to be made from simple non-infective diarrhoea, and for the increasingly common forms of diarrhoea secondary to respiratory tract and middle-ear infections. At first the differentiation may be impossible, but continued high temperature, early prostration and failure of rapid improvement on stopping food point to a primary infective origin. Careful physical examination will exclude secondary types. Epidemic prevalence is in favour of the primary variety. The nervous symptoms may simulate those of meningitis, but in case of doubt a lumbar puncture will determine the diagnosis. Very acute cases in which the colon is much involved, may resemble intussusception, but in the latter the onset is more dramatically sudden, the vomiting, collapse and passage of blood greater, and fever less, whilst in epidemic diarrhoea abdominal rigidity and tumour are absent.

**Prognosis.**—It is impossible to give any estimate of the fatality of diarrhoea, as it depends greatly on the type of the disease, and on the age, general condition and surroundings of the child, besides varying greatly in different epidemics. The younger the infant, and the poorer its general nutrition, the worse is the outlook. The existence of rickets also greatly aggravates the danger. The frequency of the stools is of less importance in estimating the chance of recovery in any given case than the amount of prostration and the degree of inelasticity in the skin. Cases with prolonged high temperature and those of the choleraic type usually do badly. Persistence of vomiting also is a bad sign.

**Treatment.**—Prevention should be given primary consideration in relation to epidemic diarrhoea. The admission of healthy or sick infants to hospitals, homes and institutions of any type must be carefully controlled. When such admission is absolutely unavoidable, isolation facilities are essential and all infants under 2 years should be nursed in cubicles which must be well ventilated. Masks and gowns should be worn by those attending small infants in hospital. Newborn babies should be nursed with their mothers as far as possible and not collected into overcrowded nurseries. The strictest hygiene must be observed by all those looking after small babies in hospital.

**Curative measures** aim at counteracting the infection and restoring the disturbed metabolism to normal. It is necessary to emphasise that an infant with acute diarrhoea and vomiting is a “medical emergency”, just as much demanding admission to hospital for expert treatment as if a “surgical emergency” were present. Such babies should, of course, be regarded as infectious and nursed in isolation with full precautions against spread. A large, airy, well-ventilated room in the country rather than the town is to be preferred. On admission, measures to deal with collapse and shock may be necessary. Hot-water bottles should be used and a mustard bath is often of help to revive a seriously collapsed child. Drugs such as nikethamide (Coramine) are of value, and brandy has a reputation in this malady for its stimulant powers, although it is fair to point out that it may also have an irritant action upon stomach and bowel. The dose is 15 to 30 minims.

Defective absorption may be present as in celiac disease or fibrocystic disease of the pancreas, or in the state of recurrent diarrhoea which may follow an attack of gastro-enteritis. Fever and infection as causes of wasting have also to be excluded. Miliary tuberculosis in a small baby, for example, may only be detected by radiogram examination. When all these causes of wasting have been excluded there remain others in which defective metabolism is the explanation. *Infantile renal acidosis* is now one of the best studied. An infant after a few months of poor progress with vague "feeding upsets" begins to vomit, is constipated, the weight falls and the urine is usually found to be alkaline in reaction. The blood chemistry shows an increase in chlorides and a reduction in the plasma bicarbonate. It is thought that the relatively immature renal tubules have not acquired the ability to retain bicarbonate. Additional alkali by mouth in the form of citrates restores the blood chemistry to normal, symptoms disappear, appetite improves and weight is gained. After a varying period the alkali can be discontinued as the metabolism (and renal defect) may right itself. In untreated or persistent cases calcium is deposited in the kidneys to produce *renal calcinosis*. The "Fanconi syndrome" (see p. 1179) is another example of renal leak producing profound metabolic changes including wasting. *Idiopathic hypercalcaemia* is found in some infants presenting a very similar picture to that of infantile renal acidosis but here the blood chemistry shows a raised calcium, often as high as 18 mg. and raised blood urea. A low calcium diet and alkalis can be used and there is a slow tendency to recovery in most instances. The exact cause is unknown. Disturbances of carbohydrate metabolism may also cause obscure wasting. Several examples of galactosuria (see p. 444) have now been published in which there is an inborn inability to deal with this sugar. A still rarer variety is sucrosuria in which sucrose is absorbed from the alimentary tract and excreted in the urine. In all these conditions careful examination of the urine, including paper chromatography, will often provide a clue, and the blood chemistry is confirmatory. A wide field of speculation is opened up by the consideration of nervous influences in the production of marasmus. Tumours in the hypothalamic region may certainly cause obscure wasting. The possibility of psychological causes cannot be ignored, and a better management of the mother-child relationship while the child is in hospital may be of importance in this connection.

ALAN MONCRIEFF.

## CÆLIAC DISEASE

**Synonyms.**—This disease was first described by Gee in 1888 under the title of "The Celiac Affection". Cheadle redescribed it in 1903 as "Achoia", and Herter in 1908 as "Intestinal Infantilism". It is sometimes spoken of in America as "Chronic Intestinal Indigestion", but in this country the term "Celiac Disease" is now generally applied to it.

**Definition.**—A wasting disease of childhood characterised by the passage of large, pale, offensive stools which contain an excess of split fat, and leading to emaciation and arrest of growth; various complications due to avitaminosis may be super-added.

**Ætiology.**—The fundamental cause of the disease remains obscure but recent work indicates that gluten in certain flours interferes with fat absorption. There is no hereditary element; girls are more susceptible than boys, and no social class is exempt. The disease appears to be rarer in the Latin countries than in the Anglo-Saxon and Scandinavian.

**Pathology.**—There is no characteristic morbid anatomy, the post-mortem changes being attributable to inanition or to intercurrent disease from secondary infection. The bones tend to show changes similar to those of rickets, and the blood chemistry is also similar. The ordinary changes of enteritis are not found.

The general views expressed in the section on idiopathic steatorrhœa can also be studied in this connection. The view that there is a fundamental disturbance of the absorption mechanism, particularly in the upper part of the small intestine, appears to be sound. Radiographic evidence in cœliac disease shows impaired motility of the small bowel, particularly well seen when an opaque meal has been given; clumps of barium can be seen in the duodenum.

**Symptoms.**—The disease begins insidiously between the sixth month and the end of the second year, possibly when wheat flour is first taken. The child loses appetite, fails to thrive and has slight diarrhœa. Soon the characteristic stools appear. They are large, but not necessarily frequent, pale, extremely offensive and sometimes frothy and fermenting. On chemical examination they contain from 40 to 60 per cent. of split fat instead of the normal 25 per cent., but the amount of unsplit fat present is not altered. Meanwhile the emaciation progresses, the face being least affected by it and the buttocks most. The abdomen, by contrast, is prominent, doughy and distended. Along with these physical signs there is a change in mentality. The child is often remarkably precocious, but is irritable, hysterical and "difficult", especially during the exacerbations. There is frequently a profound anorexia, and muscular weakness may be extreme. Anæmia is usually present, of the microcytic, iron-deficiency type. Very rarely a megaloblastic variety is found.

**Complications.**—Various deficiency symptoms are apt to appear as the result of avitaminosis induced either by impaired fat absorption or by the character of the diet which treatment demands. Rickets may show itself either early, or, after the age of 7, in the "late" form, with genu valgum as its main sign. Symptoms such as œdema and absence of reflexes may suggest beriberi and have been attributed to deficiency of vitamin B. Scurvy is not uncommon, and attacks of tetany may occur in association with a low blood calcium.

**Diagnosis.**—At the outset the disease may be impossible to recognise, but when the characteristic stools appear diagnosis is easy. Arrest of growth is of great diagnostic value. The distended abdomen may suggest tuberculosis; atonic bowel with fluid fœces mimics the signs of ascites. Cœliac disease presents many points of resemblance to sprue, but the latter is rare in childhood, and in cœliac disease the blood picture is usually that of an iron-deficiency anæmia.

A low oral glucose tolerance curve and a low vitamin A absorption curve are both found. The duodenal juice is also normal. This last point is of importance in order to exclude fibro-cystic disease of the pancreas. Here the main difference is that there is failure to thrive from birth and, frequently, chronic changes in the lungs.

**Course and Prognosis.**—If untreated or ineffectively treated the disease runs a prolonged course with many ups and downs and is peculiarly prone to relapse. It may persist into adult life (see p. 620) but usually tends to recover before puberty. The mortality may be put down at about 10 per cent., and death, when it occurs, is usually due to intercurrent disease. During the active phases of the disease growth is arrested, and even after recovery the patient may be permanently stunted (intestinal infantilism). The remarkable results obtained by a strictly gluten-free diet completely alter this picture, far more effectively than any previous regime. After a few weeks the child is found to be rapidly proceeding back to normal.

**Treatment.**—The history of the treatment of cœliac disease is marked by varying claims for widely different regimes. Originally a diet high in protein, low in fat and without carbohydrate was recommended. Then the carbohydrate of overripe bananas was found to be well tolerated. Next came the phase of an almost unrestricted diet with whole vitamin B and liver extract by intramuscular injection. Recent work in Holland and England seems to show that the gluten of certain flours, especially of wheat, is concerned with the failure of fat absorption so that gluten-free diets are now in use in which almost everything else is allowed, even normal amounts of fat. The results appear to be better and more quickly achieved than with any previous

programme. Expert dietetic advice is necessary for the mother to secure that no gluten is given, and gluten-free flour can be obtained for making "bread", biscuits, sauces, etc., for which ordinary flour is normally used. It is well to admit the child to hospital to establish the diagnosis (excluding especially fibrocystic disease of the pancreas) and to start off the diet with some restriction of fat for a short period. Concentrates of vitamins A and D should be given together with ascorbic acid tablets until the diet is going well. Iron may be needed if there is anæmia although in a neglected case a blood transfusion is a better way to bring the blood hæmoglobin up to normal. Folic acid may be used in those rare cases with a megaloblastic type of anæmia. Since there is a natural tendency to "cure" of celiac disease in the course of time a trial should be made after, say, 6 to 12 months of the gluten-free régime, to introduce a little ordinary flour while carefully watching the state of the stools. If these remain normal in appearance restrictions can be gradually stopped.

ALAN MONCRIEFF.

### IDIOPATHIC STEATORRHOEA

**Synonyms.**—Adult Celiac Disease; Non-tropical Sprue; Gee-Herter Disease; Herter-Heubner Disease; Gee-Thaysen Disease.

**Definition.**—This is the adult form of celiac disease (see above). With certain very rare exceptions it arises in childhood, though some cases remain unrecognised until adolescence or adult life is reached. The main features are: Fatty stools, with or without diarrhoea, and sometimes with dilatation of the colon; tetany; osteomalacia; anæmia of various types; skin lesions and frequently infantilism.

**Ætiology.**—This is unknown. Adults who in childhood had celiac disease, continue to be intolerant of gluten (see p. 618), but the exact mechanism of gluten intolerance is unknown. Patients affected have not lived abroad, and the disease cannot be classed with sprue, though resembling it in many respects. The affection is sometimes familial. It is slightly more common in females than in males. The disease has been described in the Scandinavian countries, Germany, Switzerland, France, Great Britain and America.

**Pathology.**—The underlying disturbance is interference with the total function of the small intestine. Attempts to demonstrate an anatomical lesion have failed even with the microscope. The symptoms develop in spite of an adequate diet, and the patient starves in the midst of plenty. Deficient absorption of various components of the diet explains many of the signs and symptoms. The fat, although split, cannot be digested and produces steatorrhœa. On a low fat diet, the percentage of total fat in the stools forms on the average more than 25 per cent. of the total weight of the dried faeces; on a normal diet this figure reaches 40 to 60 per cent. The fats are mainly split fats, the figure for neutral fat not exceeding 3 per cent.

Sometimes there is carbohydrate dyspepsia, with production of gas which distends the bowel. This arises from the bacterial hydrolysis of starch following the failure of amylolytic digestion by succus entericus. Sugar is poorly absorbed, and the blood sugar curve after glucose is much flatter than normal. Similarly, proteins are ill absorbed and the blood urea is often below normal. Poor absorption of salts is seen in the low figure for serum calcium, usually 8 mg. per 100 ml., and the low or normal plasma phosphorus. The height of the plasma phosphatase coincides approximately with the degree of active change in the bones. Calcium balance estimations reveal high figures for faecal output, and very low figures for urinary output.

Defective absorption of iron is followed by hypochromic anæmia; and a macrocytic anæmia, usually due to folic acid deficiency, often appears. Occasionally xerophthalmia and toad-skin appear, proclaiming vitamin-A deficiency. Sore tongue.

cheilosis, anosmia and pellagra-like skin result from shortage of the vitamin-B complex. Osteomalacia occurs from deficiency of vitamin D. A tendency to sudden hæmorrhages indicates vitamin-K deficiency. It is associated with a prolongation of the coagulation time and a reduction in the blood prothrombin concentration.

**Symptoms.**—The presenting symptom is either diarrhœa, pain in the bones with deformity or tetany. The stools are bulky and pale, though not always conspicuously frequent. The wasting and distended abdomen so constantly found in children with cœliac disease is not a noticeable feature, even though severe diarrhœa be present. The skin shows a dirty putty-coloured pallor, and the hair is fine, mud coloured and liable to turn grey at an early age. In 50 per cent. of cases a skin eruption is present on the limbs, and to a lesser extent on the trunk. The lesions are moist red abraded areas with scaly brown pigmented borders, resembling pellagra. In 60 per cent. of cases the fingers are clubbed. By means of the slit-lamp small flaky opacities are to be seen in the various layers of the lens. They never progress sufficiently to interfere with vision.

Most cases show some degree of skeletal deformity, including genu valgum, bending and bowing of the bones, distortion of the pelvis, beading of the ribs and spontaneous fracture. In many of these cases there is dwarfism, but this is not necessarily associated with mental or sexual infantilism. The male genitalia are poorly developed, and the voice high pitched. In women the onset of menstruation is delayed. The disease is usually accompanied by sterility, but should pregnancy occur there is often an acute exacerbation of symptoms. Pelvic deformity may interfere with the normal course of labour. Tetany commonly occurs with recurrent attacks of tinglings in the fingers and hands, followed by carpedal spasms. These interfere with writing, piano-playing and even with walking. In many patients tetany is latent only, its presence being detected on eliciting the Trousseau or the Chvostek signs.

The anæmia of idiopathic steatorrhœa is typically macrocytic and may be indistinguishable from pernicious anæmia. Erythropoiesis however is more often macro-normoblastic than megaloblastic. Iron deficiency, when present, may lead either to a normocytic hypochromic anæmia or may complicate the picture of folic acid deficiency, i.e., a raised mean corpuscular volume may be associated with a low mean corpuscular hæmoglobin concentration. Achlorhydria is uncommon, occurring in less than 20 per cent. of all cases. Hæmorrhagic phenomena are rare, even in cases treated for a long time by means of a low-fat diet. They include hæmatemesis, melæna, epistaxis, menorrhagia, hæmaturia, hæmarthroses, subcutaneous hæmatomata and intractable bleeding from wounds. Scurvy is very rarely seen.

**Radiographic appearances.** The intestinal tract shows varying degrees of a deficiency pattern when a flocculable simple suspension of barium sulphate is used. Pronounced flocculation occurs in the upper small intestine and this has been attributed to excessive secretion of mucus. With non-flocculable preparations such as Raebars the small intestine appears unduly dilated and hypotonic and its normal feathery pattern is lost. In long-standing cases opaque enema examination shows dilatation of the colon, and sometimes this assumes the proportions of megacolon. Radiographs of the skeleton may reveal the changes of osteomalacia, and if the epiphyses have not united the translucent cup-like metaphyses of rickets are present. Many cases show fine transverse lines of increased density of bone immediately to the diaphyseal side of the metaphyses of the long bones. Distortion of the limbs, spine and pelvis are common.

**Diagnosis.**—A denial of residence in a country where sprue is endemic is enough to rule out that disease. Other causes of secondary steatorrhœa include chronic pancreatitis, gastrocœlic fistula, gastro-enterostomy or gastrectomy, regional ileitis, tuberculous enteritis, diverticula or blind loops of the ileum or jejunum, Whipple's disease and neoplastic conditions of the small intestine.

**Prognosis.**—The results of treatment are disappointing in the adolescent and adult cases compared to what is seen in children. Some respond satisfactorily and remain well under treatment. In others all that is accomplished is the alleviation of one or more symptoms and the temporary offset of the downward progress. It is none the less gratifying to see the great improvement in the anaemia of many of the cases, and the recovery from the pain and disability of osteomalacia in others. Often there is a great change for the better in the mental outlook of the dwarfed, crippled, anaemic patient as he is gradually relieved of his disabilities. Unfortunately one group of symptoms and signs may clear up completely, and yet the patient may die in inanition. Thus extensive, moist, red excoriated skin lesions may heal under treatment with the B vitamins, yet relapses of diarrhoea and tetany may result in the death of the patient, the skin remaining normal.

**Treatment.**—This presents great difficulties. While nothing can be done to remedy the primary defect much care can be given to mitigate as far as possible its consequences. The steatorrhoea must be controlled by a low-fat diet. No patient with this disease can be given the amount of fat found in the average diet without risking the occurrence of diarrhoea. The diet should be high in calcium content. The best way to secure a low-fat high-calcium intake is to use skimmed milk and preparations of calcium caseinate, such as Casec or Laitproto. The items of such a diet include meat, chicken, bread, a scraping of butter, oatmeal, potato, rice, tea, sugar, skimmed milk, cheese, jam, cabbage, apple, banana and tomato. These items can be arranged as follows: carbohydrate 325 g., protein 90 g., fat 30 g. and calcium 2 g. Sometimes gas formation from carbohydrate fermentation is a prominent symptom, and then the intake of starch should be strictly controlled, and the administration of diastase may be useful.

Some patients with idiopathic steatorrhoea have few symptoms and their nutritional state is good. In these a normal diet may be tolerated. In others, symptoms often respond to simple reduction of the fat content of the diet, but when they are severe a trial should be made with a gluten-free diet. The tedious and exacting régime which this entails is amply justified when remission is induced and although the value of a gluten-free diet is not as firmly established in idiopathic steatorrhoea as it is in coeliac disease improvement undoubtedly occurs in individual patients when other methods have failed. It may still be necessary to restrict fat intake, for example from the normal 80 to 90 g. in a 2,500 calorie diet to 40 to 60 g. per diem. Additional calories can be provided in the form of glucose and milk protein (Casilan).

When tetany occurs, calcium lactate should be given in doses of 5 g. three times a day. In emergency 20 ml. of a 5 per cent. solution of calcium chloride or gluconate may be injected into a vein, and if administered very slowly no ill effects are produced. Vitamin D should be given in every case in which there are clinical or radiographic signs of rickets or osteomalacia. General ultra-violet irradiation is also of value. These measures may relieve bone pain, though any relapse of diarrhoea is liable to interfere with this good effect. Cod-liver oil, or any other form of vitamin D in an oily medium, is contraindicated in view of the defective fat absorption. Vitamin D should be given in a solid medium in the form of calciferol tablets, 50,000 units daily. In spite of large doses by mouth, the response is sometimes poor, and 10,000 units parenterally at longer intervals may then have to be given. Over-dosage can be guarded against by examining the urine with Sulkowitch's reagent.

Treatment of the anaemia must depend upon examination of the blood. When it is hypochromic, large doses of iron should be prescribed until the haemoglobin figure reaches normal. This usually occurs with ferrous sulphate gr. 6 three times a day. When the anaemia is refractory a satisfactory response may be obtained by means of intravenous or intramuscular iron (see p. 733). Macrocytic anaemia usually responds to folic acid 5 mg. t.d.s. by mouth. In some patients it may have to be given intra-

muscularly, and in others cyanocobalamin or even crude liver injections may be needed in addition. Whatever the form of the anæmia, it is essential to remember the importance of adequate dosage. For 1 week in each month a prophylactic dose of vitamin K or its derivative should be given by mouth. A suitable dose is 30 mg. of menaphthone. If hypoprothrombinæmia has already led to hæmorrhage the vitamin or its synthetic analogue should be administered by injection, double the above doses being used.

Orthopædic treatment includes splinting or even osteotomy to correct deformities, such as genu valgum. A cork sole may be necessary, and kyphosis may demand the use of a spinal jacket. The pelvic deformity may necessitate Cæsarean section.

DONALD HUNTER.

## TROPICAL SPRUE

**Synonyms.**—Cochin-China Diarrhœa; Psilosis; Ceylon Sore Mouth, etc.

**Definition.**—Tropical sprue is a disease of unknown ætiology involving the gastrointestinal tract, characterised by defects in gastric secretion and inability to absorb adequately fat, glucose, calcium and certain vitamins. Typically there is apyrexia, morning diarrhœa with bulky, pale, gaseous, fatty stools, sore tongue, megalocytic anæmia, asthenia and wasting.

**Ætiology.**—The disease is mainly confined to the tropics and subtropics, being especially common in parts of India (Bombay), China and Cochin-China, also in Ceylon, Java, the Federated Malay States, Puerto Rico and the West Indies where it was first described by Hilliary in 1759. Adult Europeans and people of mixed European blood living in endemic areas are prone to the disease. Except in Puerto Rico, the native population is rarely affected. Both sexes are susceptible, but it rarely affects people under 20 years of age. A hot, damp climate, especially on the seaboard, favours its development, while certain bungalows enjoy an unsavoury reputation in this regard. Various theories have been suggested to explain its ætiology. Some writers link up vitamin B deficiency with dysfunction in the small intestine as revealed by radiological changes. In sprue, as in a number of other diseases, a deficiency pattern has been described characterised by abnormal segmentation associated with diminished motility and alteration in the outline of the mucosal folds. It has been suggested that those changes are associated with degeneration of the cells in the myenteric and submucosal plexuses (Golden) due to a deficiency in nicotinic acid and possible other components of the B complex.

That it is not a primary deficiency disease is indicated by its frequent occurrence in the best-fed Europeans in endemic centres such as Bombay, its almost complete absence from thousands of malnourished prisoners of war in the Far East in whom deficiency diseases were very common, and its occasional onset years after leaving an endemic area. Secondary deficiencies may occur in tropical sprue but these are conditioned by derangement of intestinal absorption or the restricted diet imposed by the patient or his physician after the onset of the malady. There is evidence that a failure of phosphorylation of fatty acids, glycerol and glucose may be the immediate cause of malabsorption. It has also been suggested that riboflavin and nicotinic acid may catalyse the process of phosphorylation, and that intestinal infection, dysentery or even radical changes of diet, might alter the intestinal flora which plays a part in the synthesis of certain vitamins (Leishman).

The view that sprue is a conditioned or secondary deficiency dependent on lack of some factor or factors which play an essential rôle in the chain of chemical reactions involved both in intestinal absorption of certain food constituents and in the production of liver principle has much in its favour. The possibility that this may be

determined by a changed bacterial flora is an attractive hypothesis which, however, requires verification.

**Pathology.**—*Morbid anatomy.*—At necropsy the essential lesion consists of an absence of fat, muscular wasting, a small heart, general atrophy of the viscera and alimentary tract consequent on malnutrition, a megaloblastic hyperplasia of the red marrow of variable intensity and atrophic changes in the tongue.

Most of the specific histo-pathological findings described in the intestine in sprue have been due to necrobiotic changes in a tropical climate, but in view of the work of Golden and others further investigation along these lines is necessary—especially in regard to the nerve plexuses.

*Clinical pathology.*—The anæmia, which is by no means invariably present in the early stages, is megalocytic in type, resembling that seen in pernicious anæmia. The Price-Jones curve is also similar. The colour index is usually 1.0 or higher. The blood picture shows numerous megalocytes associated with anisocytosis and poikilocytosis, and in the severer cases polychromasia, basophilic stippling and occasional normoblasts may be observed; megaloblasts are rare. Hypochlorhydria or achlorhydria is common, but 75 per cent. of cases respond to histamine injection by an increase in HCl secretion. The total faecal fat is generally increased (30 to 70 per cent. of the dried faeces), but splitting is adequate. The glucose tolerance test frequently shows a flat type of curve, or one presenting a retarded rise due to malabsorption, while the blood calcium is decreased for the same reason. The blood bilirubin is rarely increased to the extent seen in pernicious anæmia. Malabsorption of fat accounts for the excessively fatty stool, while fermentation of glucose within the lumen of the bowel, consequent on defective absorption, underlies its acid and gaseous characteristics. The pallor of the stool is due to the transformation of stercobilin into colourless leucobilin and to excessive fat.

**Symptoms.**—The incubation period is unknown, but patients have occasionally developed sprue within a few months of arriving in an endemic area. Many years ago Rogers showed that hill diarrhœa in India sometimes passed into tropical sprue. During the War of 1939–1945 epidemics of diarrhœa occurred in Burma in which a variable proportion of the affected troops were recorded as developing tropical sprue. Some of these were undoubtedly genuine cases of classical sprue, others undoubtedly were not. Often the onset is insidious with (1) loss of energy, dyspepsia and flatulence; (2) rapid loss of weight; (3) sore tongue or buccal aphthæ; (4) diarrhœa or looseness of the bowels, especially in the early morning. It may be months before the typical bulky, pale, acid, frothy stools reveal the true nature of the malady. Pyrexia is the rule, and frequently the temperature is subnormal. Once seen, the fully developed picture of sprue makes an indelible impression. Such a patient is asthenic, emaciated, mentally taciturn and often severely anæmic; the skin is parched, wrinkled and sometimes pigmented over the forehead and malar eminences, while the nails are ridged and brittle; the tongue, which is invariably clean, may be patchily inflamed, ulcerated and atrophic, while the thin abdominal parietes scantily protect the attenuated coils of gas-distended bowel visible beneath. Physical examination also often reveals a decrease in the area of the liver dullness: this is partly attributable to atrophy and partly to intestinal distension. Hæmic murmurs may be heard over the heart which is small, while both systolic and diastolic blood pressure is lowered. On questioning, such a patient often complains of sore tongue and aphthous ulcers made worse by spiced and hot foods, of characteristic early morning stools and of abdominal distension and intestinal flatulence generally most marked towards evening and often related to the carbohydrate intake. Oedema of the feet, cramps and tetany, associated with Chvostek's and Trousseau's signs, may occasionally be observed. Paræsthesiæ are often complained of, and tendon reflexes, especially the knee-jerks, may be absent.

~ **Complications.**—Pyrexia should always arouse suspicion of some intercurrent in-



fection or complication, the commonest of which is a *Bact. coli* infection of the urinary tract. Often this infection is unassociated with fever, and in cases of advanced sprue the urine should be examined for pus cells and cultured for bacteria. Unlike pernicious anæmia, subacute combined degeneration of the cord is not encountered. Neuritic features are not uncommon, tetany with hypocalcæmia occurs in about 20 per cent. of cases, and occasionally purpuric skin eruptions are seen. Anal fissure and hæmorrhoids may develop, while venous thrombosis, eczema and pneumonia are occasionally encountered. Ulcers in the small intestine have been noted in a few cases, and perforation of the bowel has been recorded.

**Course.**—Prior to modern treatment tropical sprue generally proved to be a very chronic disease, showing spontaneous remission and exacerbations, with a tendency to natural cure only if the patient left the tropics; the disease was often fatal, the causes of death being malnutrition, anæmia and intercurrent disease.

**Diagnosis.**—The well-established case presents little difficulty, but in the initial stages and in atypical cases considerable clinical experience may be required to make a diagnosis. The differential diagnosis includes other causes of steatorrhœa such as idiopathic steatorrhœa (non-tropical sprue), gastro-colic fistula, tuberculous adenitis, lymphadenoma involving the mesenteric glands, chronic pancreatitis and carcinoma of the pancreas. Diseases like pernicious anæmia, tropical macrocytic anæmia, gastric carcinoma and Addison's disease may also need to be differentiated. A careful clinical, biochemical and radiological investigation may be essential for the differential diagnosis of conditions simulating sprue.

**Prognosis.**—This largely depends on the co-operation of the patient and the institution of combined modern treatment over an adequate period of time. In the absence of intercurrent disease or complications, patients correctly treated in England are almost invariably clinically cured, and though a proportion of them may relapse the response to subsequent treatments is equally satisfactory; sooner or later radical cure is attainable except in the aged. Unfortunately the same good prognosis cannot be given in the case of non-tropical sprue (idiopathic steatorrhœa). It is now generally permissible to let such patients return to the tropics provided they are otherwise healthy and have been free from symptoms for 6 months on a normal diet.

**Treatment.**—The essentials of treatment are: (1) The institution of alimentary rest by appropriate dietary measures and rest in bed; (2) the treatment of megalocytic anæmia; (3) the reinforcement of demonstrable deficiencies. Both in the primary attack and during relapses these asthenic, poorly nourished patients must be put to bed for 5 to 8 weeks under conditions that ensure mental as well as physical rest, while in Europe warmth and the avoidance of chill are essential. (1) *Dietary.*—Many different diets have been advocated, the best known being Manson's milk treatment and the red meat diet of Cantlie. The latter commenced with 2-oz. seeds of lean, minced, underdone steak, which were gradually increased until  $1\frac{1}{2}$  to 2 lb. were taken daily. As a result of observations on the defective absorption of fat and carbohydrate in this disease, Fairley introduced graded high protein, low fat, low carbohydrate diets, the ratios of the three fundamental foodstuffs being as 1.0 : 0.3 : 1.3 and the energy values varying from 600 to 3,000 calories. Red meat is the best source of protein when available, but the defatted dried milk powder (Sprulac) contains similar food ratios and gives very good results if used in correspondingly graded amounts. A convalescent high protein, high vitamin diet with fruit and vegetables is permitted in the fifth or sixth week, and subsequently the amount of fat and carbohydrate is gradually increased. (2) *Anæmia.*—The anæmia of sprue is megalocytic in type and almost invariably responds to adequate dosage of liver extract by mouth, provided appropriate dietetic measures are simultaneously instituted. Maximal reticulocytosis occurs about the seventh to ninth day and the blood regenerates at a rate comparable to pernicious anæmia. For the first month dried extract, equivalent to  $1\frac{1}{2}$  lb. of fresh

liver daily, should be given orally; in the second month the dosage can be reduced to the equivalent of 1 lb. daily, and in the third month to  $\frac{1}{2}$  lb. In chronic cases, which have repeatedly relapsed, a maintenance dose of  $\frac{1}{2}$  lb. liver daily may be advisable for 3 to 6 months after the blood has been restored to normal. Very rarely refractory cases are encountered in which reticulocytosis is submaximal and blood regeneration inadequate. Here oral treatment can be reinforced by parenteral injections of the more crude liver extracts such as Campolon (6 ml. daily) for 2 weeks. Davidson reports excellent results with the proteolysed liver extract Hepamino (1 oz. daily) in intractable cases. Spies and his colleagues have used folic acid as a substitute for liver therapy; a daily dose of 10 mg. given orally for 1 month is advisable, followed by a daily dose of 5 mg. for some weeks. Simultaneously a high protein diet should be administered to get the best results. Blood transfusion is only indicated in order to tide a gravely anæmic patient over the latent interval before a response to liver or folic acid therapy is obtained. The anæmia in tropical sprue is generally orthochromic or hyperchromic, but in those rare cases where hypochromia is present some complication should be suspected and iron therapy should be prescribed as well as liver extract. Also whenever the hæmopoietic response is unsatisfactory and the production of either red blood corpuscles or hæmoglobin is not maintained at a satisfactory rate, careful investigation should be made for intercurrent disease or complications. Vitamin B<sub>12</sub> may be given successfully in some cases as a substitute for folic acid or liver extracts. It should be administered as an adjuvant to dieting and not as a substitute. (3) *Treatment of demonstrable deficiencies.*—Tetany, with hypocalcæmia, calls for the administration of calcium lactate (gr. 30 thrice daily); even more important is a diet low in fat, since calcium cannot be satisfactorily absorbed when there is an excess of fat in the stools. Vitamin D in the form of calciferol may also be prescribed. Vitamin B<sub>1</sub> should be given if there is evidence of neuritis, and vitamin C if latent or overt scurvy be suspected. Many of the deficiency lesions in sprue are derived from deficiencies in the B<sub>2</sub> group of vitamins. Nicotinic acid (50 to 200 mg. daily in divided oral or parenteral doses for a week to a fortnight followed by a maintenance dose once or twice weekly) and riboflavine (3 to 5 mg. daily orally) are very effective in clearing the lesions of the mouth and tongue. The administration of vitamins will not affect the gut absorption defects. It must be regarded only as adjuvant treatment to the diet and liver therapy. Combined vitamin therapy may be given in the form of various proprietary mixtures, especially as a method of providing maintenance dosage subsequent to the use of individual vitamins.

*Bact. coli* infections of the urinary tract respond satisfactorily to sulphonamide therapy.

Once the sprue patient has regained his health he should continue with a well-balanced diet adequate in vitamins and protein, avoiding alcohol, rich, spiced and sugary foods and condiments. Aperients should be taken with caution, and care exercised to avoid chill and respiratory infection. Sprue relapses may recur after many intervening years of perfect health.

## HILL DIARRHŒA

**Definition.**—A peculiar form of gastro-intestinal derangement occurring in Europeans living at high altitudes in India, Ceylon and elsewhere during the hot season, characterised by dyspeptic symptoms, abdominal flatulence and the passage of pale-coloured or white, frothy, fluid stools early in the morning.

**Ætiology.**—The condition was often reported from the Himalayan hill stations of India during the rainy season, and the highlands of Ceylon, Europe and South America, at elevations of 6,000 feet or over. Europeans of both sexes and all ages

are liable, and in some years the condition has affected a large portion of the hill population, as in the Simla epidemic of 1880. The cause has been attributed to bacterial contamination of water with resulting infection of the bowel, as well as to a physiological breakdown of the gastro-intestinal system under conditions of low barometric pressure and high humidity. Somewhat similar epidemics were reported from Burma during the War of 1939-1945 in which classical tropical sprue supervened in some instances; here altitude was not implicated and dietary deficiency and intestinal infection were regarded as possible ætiological factors.

**Pathology.**—Little is known either of the clinical pathology or morbid anatomy of the disease, the nature of which will remain obscure until it has been adequately investigated.

**Symptoms.**—The symptoms are flatulence and abdominal distension associated with morning diarrhoea. Defæcation is urgent and generally first occurs about 5 a.m.; subsequently the bowels may be opened four or five times before noon, after which the patient is comfortable. The stools are copious, fluid, pale-coloured or white, frothy and generally not objectionable in odour. Often the condition is transient, but if it persists considerable loss of weight may ensue. The stools are said to contain an excess of fatty acids, soaps, undigested food remnants and yeasts, while stercobilin as such is either decreased or absent. These findings are similar to those encountered in tropical sprue, and in view of the marked abdominal distension, intestinal flatulence and gaseous nature of the stools, it would appear that there is defective absorption of certain food elements—especially fat and glucose.

**Prognosis.**—This is good. The only danger is that the condition may develop into sprue, and Rogers states that 20 per cent. of his Calcutta cases commenced with hill diarrhoea.

**Treatment.**—Until more is known regarding the nature of the gastro-intestinal breakdown, treatment must remain empirical. If infective in origin sulphaguanidine or other sulphonamides might well be beneficial. On the other hand, if the gastro-intestinal breakdown is associated with defective alimentary secretion and absorption, bed rest, a high protein diet such as Sprulac and liver extract or folic acid therapy would be advisable.

N. HAMILTON FAIRLEY.

## COLON NEUROSIS

**Synonyms.**—Colon Spasm; Muco-Membranous Colic; Irritable Colon.

Intermittent painful spasm of parts of the colon is a common condition in nervous people. Formerly it was frequently associated with the passage of membranes of coagulated mucus, but for no obvious reason this condition has become rare since 1914. It was commonly known as muco-membranous colitis, but as endoscopic examination showed a healthy mucous membrane and the mucus contains no inflammatory cells unless the patient has been injudiciously treated with irritating purgatives or douches, muco-membranous colic is a more appropriate name. In rare cases of allergic origin large numbers of eosinophil cells, sometimes with red blood corpuscles, are present in the mucus.

**Ætiology.**—Colon spasm occurs, especially in nervous individuals, in times of anxiety. It is a psychosomatic disorder, being primarily an exaggeration of normal function, with colon motility becoming disordered and inco-ordinated, and the mucus secretion increased. It is slightly more frequent in women than in men, and is especially found in sedentary rather than manual workers; it occurs particularly amongst those who have a hard struggle in life to maintain their positions or responsibilities. Colon spasm is aggravated by unsuitable food, irritating purgatives, over-

smoking and in some cases by allergic, endocrine or reflex organic causes such as cholecystitis or appendicitis.

In all cases the underlying mechanism is an undue irritability of the neuromuscular mechanism of the colon, mainly brought about by psychological causes, particularly fears, and is one manifestation of an anxiety state. Previous organic colon disease, such as bacillary or amœbic dysentery, may also markedly predispose to colon spasm.

**Symptoms.**—In some cases the patient suffers continuously from abdominal discomfort. In others definite attacks, which are often emotional in origin, occur at intervals of weeks or months. The pain is situated most frequently in the left flank and iliac fossa, and just above the pubes. At the same time the descending and iliac colon are often tender and can be felt as a contracted cord, in which scybala can sometimes be distinguished. Less frequently there is pain and tenderness in the cæcum and ascending colon, which are felt to be more firmly contracted than usual; the condition may then closely simulate appendicitis, but no improvement follows appendectomy. The passage of fæces sometimes gives temporary relief.

The constipation present in the intervals becomes much more severe during an attack. The stools consist of hard, small scybala, which are occasionally moulded into flat pieces as a result of anal spasm. In muco-membranous colic the mucus is passed as very thin membranous shreds, which may form long tubular casts of the colon, which are sometimes rolled into a ball. The mucus may be transparent or opaque or grey-white. The membranes may be passed alone or with scybala, the passage often relieving the pain. They are sometimes mistaken for shreds of mucous membrane or tape-worms.

Various symptoms resulting from the associated neurosis are generally present, and the patient tends to become depressed and hypochondriacal.

Intestinal sand, formed of brown granules, irregular in shape and never crystalline, composed of calcium soaps of palmitic and stearic acid and calcium phosphate, is occasionally passed, most frequently in association with mucous casts. It must be distinguished from fragments of wood cells passed after eating excess of pears or bananas.

**Diagnosis.**—It is very important to exclude the spasm which results from organic diseases such as ulcerative colitis, diverticulitis and carcinoma before diagnosing a colon neurosis. A rectal and proctoscopic examination should always be made to exclude local conditions, such as fissure, hæmorrhoids or rectal polypi.

A barium meal usually shows no bowel stasis and a normal intestinal passage except for a streak-like shadow in the descending and sigmoid colon due to spasm.

**Treatment.**—Treatment should primarily be directed to dealing with the underlying nervous condition by means of simple psychotherapy. The patient should be discouraged from examining his stools. Aperients should be avoided, as they tend to aggravate the spasm, but the stools should be kept sufficiently soft by means of vegetable mucilages or paraffin (see p. 608). Smoking should be restricted and, if it has been excessive, should be entirely prohibited. A full diet should be given, excluding only the coarser forms of "roughage", and care must be taken not to restrict too readily items of food which the patient believes she is unable to digest.

Treatment by colon lavage should only be ordered at the start of treatment and then only with considerable care: it makes the patient too bowel-conscious and upsets its normal rhythm. Most of the mucus it brings away is what has been secreted as a protective action of the mucous membrane.

The use of bowel antiseptics is not indicated, and the search for any special food sensitisation is only rarely successful, both skin tests and food elimination diets proving disappointing.

# PAROXYSMAL PROCTALGIA (PROCTALGIA FUGAX)

The term paroxysmal proctalgia which, as pointed out by Ryle, is preferable to proctalgia fugax is given to a condition in which short attacks of very severe pain occur in the rectum without demonstrable cause.

**Ætiology.**—The condition occurs most frequently in men, particularly doctors, and more often in sedentary than in manual workers. Attacks are specially apt to come on at night and during periods of worry, hard mental work or fatigue. They are often associated with migraine and nervous colon disorders, but are unrelated to hæmorrhoids, fissures, polyps or any other organic disease of the rectum or anus. The condition is almost certainly a violent cramp of the muscles around the rectum or of the rectal muscle itself, and most often begins after the age of 30. It should be regarded as a manifestation of a visceral neurosis but may occur, like cramps in other muscles of the body, without proved psychological cause, when it may possibly be due to unrecognised biochemical changes.

**Symptoms.**—The patient wakes with severe pain in the rectum, which rapidly reaches an intense climax and continues for 5 to 10 minutes, during which the sufferer sweats and groans in violent agony. There is no diarrhœa or vomiting, and nothing abnormal can be found on rectal examination. All investigations prove completely negative, including sigmoidoscopy and radiological examination.

**Treatment.**—The main essential in treatment is the diagnosis, since patients often believe that some serious disease is present. In the attack firm upward pressure on the sphincter ani was recommended by Ryle, or the injection into the rectum of cold water or air may often be successful. Amyl nitrite is ineffective, and morphine is to be avoided if possible. Measures towards relief of the patient's fatigue or anxiety and general health are important, and over-straining at stool or intense physical exercise with much sweating and salt deprivation are to be avoided.

# INTESTINAL CARBOHYDRATE DYSPEPSIA

**Definition.**—Intestinal carbohydrate dyspepsia is a condition in which discomfort results from the presence of excess gas in the colon, owing to the fermentation of carbohydrates which have escaped digestion in the small intestines.

**Ætiology.**—Under normal conditions starch is digested by the ptyalin of the saliva and the amylopsin of the pancreatic juice. The ptyalin is the less important, as it is rapidly destroyed by the first trace of free hydrochloric acid with which it comes into contact in the stomach. Normally starch is completely digested in the upper part of the small intestine so that very little reaches the terminal ileum and none reaches the cæcum. When the rate of passage through the small intestine is excessive, there is time for free starch to be digested, but the starch in intact cells reaches the terminal ileum and cæcum unaltered. Here the amylopsin penetrates the cells, and the sugars pass into the surrounding media, where they are attacked by bacteria, which are present in very large numbers, and undergo fermentation before there is time for much absorption to take place. The symptoms of intestinal carbohydrate dyspepsia are caused by the carbon dioxide and acetic and butyric acids produced by this fermentation. In some cases there is a history of food-poisoning or of some intestinal infection which has caused enteritis. The latter may still be present, but more commonly it has given place to a functional irritability of the small intestine, which results in excessive motor activity. In other cases an obvious or repressed emotional cause has given rise to the initial intestinal hurry.

**Symptoms.**—The chief symptom of intestinal carbohydrate dyspepsia is a widespread feeling of discomfort and fullness in the lower part of the abdomen, caused

by distension of the colon with gas. Gas in the terminal ileum may cause pain round the umbilicus. During the day gas often collects in the splenic flexure, which is the highest point in the colon; the discomfort produced in this way may be mistaken by the patient for gastric flatulence, and aerophagy often results from his attempt to relieve himself by belching. During the night the gas passes to the rectum, which is then as high as any other part of the colon; consequently the greater part is passed during the night and on waking in the morning. The discomfort is generally increased by meals as a result of exaggeration of the gastro-colic reflex. It is often greatest during the night, and is a common cause of insomnia. The excess of gas produces borborygmi, the noise of which may itself be enough to keep a patient awake. The distension of the bowel caused by the gas and the irritation of the mucous membrane by the organic acids may cause spasm; the patient then complains of acute pain. Excessive quantities of odourless flatus are passed, and some relief is always felt after its escape.

The abnormally rapid passage of the chyme through the small intestine can be demonstrated radiographically, even when the irritation of the colon is insufficient to cause any diarrhœa, and the radiograph shows no change in the normal rate of passage through the colon. Excess of gas can be seen to be present in the colon and terminal ileum. In severe cases attacks of mild diarrhœa are common, much gas being always passed with the stools, which are acid and have an unpleasant sour, but not putrefactive, odour. Very acid stools may give rise to a burning sensation in the anal canal. The diarrhœic stools contain an obvious excess of undigested vegetable matter, and bubbles of gas may continue to form as a result of fermentation of undigested starch.

A fresh stool should be examined whilst the patient is on his usual diet. The microscope reveals the presence of large numbers of starch granules, which are still within their cellulose envelopes and stain blue with iodine. Few or none are present in normal fæces. In contrast with the stools in pancreatic deficiency there is no excess of fat or striated muscle fibres. The normal enterococci of the colon are present in considerable excess, but the number of *Bact. coli* is not increased and no pathogenic organisms are found. On giving a starch-free diet the excess of enterococci rapidly disappears, being not a cause of the condition, but the result of the excellent culture medium afforded by the excess of carbohydrates present. If a small quantity of fresh fæces is mixed with water and incubated for 24 hours, much odourless gas is evolved and can be collected, the fæces becoming very acid. No gas is evolved from normal stools. If the examination of a stool is delayed for 6 hours or more, all undigested starch may have disappeared and no further gas is evolved on incubation. In the much less common putrefactive diarrhœa, which is caused by insufficient digestion of meat, a smaller quantity of foul gas is evolved and the fæces become strongly alkaline.

**Treatment.**—All root vegetables (potatoes, carrots, onions, beetroot, artichokes, parsnips), green peas and lentils, bananas, rice, tapioca and sago and porridge are prohibited. Bread, toast and biscuits, and puddings containing starch are allowed in small quantities, and there is no need to restrict the intake of sugar. If diarrhœa is present, it is necessary at first to exclude all vegetables and fruit, whether cooked or raw. Within a week the excess of enterococci disappears from the stools, which no longer ferment on incubation. It may be necessary to avoid potatoes and other root vegetables for a considerable period and sometimes permanently.

If a diastatic ferment of vegetable origin is taken with each meal, less restriction in diet is required, as in contrast with the amylase of pancreatic preparations it is very slowly destroyed by the gastric juice so that more digestion of starch can occur in the stomach. It helps particularly in the digestion of prepared starch, and allows more bread to be taken than would otherwise be possible. It is much better to prevent the production of gas than to try to provide for its absorption by such

substances as charcoal, but a sedative such as phenobarbitone, which helps to slow down intestinal hurry may be of assistance in a dose of gr.  $\frac{1}{2}$  two or three times a day.

## ORGANIC DISEASES OF THE INTESTINES

### ENTERITIS

#### ACUTE ENTERITIS

Acute enteritis forms part of the picture in most cases of acute food poisoning (see page 119). Acute gastritis may be present alone when vomiting is severe; more commonly gastro-enteritis occurs with diarrhoea with or without vomiting. The poison is generally so diluted when the colon is reached and its evacuation is so rapid that the colon escapes and gastro-entero-colitis is consequently less frequent. Acute enteritis may also accompany the gastritis of acute infections, such as influenza, and occurs in such conditions as uræmia, as well as from the use of many drugs and chemical irritants.

#### CHRONIC ENTERITIS

Chronic enteritis is a common sequel of acute gastro-enteritis caused by food poisoning and acute infections. It may follow infestation with worms, especially tapeworms. It is frequently caused by indigestible food, especially among people who take excess of "roughage" in the mistaken belief that it is good for their health. The small intestines are sometimes irritated by food which reaches them without undergoing the normal preparation in the stomach in achlorhydria, and after gastro-enterostomy and partial gastrectomy. Chronic enteritis is frequently caused by irritation produced by the habitual use of aperients, psyllium seeds and drugs such as iron and arsenic. The loss of the antiseptic acid barrier of the gastric juice in achlorhydria may lead to infection of the small intestines by swallowed bacteria when oral and naso-pharyngeal sepsis is present. Lastly, the stasis which results from chronic small intestine obstruction leads to a great increase in bacterial activity with the production of chemical irritants which cause severe enteritis. This explains why diarrhoea is commonly present instead of constipation in chronic obstruction of the small intestine.

As the chief symptom of enteritis is diarrhoea, the diagnosis and treatment of which are considered on pp. 611, 613, it is unnecessary to give a separate description here, but see Tuberculous Enteritis and Typhoid Fever.

### REGIONAL ILEITIS

**Synonym.**—Crohn's Disease.

**Ætiology.**—Regional ileitis is by no means rare. It occurs between the ages of 4 and 40 and is most common in young adults. Males are more often affected than females.

**Morbid Anatomy.**—The terminal part of the ileum is generally first involved. The disease may spread into the cæcum, and any part of the small intestine and colon may be attacked, sometimes with segments of healthy bowel intervening. The mucous membrane is inflamed and eventually ulcerates, and all the coats of the affected segment become thick, œdematous and rigid. Active inflammation is followed by

is generally present, mucus and occasionally traces of blood being found in the fluid stools, but there is no excess of food residue unless enteritis is also present.

The presence of mucus in the stools is often regarded as sufficient evidence to prove that colitis is present. But it is a function of the healthy mucous membrane to secrete mucus to protect itself against mechanical and chemical irritants. Consequently the unformed, clear mucus passed with hard faeces in constipation does not indicate that colitis or proctitis is present, and the same is true of the mucus passed with fluid stools, when irritating aperients have been taken. On the other hand, pus and red blood corpuscles generally indicate the presence of either ulcerative colitis or carcinoma, though the possibility of hæmorrhoids or polypoid adenoma as the source of the latter must, of course, be remembered.

**Treatment.**—The food must be thoroughly masticated and should be of an unirritating character. The use of purgatives should be avoided, though liquid paraffin or a vegetable mucilage should be given if hard scybala are passed. In infective colitis a liquid culture of *Lactobacillus acidophilus* may be tried, and a mixture of kaolin and belladonna should be given before meals with the addition, if diarrhœa persists, of codeine.

### ULCERATIVE COLITIS

**Definition.**—Ulcerative colitis is a severe inflammatory disorder of part or all of the colon, characterised by rectal discharge of blood, mucus and pus, and constitutional disturbances, such as fever, secondary anæmia, dehydration, prostration and loss of weight.

**Ætiology.**—Ulcerative colitis affects mainly young people, more than half the cases beginning below the age of 30. It occurs particularly in sensitive, shy, over-conscientious and emotionally immature individuals, and has undoubtedly a very large psychological background in its causation. A direct onset following severe emotional shock can quite often be elicited, and the disease tends to run a long course with periods of freedom and relapse very similar to that of peptic ulcer. Exacerbations often follow a time of anxiety or emotional disturbance, and experimentally such stimuli can be shown to cause mucosal congestion and muscular spasm in the colon. In one type of case, usually beginning in older people, a long history of constipation and abuse of laxatives precedes the onset of ulcerative colitis. In others the condition undoubtedly supervenes as a form of chronic diarrhœa after an attack of proved bacillary dysentery. Bacteriological examination of the stools has hitherto failed to identify any specific organisms as a cause of ulcerative colitis, though dysenteric, streptococcal and parenteric organisms have all at one time been regarded as causative agents; no good evidence incriminating a virus infection has yet been produced.

In rare cases an appearance similar to ulcerative colitis results from allergy, but the mucus then usually contains many eosinophil cells and little or no pus. Vitamin deficiency from injudicious dieting over prolonged periods may aggravate the colitis, but it is never the primary cause.

**Symptoms.**—The onset is sometimes acute with severe diarrhœa and fever. More commonly it is subacute and insidious, the first symptom noticed being the passage of blood and mucus, with or without diarrhœa. Even in cases which appear to begin acutely a history can often be obtained of slight intestinal irregularity with the occasional passage of mucus or blood for many months or even years before the onset of severe symptoms.

Diarrhœa is always present; there may be as many as twenty stools, most of which are quite small, in the day. Blood, pus and mucus are passed, with semi-fluid faeces and also alone. In quiescent periods they may appear to be absent, but microscopical examination of the stools shows that this is not the case. Blood may be passed in large quantities by itself, but it is generally mixed more or less intimately with the mucus and pus. It is bright red, and the stools are never black and tarry as are seen



with gastric and duodenal ulcer. It is mostly fluid, but small clots are often present. The mucus is clear, or opaque owing to the presence of pus; membranes are never passed. In most cases small collections of pus are easily recognised with the naked eye in addition to that mixed with the mucus and unformed faeces.

Abdominal discomfort is often, but not always, present. Any severe pain is rare except immediately before defecation, when colic may occur; this disappears as soon as the bowels are opened, especially if flatus is passed. Tenesmus is unusual and occurs only if the anal canal is involved. The abdomen is often retracted. In acute cases and acute exacerbations, however, it may be distended, a sign of some gravity. Tenderness is often completely absent, even in severe cases, but pressure over the colon, especially in the left iliac fossa, may cause discomfort. When the tenderness is considerable, the inflammation has generally spread to the peritoneum and local peritonitis is present. A moderate degree of muscular rigidity is often found in severe cases, especially if there is any local peritonitis.

In acute cases, and in acute exacerbations of more chronic cases, irregular fever is generally present. Apart from this, the patient has generally a good appetite. The constant diarrhoea leads to progressive emaciation and weakness; but in mild cases the patient may feel so well that he is unwilling to undergo treatment in bed. The loss of blood leads to secondary anaemia, which may be severe; the haemoglobin is often only 50 per cent. of normal, and may fall to 20 per cent. In such cases oedema of the ankles and ascites may develop as a result of hypoproteinaemia.

**Complications.**—In the course of healing, strictures, which may be multiple and of considerable length, may develop, especially in cases of long standing. The symptoms do not alter with the development of the strictures, as the stools are so soft that they pass without difficulty through the narrowed bowel. A narrowing can sometimes be recognised with the sigmoidoscope, but the exact degree and localisation can only be discovered with the aid of the radiogram. A stricture does not require surgery unless it causes sufficient stasis to be recognised with an opaque meal as well as with an enema. Radiography also gives an indication of the extent of colon involved, as the normal "haustration" produced by the constant activity of the muscularis mucosae disappears when it is paralysed by inflammation spreading from the mucous membrane to the submucous tissue. In the majority of early cases the distal half of the colon or the pelvic colon and rectum are alone affected. In addition to the absence of haustration the normal mucosal relief pattern is lost and the outline of the narrow tubular colon may be made ragged by the craters of multiple ulcers. A barium enema must be given with care during an acute phase of the disease, and the rubber tube should be soft and introduced not more than 2 in. from the anus in order to avoid damaging the inflamed rectal mucosa. Healing may also be associated with the development of multiple small polypi from tags of inflamed mucous membrane. They may closely resemble adenomatous polypi to the naked eye, but it is doubtful whether true adenomata ever develop from them. They may, however, undergo malignant degeneration, and secondary carcinoma develops in some 5 to 8 per cent. of all cases of chronic ulcerative colitis.

General peritonitis is a very rare complication, and may be caused either by perforation or direct spread of infection through the wall of the colon. Localised abscesses are also unusual, but may give rise to multiple fistulae-in-ano if they occur in the perianal region.

Non-suppurative multiple arthritis may develop, as it does in bacillary dysentery. Clubbing of the fingers may occur.

**Diagnosis.**—The association of blood in the stools with pus and mucus indicates the presence of an ulcerative lesion in the colon, or of a growth of the pelvic colon or rectum. The latter can usually be excluded by rectal and abdominal palpation, and by the sigmoidoscope. Even if the growth is too high to be reached by the instrument, its presence is rendered very probable when the accessible part of the

colon appears normal, and blood, mucus and pus are seen coming from above. The instrument should be passed with care under visual guidance and without much air inflation; no anæsthetic is required and no force should be used. If there is much difficulty or pain in carrying out the investigation it should be abandoned. In ulcerative colitis the mucous membrane is bright red, thick and sometimes granular. It bleeds very readily when touched, and small submucous hæmorrhages are frequently seen. Its surface is covered with blood-stained, purulent mucus, some of which should be removed on a sterile swab for bacteriological and cytological examination. Superficial ulcers are invariably present; but in early cases they may be so small that they are difficult to recognise without a magnifying eyepiece. Later they are large, and are sometimes so extensive that only small islets of mucous membrane are left, which may feel like small, flat polypi on rectal examination, the floor of the confluent ulcers being mistaken for the surface of the mucous membrane. The ulcers are always superficial, with irregular edges; the thick mucous membrane may be undermined. The floor of the ulcers appears greyish-yellow when the blood and mucus are wiped from their surface.

If the patient has been in the East the possibility of amœbic dysentery should be considered, though the absence of such a history does not exclude it, as cases may occur in people who have never been out of England. The endoscopic appearance is so distinct that a definite diagnosis can usually be made from this alone. Small, round, red elevations are seen on the otherwise normal-looking mucous membrane, corresponding with the collection of broken-down material in the submucous tissue caused by the invasion of *Entamœba histolytica*. In the centre of each elevation is a depressed yellowish ulcer, where the submucous abscess has broken through the mucous membrane.

Other conditions which may give rise to difficulty in diagnosis are intestinal tuberculosis (*q.v.*), the hæmorrhagic blood diseases, or a foreign body in the rectum.

**Prognosis.**—Very acute ulcerative colitis may cause death in a few weeks. More commonly, it becomes chronic with periodic acute exacerbations, and thus approximates to the ordinary form of ulcerative colitis, in which the onset is insidious and the course very prolonged. In a few cases complete and lasting recovery occurs. The mortality of all cases is between 10 and 15 per cent. Death is generally the result of exhaustion from prolonged diarrhœa, anæmia caused by constant bleeding, and toxæmia.

The commonest cause of relapse is anxiety, which may be either prolonged or acute, when the return of severe symptoms may be quite sudden. Relapses may also occur with acute infections, especially tonsillitis, and with food poisoning, dietetic indiscretions, exposure to cold and damp, and fatigue from mental or physical overwork.

**Treatment.**—(a) **GENERAL.**—The most important factors in the successful treatment of ulcerative colitis are confidence, patience and perseverance on the part of both doctor and patient. Even in early cases several weeks of strict treatment are generally required, and in chronic and late cases very much longer periods, up to many months, may be necessary. The patient should be kept at rest in bed as long as there is pyrexia and whilst there is much diarrhœa, but fresh air and some form of occupational therapy are most important during this time. A warm bath once a day may be allowed except during the most acute phase.

(b) **PSYCHOTHERAPY.**—Attention must be paid to the emotional make-up of the patient and dramatic improvement may follow the physician's simple reassurance, encouragement and explanation of the psychological problems which may be affecting the case. Very much more specialised and prolonged psychological treatment has also been widely advocated in early cases, especially by American writers. Many remarkable recoveries in ulcerative colitis have undoubtedly been due to suggestion and the enthusiasm of the physician in some particular form of remedy.

(c) **DIET.**—Too limited a diet results not only in loss of weight and strength,

but the food may contain insufficient iron to compensate for the loss of blood in the stools so that microcytic anæmia develops. The anæmia, malnutrition, and particularly deficiency in vitamins aggravate the colitis, and may lead to serious cutaneous and other complications, all of which respond rapidly to a change to a more liberal diet. Patients with ulcerative colitis often have quite a good appetite, and there is no reason for limiting their allowance of meat and other foods containing no indigestible residue. Indeed a high calorie and high protein diet is advisable, and extra vitamins, particularly ascorbic acid, 100 mg. daily, and the B. complex, especially nicotinic acid, 150 mg. daily, should be ordered. Fruit is best given in the form of juice and strained purées, and green vegetables as purées. Marmite is a valuable addition. Nuts, pips and foods with a hard residue should be avoided.

(d) **LOCAL TREATMENT TO THE COLON.**—Colon lavage is little used, and rectal injection of penicillin or sulphonamide drugs have on the whole proved disappointing and less successful than when given systemically; the host of other antiseptic solutions that have at different times been advocated have probably only a mechanical effect in washing away bowel debris. Any large rectal wash-out is likely to cause serious discomfort or even danger.

(e) The *Sulphonamide* drugs have on the whole given disappointing results but a course of succinylsulphathiazole, 24 g. a day for 5 days, or phthalylsulphathiazole, 12 g. daily for 5 days, each given at 3-hourly intervals is sometimes followed by a brilliant result.

*Penicillin* has been used in a number of cases, and is worthy of trial. Approximately one-third of the cases may be expected to benefit temporarily, the effect probably being largely through relief of secondary streptococcal and other infection. Penicillin should be given intramuscularly in a dosage of not less than 500,000 units twice daily for 5 to 7 days; rectal injection of a similar quantity once a day dissolved in 5 oz. of saline may be combined with systemic administration. *Chlortetracycline* and other antibiotics may sometimes be of help, but more often prove disappointing.

(f) *Cortisone* and *corticotrophin* have been the subject of extensive therapeutic trials, and in primary attacks 200 to 300 mg. of cortisone daily for 3 to 6 weeks has given excellent results in about half the cases treated.

(g) **BLOOD TRANSFUSION.**—Most patients with ulcerative colitis are anæmic. If this is marked a large transfusion of 3 or 4 pints given slowly by drip is advisable. In less severe cases smaller and repeated transfusions are very valuable, and not only improve the patient's general condition but often seem to hasten healing of the colon. It may be worth advising a blood transfusion in cases in which the anæmia is slight or even absent altogether. Iron in the form of ferri et ammonium citrate, gr. 30 four times a day, may be given even in acute cases.

The improvements reported following the use of vaccines, bacteriophage, intestinal mucosal extracts, thiouracil, folic acid and numerous other substances have probably been mainly due to spontaneous remissions, perhaps partly as a result of the doctor's own enthusiasm.

(h) **SYMPTOMATIC TREATMENT.**—When the diarrhoea is severe the patient is likely to become exhausted by want of sleep. A dose of codeine sufficient to keep the bowels from acting more than once in the night should be given at 10 p.m. and a smaller dose before meals two or three times a day. A barbiturate such as phenobarbitone gr. 2 or 3, may also be safely used at night, but opium may be essential and should be administered as the tinct. opii min. 10 to 20 in a bismuth mixture. Injections of morphine should be avoided if possible. Pain is not a common complaint in ulcerative colitis, though severe colic due to distension of the bowel with gas may occur shortly before the bowels act. A mixture containing belladonna, min. 5 to 20, with tr. chloroformi et morphinæ Co. min. 5 and kaolin half an ounce as required may relieve these attacks, and the dose of belladonna may be increased until the mouth begins to become uncomfortably dry.

(f) **AFTER-TREATMENT.**—The danger of recurrence is reduced if treatment is continued until sigmoidoscopy shows no inflammation, even if symptoms have already disappeared for some weeks. Associated conditions, such as oral and pharyngeal infections and anal complications, must be treated, as a relapse may follow an acute sore throat or the development of a peri-anal abscess or fistula-in-ano. Cold and chill are particularly to be avoided. The patient should keep permanently on a low roughage diet and, when necessary, take sufficient Isogel or paraffin to keep his stools soft. He should be helped to solve any problems connected with his home, his business or other matters which are causing anxiety, as there is no doubt about the importance of psychological factors in causing relapse and recurrence.

(g) **SURGERY.**—The possibility of surgical treatment should be considered in every case. It has in the past been undertaken mainly for intractable chronic cases which have been wholly incapacitated for many months or years, but it also has an important place in the treatment of earlier cases which do not respond to medical treatment.

An ileostomy affords complete rest to the colon, and the constant irritation of the mucosa by faeces and decomposing inflammatory exudate, and the frequent peristalsis and spasm which it causes are prevented. The main indications for the operation are as follows :

- (1) In the very rare fulminating cases with high temperature and passage of large quantities of pus and blood, when it offers the only good chance of recovery. The mortality of such cases is high, but if the patient survives the operation, improvement is remarkably rapid.
- (2) When continuous treatment under good conditions for some months has led to little or no improvement, or the patient over the years has become a chronic invalid.
- (3) When fibrous strictures, polypi, fistulae or severe perianal infection has developed.
- (4) In cases of progressive arthritis.
- (5) When severe hæmorrhage is recurrent.
- (6) If malignant degeneration has occurred or is suspected.

If surgery is decided upon, the objective should be total removal of the diseased colon : segmental removal is rarely of lasting benefit. In some cases a combined colectomy and ileostomy may be performed at a single operation, but more usually a preliminary ileostomy is needed. In this case about 1 to 2 in. of ileum are brought out beyond the abdominal wall and a bag is cemented to the skin so that no leakage occurs around the opening. As a rule this causes patients surprisingly little difficulty or inconvenience and they may lead fully normal and active lives.

After the ileostomy has been well established, the final stages of colectomy and perhaps an ultimate abdomino-perineal resection of the rectum should be advised owing to the appreciable risk of malignant degeneration occurring in the diseased colon. This is especially necessary if any strictures or polypi are present. In a few cases it is possible to anastomose the ileum to the rectum provided the latter is sufficiently free from disease.

## TUBERCULOUS ENTERITIS AND COLITIS

**Ætiology.**—Miliary tubercles may be present in the intestines in general tuberculosis, but they have no clinical importance. Primary infection of the bowels from tuberculous milk is not infrequent in children, but is comparatively rare in adults. Secondary infection from swallowing tuberculous sputum is very common, ulceration being present in from half to three-quarters of all fatal cases of pulmonary tuberculosis. The lower end of the ileum and the cæcum, where the rapid passage of chyme along the alimentary tract is first arrested so that there is time for the muco-pus in which

the tubercle bacilli of the sputum are enmeshed to be digested, are the parts most frequently affected.

**Symptoms and Diagnosis.**—In at least one quarter of the cases no symptoms are present, although extensive ulceration may be found post mortem; in the reverse manner, too, it must be remembered that digestive symptoms are very frequent in cases of pulmonary tuberculosis without any organic intestinal lesion being present. Tuberculous enteritis should be suspected in children suffering from diarrhoea with fever, abdominal distension, enlarged glands, anaemia, wasting and weakness. It should also be suspected when pulmonary tuberculosis is associated with diarrhoea, especially if abdominal pain and tenderness are present and blood is found in the stools. A bad general condition in combination with an apparently not bad pulmonary condition is always suggestive of an intestinal infection. Tubercle bacilli are often present in the stools as a result of swallowing infected sputum even with healthy intestines. In the absence of abdominal pain the diarrhoea in advanced phthisis is sometimes due to the achlorhydria which is commonly present, and as a general rule diarrhoea is a late occurrence in tuberculous enteritis and often indicates an associated involvement of the colon.

The diagnosis may be impossible to make with certainty clinically unless a tumour is present in the right iliac fossa, and this does not occur in more than 30 per cent. of cases at the most. Radiography is often able to provide a definite diagnosis, but in some cases no abnormal changes in the small intestine can be made out at all. A slight or moderate enlargement of the liver is present in rather less than half the cases.

Perforation of a tuberculous ulcer is rare owing to the adhesions which form between the coils of intestine. Cicatrisation of ulcers may lead to single or multiple strictures of the small intestines; as these are incomplete and the contents of the bowel are fluid, obstruction is rarely produced. External adhesions and the formation of bands may, however, lead to acute intestinal obstruction.

What has been described in the past as *hyperplastic tuberculosis of the caecum* is probably a form of regional ileitis (p. 631) in which the caecum is involved as well as the end of the ileum. It was always recognised that the condition was not associated with tuberculous foci elsewhere and tubercle bacilli were never found in the stools; there was in fact no evidence that the condition was tuberculous in origin.

**Treatment.**—The treatment is that of tuberculosis in general, combined with the dietetic restrictions required for non-tuberculous enterocolitis. Especial care should be taken to avoid the swallowing of sputum, and hydrochloric acid may be given with meals, as for achlorhydric gastritis.

## POLYPI OF THE COLON: POLYPOSIS

**Ætiology and Pathology.**—Solitary polypi of the colon are common and cases with two to twelve or more are not infrequent. Most of these polyps are simple adenomata, and it is estimated from post-mortem studies that they are present in approximately one in every ten people. True polyposis, in which the whole or part of the colon is studded with innumerable polypoid adenomata, is very rare. Most cases of primary generalised polyposis are familial, several members of one or more generations of a family being affected. Less frequently single polypi are also familial. Males are more often affected than females, and the symptoms generally begin before the age of 30.

The polypi usually commence as small flat patches of mucosal overgrowth which soon become polypoid. The polypi which develop in the process of recovery from ulcerative colitis are inflammatory in origin and are not adenomata. They are generally present in small numbers but occasionally a condition simulating generalised polyposis develops.

Both single and multiple polypi show a considerable tendency to become malignant, and the majority of patients with familial polyposis ultimately die of carcinoma. In some cases of carcinoma of the rectum and colon the lesion is grafted on a simple polypous adenoma, but in some 4,000 cases of rectal and colon cancer examined at St. Mark's Hospital, not more than 1 per cent. showed true polyposis. In early cases of carcinoma an adenomatous origin can sometimes be recognised and in some cases of cancer of the bowel simple adenomata are also coexistent.

**Symptoms.**—Recurrent passage of bright-red blood, unmixed with mucus or pus, sometimes with and sometimes independent of faeces, is generally the first and often the only symptom. In adults internal hæmorrhoids give rise to similar symptoms, but in children polypi are the only common cause. In polyposis diarrhoea develops sooner or later as a result of secondary infection and inflammation, and the fluid faeces are mixed with mucus, pus and bright blood, being indistinguishable from those passed in ulcerative colitis. The hæmorrhage may lead to severe anaemia, and the diarrhoea to malnutrition and, when it begins in childhood, to infantilism. Tenesmus and abdominal pain are uncommon.

The polypi can often be felt on rectal examination and can generally be seen with a proctoscope or sigmoidoscope, but occasionally they are situated too far from the anus, when radiography is the only means of making a definite diagnosis. Their exact extent can be estimated by means of an opaque enema which gives a characteristic picture, showing rounded semi-translucent areas in the shadow of the colon. Sometimes they are best demonstrated by inflation of the colon with air after the greater part of the opaque enema has been evacuated.

Polypi are the most common cause of chronic intussusception.

**Treatment.**—Single and multiple polypi in the rectum and pelvic colon can be removed with a diathermy snare or destroyed by a diathermy cautery through a proctoscope or sigmoidoscope. The specimen must be examined histologically, and further surgical treatment undertaken at once if any evidence of malignant change is found. The patient should be re-examined every 3 months for at least 10 years, so that any new polypi which develop can be destroyed before they have time to undergo malignant degeneration. Multiple small polypi sometimes disappear when treated with X-rays. When the whole colon is involved, the terminal ileum should be anastomosed with the lower end of the pelvic colon, the rest of the colon being excised. The polypi present in the remaining part of the pelvic colon and in the rectum are removed or destroyed by diathermy.

## CANCER OF THE COLON

**Ætiology.**—Primary columnar-celled carcinoma of the colon attacks men with slightly greater frequency than women. It is most common between the ages of 40 and 65, although cases have been recorded in early childhood.

**Pathology.**—Only a little over 1 per cent. of cases of intestinal cancer affect the small intestine. Of the remainder 50 per cent. are in the rectum and at the pelvic-rectal flexure, and 25 per cent. in the iliac and pelvic colon; thus 75 per cent. of cases occur in parts of the colon where the faeces are solid. Nearly half of the remainder are in the caecum and ascending colon. The majority of the cancers are of the scirrhus type with much fibrosis, but those in the right half of the colon are frequently of colloid type with great production of mucous material.

Extension to the peritoneum and secondary deposits in the lymphatic glands, liver and other organs develop later and rather less frequently with cancer of the intestine than with cancer in most other situations, obstruction occurring in more than 50 per cent. of cases before the glands are involved. The prospect of a radical cure by operation, if an early diagnosis is made, is therefore comparatively good.

The rectum has a moderate supply of lymphatics and gives operative results intermediate between gastric and colonic carcinoma.

**Symptoms.**—The average age of onset of carcinoma of the colon and rectum is between 55 and 60, but the possibility of its presence should be considered whenever an individual over the age of 35, whose bowels have previously been regular, develops constipation or diarrhœa without change of diet or habits, or when a patient of the same age, who is habitually constipated, becomes more so without obvious reason. Constipation occurs earliest in the common annular form of intestinal cancer, which narrows the circumference of the bowel while the actual size of the growth is still very small. Less obstruction is caused by papillomatous carcinoma, which forms a friable and ulcerated mass, projecting into, but not obliterating, the intestinal lumen. Constipation is at first intermittent and relieved by purgatives, which gradually become less effective and cause more pain. Enemata are generally of use for a longer period, but they also finally fail to act. Sometimes, however, there is persistent diarrhœa from the start, especially when the growth is situated in the pelvic colon. More frequently the initial constipation is interrupted by attacks of diarrhœa. In the majority of cases the constipation becomes steadily more severe until it ends in complete obstruction, which is sometimes hastened by the impaction of a hard mass of fæces in the narrowed lumen.

The stools do not generally differ in shape from those seen in ordinary constipation. Occasionally thin pieces, resembling the fæces formed in some cases of constipation associated with spasm, are passed, especially when the growth is in the pelvic colon or in the rectum; they sometimes owe their shape to spasm of the anal sphincter, produced reflexly by the growth or by the irritating discharge from its surface, but may be due to a stricture well above the anus. The stools in cancer of the rectum and lower part of the pelvic colon generally contain obvious blood, pus and mucus. In rare cases the passage of a large quantity of bright-red blood is the first symptom. The stools may closely resemble those of simple ulcerative colitis, but faecal matter is often absent and fragments of more or less solid fæces can sometimes be recognised, whereas in ulcerative colitis unformed fæces are almost always present. When the growth is proximal to the middle of the pelvic colon, blood and pus can rarely be recognised with the naked eye, but occult blood can almost always be found by the guaiac test.

Vague discomfort in the lower part of the abdomen is often present, sometimes without any irregularity of the bowels, and slight attacks of colic occur when constipation becomes severe, but they rarely reach any great intensity until the obstruction is almost complete. In some cases the pain is in the region of the growth, or it may travel towards this point, where the patient occasionally feels a rumbling sensation. When the pelvic colon is involved, the pain is always below the umbilicus and is often most marked on the left side. In carcinoma of the transverse colon the pain is situated above the umbilicus as frequently as below.

The over-activity of the colon above the obstruction leads to hypertrophy of its musculature. When the obstruction becomes complete, failure of the muscle ultimately occurs and extreme paralytic distension results; ulceration and perforation, especially of the cæcum, may follow.

When the obstruction is sufficient to give rise to severe pain, strong spasmodic contractions of the colon, but not peristaltic waves, are often visible and palpable. They never occur in the colic associated with lead poisoning or colitis, and very rarely with obstruction due to simple impaction of fæces.

In cancer of the colon, especially the ascending part, or the cæcum, general symptoms, particularly weakness and anæmia, are often present for a considerable time before any change takes place in the activity of the bowels. Severe anæmia may indeed, though rarely, develop in the absence of any symptoms pointing to abdominal disorder. This is not the result of massive hæmorrhage, which is rare, but is due

to slight continued loss of blood from the growth, together with the poor appetite and deficient nutrition which is often present. Occult blood is almost always to be found in the stools if this is looked for on several occasions.

In about 30 per cent. of cases when the patient is first seen, a tumour is palpable either on abdominal or rectal examination. In some of the remainder the growth is inaccessible to palpation owing to its situation at the splenic flexure; in others it is too small to be palpable. It is often impossible to reach a growth in the lower end of the pelvic colon or at the top of the rectum either by abdominal or rectal examination, though it may be accessible to bimanual palpation. In such cases the sigmoidoscope alone makes an early diagnosis possible. If acute obstruction is not an early occurrence, the growth develops into a large and easily palpable tumour, which invades the neighbouring peritoneum and viscera. The tumour often varies in size from time to time, as it is formed not only by the growth itself, but partly by impacted faeces or by thickened peritoneum and adherent coils of intestine, with perhaps a localised abscess. The disappearance of a tumour after treatment with purgatives or enemata does not therefore mean that cancer is absent, even if its disappearance is associated with improvement in the symptoms. For a mass of faeces can become impacted above a cancerous stricture and produce obstruction, which may be partially relieved when the faeces are removed. A diagnosis of cancer can be excluded only when the disappearance of the tumour is accompanied by complete and lasting cure of all the symptoms. The tumour produced by a growth is hard; it is rarely very tender, unless complicated by local peritonitis. When situated in the ascending, descending or iliac colon it is generally fixed; in the caecum and transverse colon it is frequently very movable.

Radiography often affords considerable help in diagnosis. The shadow of the colon may be visible as far as the seat of obstruction unusually soon after the opaque meal, which, however, should not be given in the presence of obstruction; little or no barium may pass beyond this point for a considerable time, but a similar localised delay may also occur in simple constipation. A barium enema, however, will in most cases demonstrate the presence of a growth either by a failure of the enema to pass beyond the site of the obstruction or by the appearance of a narrowed rigid segment of colon with an irregular outline or an obvious filling defect. Tenderness may also be noted at this site by palpation under screen control, and when an abdominal tumour is present, the combination of palpation and radiographic examination shows whether any delay observed occurs in the neighbourhood of the tumour and whether the latter arises from some part of the alimentary canal. Radiography may completely fail to give any evidence of a growth until some months have elapsed since the onset of symptoms, but with modern technique this should happen very rarely.

In exceptional cases symptoms are produced by complications before the intestinal functions become affected. Thus secondary deposits in the brain may cause cerebral symptoms sufficient to overshadow everything else, and an abscess developing in connection with an ulcerated growth or a stercoral ulcer above the obstruction, or general peritonitis resulting from perforation of the ulcer may constitute the earliest clinical manifestation. In rare cases distension from ascites is the first symptom noticed; in others jaundice from secondary glands pressing on the common bile duct. It is frequent for a liver much enlarged with metastases to be the first cause of bringing a patient to the doctor, and early symptoms are sometimes ignored or disregarded until the development of a gastro-colic fistula.

**Diagnosis.**—The diagnosis depends upon the history combined with the results of abdominal and rectal palpation, examination of the stools for visible or occult blood, sigmoidoscopy and radiography. A tumour in the right iliac fossa may be caused by an inflammatory mass developing round a small chronic appendicular abscess, by regional ileitis, tuberculosis and by actinomycosis of the caecum as well as by cancer. In the left iliac fossa confusion with diverticulitis is likely to occur.



In the latter occult blood is often absent, tenderness is more marked and the diagnosis can generally be settled by means of radiography. The chronic obstruction caused by a local band of adhesions may simulate that caused by a growth, the difficulty being increased by the fact that the stools may contain occult blood. Many cases are at first wrongly regarded as psychoneurotic, owing to the combination of general weakness and indefinite abdominal symptoms; others are diagnosed as colitis, owing to insufficient or incompetent investigation. The need for an immediate rectal examination in any patient whose symptoms might possibly be due to a carcinoma of the colon cannot be emphasised too strongly, nor must it be forgotten that a normal result on barium enema examination does not rule out a carcinoma of the rectum. In doubtful cases a rapid blood sedimentation rate if found may be of help in pointing to an organic and not a nervous cause of bowel symptoms.

**Prognosis.**—Improved methods of examination have made it possible to diagnose the large majority of cases of cancer of the colon as soon as symptoms appear and before any serious degree of obstruction has developed. As glandular involvement and secondary deposits in the liver and other organs occur comparatively late, in most such cases the growth can be completely removed. At the same time it must be admitted that many patients do not present themselves to the doctor before either metastases have occurred, or acute obstruction has supervened. In the latter case operation has a high mortality. In subacute obstruction preliminary colostomy with later resection is less dangerous, whilst in early cases with modern methods the immediate prognosis is excellent, and the five-year survival rate may be as high as 50 to 60 per cent. The prognosis is better in older patients and in women than in men, and with growths on the right side of the colon than the left. The actual size of the growth is no guide whatever to prognosis, as widespread metastasis may be present with only a very small primary tumour, and vice versa. Soft colloid growths are of bad prognosis, but purely local spread to adjacent tissues does not necessarily make the outlook hopeless. Untreated cases of carcinoma of the colon or rectum receiving symptomatic treatment only, rarely live more than 6 to 12 months from the time of diagnosis, but simple colostomy alone is likely to prolong life by 1 to 2 years.

In general, only about half the cases are resectable when first diagnosed, but even so prognosis of carcinoma of the colon as a whole is at least twice as good as in carcinoma of the stomach.

**Treatment.**—Cancer of any part of the large intestine proximal to the middle of the transverse colon is best treated by the removal of all the colon up to 3 in. beyond the growth, an ileo-colostomy being simultaneously performed. Beyond this point resection of the growth and of a sufficient margin on each side with end-to-end anastomosis may be more satisfactory.

With the introduction of sulphonamides and antibiotics it is now possible completely to sterilise the contents of the bowel before operation and with this safeguard to undertake a one-stage abdominal resection with enormously diminished risk compared to earlier days. With careful general preparation and pre-medication it is possible to resect the left as well as the right half of the colon with an operative mortality even in advanced cases of less than 10 per cent. In cases of subacute obstruction temporary improvement may be obtained by aspiration of the intestinal contents through a Miller-Abbott tube, and the use of small doses of paraffin and magnesium hydroxide.

In inoperable cases a permanent colostomy may enable a patient to enjoy a considerable period of useful life with relatively little inconvenience from the artificial opening.

All patients after resection of a carcinoma of the colon should be re-examined every 3 months for 5 years, especially if there is evidence that the growth developed in a polyp, as so-called recurrences are often really new growths which may in this way be recognised before they have given rise to any symptoms.

## DIVERTICULOSIS: DIVERTICULITIS

**Ætiology and Pathology.**—Diverticulosis, the presence of diverticula in the colon, occurs in about 5 per cent. of men and women over the age of 40. They are especially likely to develop if aperients have been habitually used for many years. Owing to the atrophy of the muscular coat of the colon which occurs in old age, pressure from within produces diverticula more readily than in earlier life. The presence of fat diminishes the resistance of the intestinal wall, so that diverticula are especially likely to occur in the obese and they often form in the appendices epiploicæ.

The diverticula increase in number and size as the lower end of the pelvic colon is approached, but they are very rare in the rectum owing to the thickness of its muscular coat. A large number are generally present. Some are so small that they are barely visible to the naked eye, whilst others attain a diameter of half an inch. They very rarely become larger than this, as secondary pathological changes interrupt their growth. In the walls of the smaller diverticula all the coats of the bowel are represented. As they grow larger the muscular layer gradually disappears and the mucous membrane frequently becomes atrophied.

**Symptoms.**—*Diverticulosis*, the simple presence of diverticula of the colon, is a very common condition and gives rise to no symptoms. Inflammation of diverticula, *diverticulitis*, occurs in about 15 per cent. of cases. Most frequently the patient complains of discomfort in the lower part of the abdomen and, after a time, attacks of severe pain or colic, which gradually increase in severity and in frequency. The discomfort is generally most marked in the left iliac fossa. At the same time the constipation, for which the patient has taken aperients for many years, may become more severe. Aperients aggravate the pain, which is relieved to some extent by the passage of flatus or fæces. Mucus may be present in the stools, and pus cells can occasionally be discovered on microscopical examination, but obvious and occult blood is generally absent.

The temperature is sometimes slightly raised, and in acute exacerbations it may be very high and accompanied by severe constitutional symptoms with polymorphonuclear leucocytosis.

The bladder is often irritable, the patient having to pass urine with abnormal frequency. At a later stage adhesions with the bladder may develop, and in rare cases gas and fæces are finally passed *per urethram* owing to the development of a colo-vesical fistula, diverticulitis and not cancer of the colon being the cause of the majority of cases of this condition. The actual perforation is a result of inflammation, but when the acute attack of diverticulitis which preceded it has subsided, cystoscopy generally shows that the inflammation is localised to the immediate neighbourhood of the fistula, the rest of the bladder wall being unaffected by the contamination of the urine with fæces. Attacks of subacute cystitis are likely to complicate each recurrence of acute or subacute diverticulitis, but these are often less frequent and less severe than before the fistula developed, the opening into the bladder apparently acting as a safety valve.

Tenderness is most marked in the left iliac fossa and occasionally immediately above the pubes. The rigidity of the abdominal wall over the area may make palpation difficult, but in most cases it is possible to feel the irregularly thickened and tender iliac colon. When a local perforation with pericolicitis has occurred a fixed, rounded and very tender mass may be felt. Digital examination of the rectum generally reveals nothing abnormal, but a mass may be felt suggestive of a secondary malignant deposit in Douglas's pouch caused by thickening round inflamed diverticula of the pelvic colon. The sigmoidoscope often cannot be passed farther than the pelvi-rectal flexure or an inch or two beyond, the bowel at this point appearing to be abnormally fixed and its lumen narrowed.

An opaque meal shows that there is generally little or no delay in the passage through the bowel till the iliac colon is reached. The presence of diverticula can often be recognised when the barium reaches the affected part, as some of it enters and remains in them, often for a considerable time, after the rest has been evacuated. A barium enema should also be given, as whenever diverticula are present their number and localisation can be more accurately determined in this way than by any other method. They may be discovered directly the enema is given, but more often only after it has been evacuated, a double row of small rounded shadows representing the diverticula being then seen, especially in the position of the iliac and pelvic colon. They often remain visible for several days.

**Diagnosis.**—Discomfort and colicky pain in the lower part of the abdomen in middle-aged and elderly patients, especially if associated with increasing constipation, should raise the suspicion of diverticulitis or a growth of the colon. If the pain is most marked in the left iliac fossa and if it is associated with bladder irritability, the former is the more probable diagnosis. A tender tumour in the left iliac fossa, associated with muscular rigidity is much more frequently due to diverticulitis than to cancer. A radiographic examination after an opaque meal and an opaque enema generally settle the diagnosis. Diverticulitis is not a pre-cancerous condition, as the occasional association with cancer is no more frequent than can be explained by coincidence, and the incidence of cancer in simple diverticulosis is as great as in diverticulitis. The discovery of diverticula in a patient with abdominal symptoms does not necessarily mean that these are the cause of such symptoms, especially if the pain is atypical, or the symptoms point to some other disease.

**Treatment.**—The accidental discovery of diverticulosis in the course of a routine radiographic examination indicates the advisability of keeping the stools soft by means of an unirritating vegetable mucilage, such as Isogel, and the avoidance of pips and skins of fruit, nuts, pickles, salads, and hard or stalky vegetables. No aperients should be used, as they tend to force the fluid faeces into the diverticula. In mild diverticulitis the same treatment is effective. In more severe cases with pyrexia and abdominal rigidity the patient should be kept in bed till all signs of active inflammation have disappeared. The diet already mentioned should be given together with an ounce of paraffin three times a day. Belladonna in frequent and maximal doses may be required to control the secondary spasm. Six fluid ounces of paraffin should be injected into the rectum every evening and retained during the night. If the bowels do not act satisfactorily in the morning, water should be run into the rectum slowly and under low pressure in quantity insufficient to cause pain. By this means the accumulation of faeces generally present is gradually evacuated, and the pain and inflammation subside. Treatment with sulphonamide drugs and antibiotics should also be given.

Very few cases require operation. Large inflammatory masses associated with a high temperature and leucocytosis often completely disappear following treatment with antibiotics and sulphonamides, and a considerable degree of obstruction may be overcome. Only if the symptoms become worse in spite of treatment, or if the condition is complicated by the development of an abscess or signs of spreading peritonitis, is an operation indicated. It is sometimes possible to excise or short-circuit the whole of the affected portion of the bowel, but more often a colostomy has to be performed.

On theoretical grounds it has generally been assumed that the correct treatment of a colo-vesical fistula is to perform a colostomy at once, and, if possible, to separate the colon from the bladder at a later date. But colostomy does not always result in closure of the fistula, and a fistula may even develop after a colostomy performed for obstruction. A subsequent operation for separating the colon from the bladder is extremely difficult and does not prevent recurrence. A patient with diverticulitis and a colo-vesical fistula is often little the worse for them, and prefers the minor

discomfort which he may have from time to time to the perpetual inconvenience of a colostomy. It is important that he should keep his stools soft but formed; diarrhoea is much more dangerous than constipation, as soft or fluid faeces easily escape through the fistula whereas solid faeces pass it by. He should take no aperients, and should use Isogel instead of paraffin, which makes the faeces too sticky and too liable to enter the bladder. On such a régime little or no faeces may enter the bladder for long periods, although small quantities of gas may escape from time to time without causing any discomfort. The fistula is in fact valvular and generally remains closed for long periods. Should an attack of cystitis develop, rest in bed and the administration of sulphathiazole for 48 hours is generally sufficient to overcome it.

## CHRONIC INTUSSUSCEPTION

**Ætiology.**—Chronic intussusception is a rare disease occurring only in adults. Twenty per cent. are secondary to innocent and 15 per cent. to malignant tumours, most of which project as polypi into the lumen of the bowel.

For Acute Intussusception see Acute Intestinal Obstruction, p. 649.

**Symptoms.**—A chronic intussusception may last for a month, a year or longer before it terminates in an attack of acute obstruction or of general peritonitis from perforation. It may finally reach the anus, from which it may project for some inches without preventing the passage of faeces. The onset is generally insidious; occasionally it is acute, but the severity of the symptoms generally diminishes and the subsequent progress of the case is chronic. Only about half of the cases are accompanied by constipation, diarrhoea being present in the majority of the others. The most prominent symptom is colic, occurring in attacks which steadily increase in frequency and severity and may be brought on by taking food or by aperients. Constipation is present during the attack, and blood and mucus may be passed at frequent intervals in entero-colic and colic, but not in enteric, intussusceptions. A palpable tumour is present in half the cases; it becomes harder and longer during an attack of colic, and appears to recede in the intervals. Severe attacks are accompanied by vomiting, especially in the enteric form. Visible peristalsis and dilatation may occur in the intestines above the intussusception. An opaque enema, given for suspected chronic obstruction, may reveal the presence of an intussusception by the typical appearance produced when a small quantity of fluid penetrates between the intussusceptum and the intussusciptens.

**Treatment.**—The treatment is always surgical.

## MEGACOLON: HIRSCHSPRUNG'S DISEASE

**Definition.**—Megacolon is a condition in which the rectum and pelvic colon and sometimes the whole of the large intestine are dilated and hypertrophied, although no organic obstruction is present. The condition was described by Hirschsprung in 1887 and occurs in children, untreated cases rarely reaching adult life. It occurs about once in every 30,000 births and shows some familial tendency, being more frequent in males than in females. It must be distinguished from simple dilatation of the colon resulting from constipation, paralytic ileus, obstruction in the sigmoid or rectum, or from gaseous distension in some forms of dyspepsia (*q.v.*).

Megacolon must also be distinguished from a colon of unusual length but normal diameter—dolichocolon. The pelvic colon varies greatly in length, but although a very long pelvic colon may predispose to volvulus, there is no reason to believe that it predisposes to megacolon.

**Ætiology and Pathogenesis.**—Recent work has shown that Hirschsprung's disease is due to a congenital aplasia of the ganglion cells of the plexus of Auerbach

and Meissner, in a short segment of the sigmoid colon or rectum. This segment appears normal to the naked eye, but the bowel above it is dilated and thickened. No evidence of inflammation is found, and it is the failure of the aplastic segment to carry on the peristaltic expulsion of the faeces that produces the functional obstruction and enlargement of the colon. This condition is present from birth, and is often fatal before the child is a year old. Other cases of megacolon may develop later in infancy and are due to simple constipation with faecal accumulation in the sigmoid and rectum. Lack of care as to bowel routine, alterations of diet, or painful defaecation are the most frequent causes.

**Symptoms.**—In Hirschsprung's disease there is always a history of constipation dating from birth or from the first few weeks of life. At an early stage the bowels cease to act spontaneously, and drugs gradually lose their effect until an evacuation can be procured only by means of enemata. The stools are generally soft, but in early cases hard scybala may be passed. Soon after the onset of constipation the abdomen, which is normal in appearance at birth, begins to increase in size owing to distension of the colon with gas and faeces, the size varying from time to time according to the extent to which the bowels are opened. Enormously dilated segments of colon can often be recognised through the stretched abdominal wall; they are dull on percussion, and palpation shows that they are filled with soft unformed faeces. The rectum is empty but a mass of faeces may be felt through the rectal wall in the sigmoid colon. With proper treatment the child can lead an ordinary life without symptoms of toxæmia, but otherwise severe malnutrition and anæmia gradually develop. Attacks of acute obstruction are often superimposed upon the chronic condition.

In cases of megacolon due to faecal impaction the constipation usually becomes complicated by incontinence in which small amounts of soft faeces are continually being extruded past the hard masses in the rectum. On rectal examination hard faeces are felt and rectal prolapse, fissures or piles frequently develop. Constitutional symptoms may be slight and abdominal distension is much less than in Hirschsprung's disease.

Megacolon in adults may give rise to no symptoms beyond a mild degree of constipation. The abdomen is often not obviously distended.

The gas in the dilated pelvic colon is under considerable pressure. In small children it pushes the diaphragm up and the abdominal wall forward, but in older children and in adults the appearance of the abdomen is generally less abnormal, as the diaphragm, which receives no support from above owing to the negative intra-thoracic pressure, gives way earlier than the abdominal muscles. In spite of the fact that the diaphragm may thus be almost completely out of action and that the capacity of the chest is much reduced, there is no complaint of dyspnœa, and patients may be able to take strenuous exercise without any difficulty. In most cases the left dome of the diaphragm is alone involved; it may reach the level of the third or fourth rib and is always higher than the right dome. In rare cases the dilated pelvic colon may displace the heart to the right, or cross the mid-line and pass upwards between the upper surface of the liver and the right dome of the diaphragm.

**EVENTRATION OF THE DIAPHRAGM.**—As the diaphragm in megacolon is displaced into what is normally part of the thoracic cavity, the condition present might with justice be called eventration (*i.e.* out of, "venter," belly) of the diaphragm. This name is, however, generally reserved for a condition in which the high position of the diaphragm is the result of a congenital defect in the musculature of the left half of the diaphragm, which is represented by a fibrous membrane containing only a few scattered muscle fibres. In deep respiration it moves passively up in inspiration and down in expiration—*i.e.* in the reverse direction to that taken by the normal right half of the diaphragm. When the high position of the diaphragm is secondary to megacolon there is a small movement in the normal direction.

The eventration of the diaphragm which results from maldevelopment of its musculature is rare compared with that due to megacolon, other causes being disease or injury to the phrenic nerves and pressure from gastric distension as in *airocoche bloquée*.

**RADIOLOGICAL EXAMINATION.**—Every radiographic examination should begin with an inspection of the patient in the erect position before he has had an opaque meal or enema. The possibility of a megacolon is at once suggested by the discovery of eventration of the diaphragm. The abnormally high position of the left dome of the diaphragm presents such a striking appearance that it can hardly be missed, and as has been pointed out it is more frequently caused by megacolon than by primary atrophy of the diaphragm, in which the left side moves upwards during inspiration while the right side moves downwards in the normal manner. It is generally possible in megacolon to recognise the outline of the enormously dilated air-containing loop of pelvic colon and to distinguish it from an abnormally large gas-bubble in the fundus of the stomach, which is always limited below by the horizontal upper border of the shadow of the gastric contents. When a gas-containing cavity is seen under the right dome of the diaphragm, as well as the left, the diagnosis of megacolon is certain.

An opaque meal does not help greatly in the diagnosis of megacolon, but radiogram examination after an opaque enema gives the only means of recognising the exact anatomical condition present. It is, however, essential to watch the fluid being run in, as it is otherwise impossible to interpret a radiograph owing to the large amount of overlapping of different segments of the bowel caused by the enormous dilatation of the pelvic colon, the uppermost loop of which is often mistaken for the splenic flexure. The fluid is seen to run straight upwards through a greatly dilated rectum and pelvic colon to the left dome of the diaphragm. Small amounts of barium emulsion are run in during screening so that in this way the narrowed segment of rectum and recto-sigmoid may be demonstrated distal to the dilated bowel above. Very large quantities of fluid are required to visualise the whole colon, and the pelvic colon alone may have a capacity of 6 to 12 pints. The colon in children may hold as much as 4 to 6 pints, and in babies  $1\frac{1}{2}$  to 2 pints.

The size of the colon, as shown in a radiograph taken after the injection of an opaque enema, is not an indication of its actual size nor a measure of its tonicity, but an indication of its distensibility. Even if the fluid is injected at a pressure insufficient to cause discomfort, the size of the various segments is often much greater than it is when seen with the sigmoidoscope or after an opaque meal.

**Complications.**—*Volvulus.*—In a small proportion of cases the patient complains of sudden attacks of very severe pain with abdominal distension. Slight attacks, in which the pain is not very severe and the distension is slight, occur much more frequently; they are probably of the same nature as the severe attacks and are caused by the twisting of a loop of the dilated pelvic colon. Both types of attack may last a few hours or a few days, and almost always subside spontaneously.

**Prognosis.**—In Hirschsprung's disease the prognosis is bad unless treatment is successfully carried out, and many children die before adolescence. In cases due to infantile constipation the outlook is good, and gradual improvement is the rule as the child grows older.

In many cases megacolon is compatible with perfect health. Most of the patients complain only of constipation no more severe than occurs in many people with no organic disease of any kind; in some the condition is discovered accidentally during routine investigation of abdominal symptoms due to some other cause.

Toxic symptoms are rare unless aperients have been taken in excess. Only in exceptional cases, in which radiographs show that severe stasis occurs in the cæcum and ascending colon as well as in the pelvic colon, may true intestinal toxæmia occur.

**Treatment.**—In Hirschsprung's disease the most successful form of treatment

is the operation of recto-sigmoidectomy in which the terminal narrowed segment of bowel is removed and the dilated colon anastomosed to the anus with its sphincter mechanism intact. Other surgical measures such as excision of the dilated colon, sympathectomy or the use of spinal anæsthetics have produced only temporary improvement. Conservative medical treatment never leads to lasting cure.

In cases of megacolon due to chronic constipation bowel wash-outs should be given for several weeks, preceded, if necessary, by digital removal of faecal masses under an anæsthetic. After the colon has been thoroughly evacuated a magnesium and paraffin emulsion should be given and regular training in bowel habits instituted.

When attacks of pain and distension, presumably caused by a partial volvulus, recur in spite of treatment, immediate relief can often be obtained by the passage of a long flatus tube with the patient in the knee-elbow position. If this fails and the pain is severe, morphine and atropine should be injected. Relief almost always follows, but if the attacks are frequent and severe, the dilated loop forming the volvulus should be excised in a free interval.

THOMAS HUNT.

## ACUTE INTESTINAL OBSTRUCTION

Acute intestinal obstruction is a condition in which the passage of the contents along the intestinal canal is more or less suddenly obstructed either completely or in greater part. The blood supply to the involved region is also often obstructed, thus converting something already serious into something critical. Only those forms due to mechanical causes will be dealt with here, those due purely to paralysis or spasm being considered elsewhere.

**Ætiology.**—The causes of acute intestinal obstruction are numerous, and may best be considered under (1) causes within the lumen of the bowel, (2) causes in the wall of the bowel and (3) causes outside the bowel, while there are two additional conditions—intussusception and volvulus—which do not come under any of these categories.

1. Causes within the lumen of the bowel giving rise to acute obstruction are gall-stones, faecal accumulations and, very rarely, true foreign bodies. Gall-stones large enough to cause intestinal obstruction are usually of about 1 inch diameter and enter the intestine, not by the bile ducts, but by a fistulous opening between gall-bladder and duodenum. The stone becomes impacted where the bowel lumen has narrowed sufficiently, a foot or two above the ileo-cæcal sphincter. Faecal accumulation may produce an acute termination in a case of chronic obstruction due to some other cause, but it may cause obstruction by itself. Then the faecal mass may be enormous in size and of a stony hardness; it leads more frequently to the pseudo-diarrhoea of partial obstruction than to complete constipation. The *meconium ileus* of new-born infants is another cause in this category.

2. Causes in the wall of the bowel give rise more commonly to chronic rather than to acute obstruction; the commonest of such narrowings are those due to cancer. These conditions are discussed elsewhere, and it is only their liability to an acute termination which needs consideration here. Such a final catastrophe may result from the impaction of faeces, or acute paralysis of the intestinal wall with or without peritonitis may develop. Congenital stricture is a rare cause of acute intestinal obstruction in early infancy; apart from imperforate anus, the commonest site is in the duodenum.

3. The most common cause outside the intestine is strangulation of a portion of intestine by congenital or adventitious bands, diverticula or peritoneal adhesions. Such bands may result from old inflammatory disease or may be a sequel to a laparotomy. They may be produced by the adherence of normal structures, such as the

omentum, Fallopian tube or appendix, to other abdominal organs, or may result from the presence of a persistent Meckel's diverticulum. The latter may remain attached to the umbilicus, or its free end may become adherent. Such bands may obstruct by bridging across a portion of bowel, or a knuckle of bowel may become twisted round or under them, or, if the band is not long, mere kinking at its point of attachment may be sufficient to obstruct the lumen. Internal herniæ may give rise to strangulation and intestinal obstruction; their commonest sites are congenital or acquired slits or tears in the mesentery or omentum, one or other of the normal peritoneal fossæ, or, more rarely, the foramen of Winslow, or congenital or acquired apertures in the diaphragm. The peritoneal fossæ into which such internal herniæ may pass are situated in the neighbourhood of the duodeno-jejunal flexure, in the peri-cæcal region, and in the root of the pelvic mesocolon. Since almost always the part of bowel involved in this type is a mobile one, its mesentery is also involved and its blood supply thus greatly endangered. Strangulated external herniæ are, of course, other examples of acute obstruction.

4. *Intussusception*.—By intussusception is meant the passage of a segment of intestine into the lumen of another segment immediately below. When this occurs a tumour is formed consisting of three layers, the outermost or intussusciens being the portion of bowel into which invagination is occurring, and the inner two constituting the intussusceptum, which therefore consists of an entering layer and a returning layer. Between these latter is the strangled mesentery, interference with the vessels of which speedily occurs and induces changes in the intussusceptum. The apex is the distal part of the intussusceptum and the neck the narrow part where the returning layer turns to become the sheath or intussusciens.

Intussusception most frequently occurs in the first two years of life and is then regarded as brought about by irregular peristaltic movements initiated by swelling of the lymphatic tissue on the inner wall of the bowel. In adults an intestinal polypus or carcinoma is often the starting-point of the invagination, which generally differs from that occurring in infants by being chronic instead of acute.

Various forms of intussusception occur, of which the ileo-cæcal variety, with the ileo-cæcal valve as its apex, constitutes about 70 per cent. Enteric, colic, ileo-colic and multiple intussusceptions are less frequent. An intussusception always increases at the expense of the ensheathing layer, its apex remaining constant.

5. *Volvulus* is a condition in which a coil of intestine becomes twisted on itself around its mesenteric axis, leading to interference with its circulation and with the passage of its contents. It occurs most frequently in the pelvic colon and the ileum, but may affect the cæcum or any part of the intestine with a mesentery. The pelvic colon type usually occurs late in life, is commonest in males, and depends partly upon an abnormally shaped mesentery and partly upon loading of the loop from chronic constipation.

*Pathology*.—In acute intestinal obstruction the conditions found fall mainly into two groups, depending on (1) the occurrence of obstruction of intestine with a previously normal lumen and (2) acute obstruction supervening upon gradually increasing chronic obstruction.

1. In most cases in this group a portion of intestine is strangulated in addition to the obstruction to the lumen of the bowel, and consequently the condition of the intestine must be considered in three regions—namely, above the obstruction, below it and in the strangulated coil itself. An exception occurs in the acute obstruction produced by an impacted foreign body, where, of course, there is no strangulation.

(a) The intestine above an acute obstruction is usually greatly distended, its walls are at first pale and thin, and later œdematous and purple in colour, and the extent of these changes rapidly increases upwards as the obstruction persists. The distended coils are full of fluid (partly the normal dammed-back secretion, partly an exudate of serum), and as the case progresses bacteria escape through the distended and



paralytic coils and lead to peritonitis. These changes are far more marked in small intestine obstruction than when the colon is affected.

(b) Below the obstruction the coils are, as a rule, empty, contracted and pale.

(c) As a result of circulatory interference, the strangulated coil itself becomes distended with effused blood and gas, the latter mainly  $\text{CO}_2$ , which cannot be absorbed. It is purple in colour, tense, oedematous and paralysed, and it exudes bloodstained fluid both into its lumen and into the surrounding peritoneal cavity. If the strangulation is sufficiently severe to obstruct arteries as well as veins the coil becomes gangrenous in less than an hour. Such a coil is grey and loses its peritoneal sheen; it is flaccid and exudes free gas and stinking fluid into the peritoneum. This condition is, of course, irreversible; fortunately, complete arterial obstruction does not usually occur for several hours and the intestinal wall quickly returns to normal when the strangulation is released. A strangulated coil soon loses power to prevent the passage of bacteria, and if left alone its vessels inevitably become thrombosed, and its walls become gangrenous and ultimately perforate. The contents of an obstructed loop are profoundly toxic, the toxicity being greater the higher the obstruction is situated.

2. When acute supervenes on chronic obstruction, the bowel has already had time to accommodate itself in some degree to the presence of narrowing of its lumen. The final blockage of the passage is most frequently due to impaction of faeces in the narrowed part, or to kinking adhesion, volvulus or acute paralysis of the intestine above it. In such cases the already existing hypertrophy above the obstruction gives place to rapidly increasing distension, and as a result the intestinal circulation is interfered with, and gas, being no longer efficiently absorbed, collects within the bowel. The enteritis and ulceration usually present in some degree above a chronic obstruction rapidly increase, and perforation and consequent peritonitis speedily follow.

**Symptoms.**—The symptoms of acute intestinal obstruction vary somewhat with the particular cause of the condition, but some of them are always present. Of the general symptoms, pain, vomiting, constipation and collapse are the most important.

Pain is an early symptom and is severe; a person in perfect health may be suddenly seized with an acute abdominal pain which doubles him up and never remits. At first the pain is stabbing in nature, but later there are exacerbations which are colicky in character, and which occasionally serve to localise the obstruction. If the condition is allowed to progress until peritonitis supervenes, the continuous pain and tenderness associated with that condition are present in addition.

Vomiting, preceded by nausea and severe retching, usually comes on about an hour after the pain, but it may be delayed for 8 or 10 hours. Once it has begun it continues with increasing frequency, and from the second to the fourth day it becomes stercoral in character. The higher the obstruction, the greater the vomiting, and the sooner does the latter become stercoral. Stercoral vomiting is not due to antiperistalsis, but is caused by the stagnant and excessive secretions of the bowel above the obstruction, gradually extending upward until they overflow into the stomach and cause vomiting. The stercoral character is accounted for by the remarkable speed with which *Bact. coli* and other organisms multiply in the stagnant contents.

Constipation is, as a rule, absolute, although the bowel below the obstruction may empty itself shortly after the onset of the pain and vomiting. Neither faeces nor flatus are passed and enemata, after washing away any faecal material present in the bowel below, are either retained or return slowly without force or flatus.

Collapse is early and severe. The patient is prostrated, anxious and restless; the pulse is rapid, small and thready; the temperature is subnormal and the extremities cold and clammy. The collapse is partly due to a reflex from stimulation of the vagal and splanchnic nerve endings in the abdomen, and partly to loss of fluid from sweating and vomiting. An important part is also played by the toxic intestinal contents; the higher the obstruction the greater is the toxicity of the stagnating contents.

In addition to these cardinal symptoms the patient presents certain other important signs. The tongue is dry and the teeth soon become covered with sordes. The abdomen is at first not tender to the touch, and sometimes pressure may relieve the pain. The higher the obstruction, the less will be the distension. If acute obstruction supervenes on chronic obstruction, visible peristalsis may be present, and the coils can be felt to harden under the hand. Occasionally a tumour is felt in the abdomen, especially in intussusception, where a sausage-shaped mass can frequently be felt. On auscultation intestinal sounds are present in increased intensity, and are high-pitched in character. If peritonitis supervenes the symptoms of that condition develop and consequently the abdominal picture changes. In acute intestinal obstruction the urine is scanty and highly coloured, and when the obstruction is low in the bowel it contains a great excess of indican.

**Diagnosis.**—The diagnosis of acute intestinal obstruction is usually easy, but the further differentiation of the site and nature of the obstruction, though sometimes fairly simple, is often impossible before operation. The history is of importance in deciding whether the acute symptoms have supervened on those of chronic obstruction, when similar but less severe attacks which were relieved by enemata or purgatives may have occurred. Enquiry should be made for evidence of past abdominal pains suggesting appendicitis, salpingitis or other conditions which might produce bands.

The presence in an infant of a sausage-shaped tumour, which can be felt to harden and is situated usually in the upper abdomen, with tenesmus and the passage of blood and slime, associated with acute attacks of colic causing the child to scream and draw up its legs and with occasional vomiting, forms a characteristic picture of intussusception, and enables a confident diagnosis to be made. In doubtful cases examination under anæsthesia may be required, and rectal examination may enable the intussusception to be felt.

In volvulus the onset is acute, but collapse may be absent. Vomiting is not frequent at first, but the characteristic feature is the rapid onset and extreme degree of distension. This distension may at first be localised and indicate the seat of the volvulus, but it soon involves the whole abdomen and may cause severe cardiac and respiratory embarrassment.

Distension implies interference with the blood supply and consequent deficient absorption of gas from the bowel; it may be a valuable indication as to whether strangulation has taken place as well as intestinal obstruction.

The conditions from which acute intestinal obstruction have to be differentiated are numerous. The most important is strangulated hernia, and a careful examination of the hernial apertures must always be made. In fat patients with femoral herniæ it is easy to overlook the condition, and in the rare obturator hernia diagnosis is frequently only possible on opening the abdomen. Fæcal impaction is another important condition to be considered, particularly in view of the grave results of laparotomy mistakenly undertaken for its relief. The history of chronic constipation and the presence of hard or putty-like masses in the rectum or pelvic colon should prevent errors. Digital examination of the rectum should never be omitted in acute obstruction, since such masses or a growth may be palpable.

The differential diagnosis from acute peritonitis may be difficult. The extreme tenderness and rigidity in the latter, the absence of stercoral vomiting, the partial nature of the constipation at first, as well as the temperature and history are distinguishing features. Difficulty may arise from conditions causing acute stimulation of the sympathetic nerve, such as torsion of the testicles, ovary or omentum, or the passage of a renal or biliary calculus. Careful enquiry of the history, the characteristic distribution of pain in the colics, examination of the scrotum and vagina and of the urine will usually lead to a correct diagnosis. Further, in these conditions enemata generally result in passing of flatus, and the course of the disease does not follow the

usual sequence in acute intestinal obstruction. In acute pancreatitis the pain is localised in the epigastrium and constipation is usually not absolute.

Lead colic can be distinguished by the blue line on the gums, the history, the blood picture, the absence of stercoral vomiting and the result of enemata; a routine neurological examination will distinguish tabetic crises.

Rare conditions which may lead to mistakes are embolus or thrombosis of the superior mesenteric vessels. In embolus some cardiac lesion is usually present, and in thrombosis there may be evidence of cirrhosis, gall-bladder disease or thrombosis of other veins, while hæmatemesis and melæna are common in both conditions.

**Prognosis.**—Spontaneous cure is remotely possible in all cases of intestinal obstruction, but in the majority, if operation is not undertaken, death occurs. This termination may be at a variable time after the onset, the average being after 6 days. Once the obstruction has been relieved by operation recurrence is uncommon, excepting perhaps where the cause was peritoneal bands following a previous operation. Even when operation is undertaken, acute intestinal obstruction has a grave outlook, depending partly on the length of time elapsing before intervention and partly on the nature of the lesion. Other conditions materially affecting the prognosis are the age and general condition of the patient, and the presence of toxæmia, septicæmia, peritonitis or complicating conditions elsewhere.

**Treatment.**—*Excluding cases of fecal impaction the treatment of all cases of acute intestinal obstruction is immediate operation.* The object of the surgeon is to locate the seat of the obstruction, and to relieve it as quickly as possible with the minimum of handling and exposure of the abdominal contents. When the abdomen is opened a collapsed portion of gut is sought, as this helps to localise the seat of obstruction. When found, the obstruction is relieved in the simplest possible manner, by reducing a hernia, dividing a band, reduction of an intussusception by manipulation, removing a gall-stone, etc. Where simple measures are insufficient, as where the bowel is not viable or a carcinoma is the cause, further immediate procedures depend upon whether small or large bowel is implicated. In the large bowel, resection and anastomosis must not be attempted; the risk of leakage from the suture line is too great. In cancer cases either a proximal colostomy or cæcostomy is made to give immediate relief, the opening being made far enough from the site of the growth to allow a clean field for later deliberate resection, or the growth and adjacent bowel are mobilised and exteriorised, to be cut away after closure of the abdominal wall, thus leaving a double colostomy which is closed when the upper distended bowel has regained normality. Strangulated large bowel is rarely found and is similarly exteriorised. In the small bowel, however, external openings are to be avoided because great loss of fluid ensues and the contained secretions digest the skin around such fistulæ. Resection and anastomosis here carry much less risk of leakage and can usually be confidently performed. Apart from operation, saline and glucose solution should be given intravenously by the continuous drip method to combat the loss of chlorides and fluid, and opium may be given to relieve pain once the diagnosis is established and operation agreed to. As a preliminary to operation, distension should be to some extent relieved by the passage of a Ryle's tube into the stomach with intermittent or continuous suction. The passage of a Miller-Abbott tube farther down the intestine will accomplish this even more satisfactorily but it is often a difficult matter to pass this instrument in a sick patient and, while it may be attempted with advantage, it should not be persisted in.

## APPENDICITIS

**Ætiology.**—The two sexes are affected equally. No age is exempt, but the disease is most common in young adults.

The appendix may become infected either by organisms spreading from the lumen of the cæcum or conveyed by the blood. In the former, the original infection may presumably come from infected food, but septic foci in connection with the teeth, tonsils and naso-pharynx are probably of more importance. The latter are also the likeliest sources of hæmatogenous infection. The commonest organism is *Bact. coli*; next in order of frequency come streptococci and staphylococci. Congenital or acquired abnormalities are present in a considerable proportion of cases. In the former the appendix is not fully descended, is of the infantile variety or is twisted on itself. In the latter there are adhesions or kinks caused by previous inflammation either of the appendix itself or of neighbouring organs. Obstruction to the lumen from any of these causes produces stagnation of the contents and provides the necessary conditions for bacterial invasion. Foreign bodies are another cause, but they occur less frequently than might be expected. Intestinal worms, pins and fruit pips and stones have all been met with, but by far the commonest foreign body is the so-called "appendicular concretion", formed of inspissated faecal material moulded into shape by the appendix itself.

### ACUTE APPENDICITIS

**Pathology.**—In catarrhal appendicitis the mucosa only is affected, but in the commoner diffuse type all the coats are involved, the organ being hyperæmic, rigid, tense and swollen, and the mucous membrane frequently ulcerated. Later the lumen of the appendix becomes filled with pus, and, if there is obstruction, empyema of the organ results. Later still, local or general gangrene occurs, the most frequent sites being the tip or the base. Perforation is very liable to take place at any of these stages, leading either to a localised appendicular abscess or to generalised peritonitis. The chief factor in determining which of these two complications will occur is the virulence of the organism, since it requires time for the reaction of the peritoneum to come into play sufficiently to localise the results of perforation to the immediate neighbourhood. If the lumen of the appendix is obstructed by a stercolith, acute appendicular obstruction results, and the tension of decomposing faecal matter within its lumen leads to rapid gangrene and perforation. In milder cases the inflammation tends to resolve, and the appendix may return to an apparently normal condition, but if the attack has been at all acute, either adhesions or narrowing of the lumen generally remain, leaving it far more liable to further attacks of inflammation. If perforation and abscess formation occur and operation is not undertaken, spreading peritonitis results. Suppurative pylephlebitis may result from spread of infection along the mesenteric veins either with or without perforation of the appendix.

**Symptoms.**—In nearly all cases the following symptoms are present, though they may vary in degree—(1) sudden abdominal pain, (2) pyrexia, (3) increased pulse-rate, (4) gastro-intestinal symptoms, (5) local signs.

1. *Sudden abdominal pain.*—The onset is usually sudden, the patient being seized with severe abdominal pain which is typically central or generalised at first, later moving to the right iliac fossa. In the obstructive type, colicky pain marks the onset, unassociated with fever or increase of pulse-rate, and continues until perforation results or operation is undertaken. In very severe cases, especially in children, and where early gangrene occurs, the pain may be comparatively slight after the initial onset, and in other cases the affection may progress to abscess formation with relatively little pain. Such types are, however, the exception and pain is usually a prominent symptom.

2. *Pyrexia* is almost always present at some time during the attack, except in cases of the obstructive type, where its absence is apt to lead to mistakes in diagnosis, but its height is no measure of the severity of the lesion. There is sometimes a rigor

at the onset but the temperature is rarely greater than from 100° to 102° F. A rise only to 99° or 100° F. is not uncommon but is important, as some pyrexia is almost invariably present at some period during an attack. When a localised abscess has formed, and in very severe cases with perforation and generalised peritonitis, the temperature may be normal or subnormal throughout.

3. The *pulse-rate* is usually increased and tends to continue to increase as the disease progresses. In cases of appendicular obstruction there may be no increase in the pulse-rate until perforation has occurred.

4. *Gastro-intestinal disturbances* are almost invariably present. The tongue is furred and rapidly becomes dry. There is usually vomiting at the onset of the attack but it does not precede the pain and, though it persists in the severe cases with peritonitis, it may pass off although nausea usually continues. While constipation is the rule, diarrhoea sometimes occurs and indicates usually a pelvic position of the appendix, in which the inflammation spreads to and irritates the rectum. If the process does not settle and is allowed to progress, complete constipation resulting from peritonitis and consequent paralysis of intestinal movements ensues.

5. *Local signs*.—There is usually no distension of the abdomen at the onset of the attack, but on inspection it will be seen that the lower abdomen moves less freely than the upper on respiration, and the right side less than the left. There is frequently hyperæsthesia of the skin in the right iliac fossa, and occasionally some œdema can be discovered by loosely picking up the skin and subcutaneous tissues between the fingers and comparing with the other side. There is great rigidity of the right rectus muscle and this is probably the most important single sign; the rigidity is often too great to allow of any proper deep palpation. In addition to the rigidity there is great tenderness and pain on palpation, which has its maximum at MacBurney's point, situated at the junction of the outer and middle thirds of a line drawn from the anterior superior iliac spine to the umbilicus. In some cases an ill-defined mass can be felt in the right iliac fossa, and the longer the history the more likely is such a mass to be present. It is constituted mainly of adherent coils of intestine and omentum surrounding the inflamed or perforated appendix. Rectal examination is often of value and sometimes a tender mass can be felt on the right side of the rectum when none can be made out from above. Considerable irritability of the bladder may be present, especially where the appendix is pelvic in position, and the urine, which is scanty, frequently contains albumin.

A blood count is often of value for purposes of differential diagnosis, and usually shows a leucocytosis of from 15,000 to 20,000.

In many of the worst cases, some or all of these signs and symptoms may be absent, but with a careful examination and a clear history it is usually possible to reach a correct diagnosis.

Sometimes an abnormally situated appendix gives rise to characteristic symptoms. With a retro-cæcal appendix, *local signs in the right iliac fossa may be absent, there being instead great pain and tenderness in the loin, and rigidity without great tenderness of the right rectus*. These cases are specially apt to develop subdiaphragmatic abscess. An appendix running down into the pelvis is apt to give diarrhoea and bladder irritability, local rigidity may be slight and a mass can usually be felt per rectum. An appendix running directly inwards may occasionally give rise to left-sided symptoms.

*Course*.—Where a correct diagnosis is made, operation should be undertaken at once for reasons to be discussed later, but if operation is delayed the case may take one of three possible courses.

(a) Gradual recovery may ensue and in first attacks this will occur in a large number of cases. Improvement begins about the second or third day and the acute symptoms generally subside in a week. Similar recovery may occur, taking a few

weeks, where a mass is palpable. The mass in this instance is due to œdema of the walling-off structures, particularly the omentum, although there may conceivably be a little pus, which is absorbed, in the centre of the mass. In all these cases the patient is extremely liable to have further attacks, a liability which is increased in proportion to the degree of change which has occurred in the appendix.

(b) Often, as the result of ulceration or perforation of the appendix, the local symptoms not only do not disappear at the end of the first week, but persist and become aggravated. The temperature usually rises and there may be rigors, while at the same time a tumour becomes palpable in the iliac fossa. In some cases the abdominal wall may become œdematous and indurated, and the patient frequently begins to lose weight rapidly, to sweat profusely and to show all the signs of closed suppuration. If an operation be now performed, an abscess is found with walls composed of adherent and matted intestines, omentum and parietal peritoneum. Such abscesses often contain large quantities of very foul-smelling pus and if left alone may burst into the rectum or general peritoneal cavity, or more rarely on to the surface, usually in the neighbourhood of the umbilicus. Spontaneous recovery may follow rupture into the rectum or on to the surface, but death is likely to ensue where the rupture occurs into the peritoneal cavity.

(c) The third result of an unoperated attack of acute appendicitis, and by far the commonest cause of death in this disease, is generalised peritonitis. This may occur either from perforation of the appendix before limiting adhesions have had time to form, as in cases of the obstructive type, or it may occur without any perforation at all. In the latter instance bacteria pass through the wall of the inflamed appendix and set up suppuration in the neighbourhood; if the resistance is poor, this involves the neighbouring peritoneum and ultimately leads to a generalised infection. In other cases a localised abscess may form and later burst into the peritoneum, a result often precipitated by sudden exertion on the part of the patient, injudicious palpation or the administration of aperients. The great danger of appendicitis, and one that can only be met by immediate operation, is that general peritonitis may occur from the very beginning, and its symptoms may be indistinguishable from those of the acute appendicitis itself. In the hands of competent abdominal surgeons, operation in the early stages is one of almost absolute safety, and in these circumstances any delay, with the shadow of possible peritonitis menacing the patient at any time, is quite unjustifiable.

**Diagnosis.**—As appendicitis is by far the commonest acute inflammatory condition occurring in the abdomen in people under middle age, it must always be thought of in the presence of acute abdominal disease. In a typical case, with acute onset of abdominal pain, generalised at first and later settling into the right iliac fossa, with vomiting, constipation and local rigidity and tenderness, the diagnosis is easy, but one or more of these signs may be absent and then it is well to remember that a single positive sign is worth several negative ones. The most constant single sign is tenderness on deep pressure in the iliac fossa, and if this is present even in moderate degree, the patient must be carefully watched before a diagnosis of acute appendicitis can be safely discarded.

A general examination is essential in order to eliminate certain other conditions which sometimes lead to mistakes. Right-sided pneumonia may cause difficulty, as its onset is sometimes associated with considerable pain and rigidity in the right side of the abdomen, but as a rule the accompanying respiratory symptoms and signs, especially the rapid respiration, will prevent error. In children, contraction of the right psoas muscle with flexion of the hip may suggest an acute arthritis or even a psoas abscess, whilst a psoas abscess is occasionally mistaken for appendicitis. Of the abdominal lesions most likely to cause confusion the most difficult to differentiate is acute tubo-ovarian disease in women. In some of these cases, appendicitis co-exists from spread of infection, and where doubt remains after a thorough pelvic

examination it is safer to operate than to risk leaving a possible acute appendicular lesion.

In perforation of gastric or duodenal ulcers, the general shock is more profound, the rigidity is more general and board-like, and the pain is diffuse and not localised; *in biliary and intestinal colic*, the nature and distribution of the pain usually suffice to prevent mistakes. The urine should be routinely examined and pyelitis and renal colic excluded by the findings and by the site of the pain. Twisting of a small ovarian cyst may be impossible to differentiate, but operation is called for in either case. In certain cases of typhoid fever the clinical picture may closely simulate appendicitis. *The relatively slower pulse and higher temperature, the constant headache and the absence of any definitely acute onset*, are of the greatest help in distinguishing, and a leucocyte count may be of considerable assistance, as leucopenia is present in typhoid fever in contrast with the leucocytosis of appendicitis.

**Prognosis.**—If left alone a considerable proportion of patients with acute appendicitis tend to recover, but it is not possible to give an accurate prognosis of the course in any particular patient within the first 48 hours. The chief cause of death is peritonitis and less often pylephlebitis, septicæmia or pulmonary embolism. Even if recovery from a first attack does occur, the patient is left with a far greater liability to subsequent attacks. Successive attacks of appendicitis tend to be more severe, and a patient who has had two is almost certain to have further trouble.

With early operation the prognosis is extremely good, death being rare after operation within 36 hours. Even when operation is undertaken later in the attack, the prognosis is still good unless general peritonitis has ensued, when the prognosis without operation is uniformly bad. A further great advantage of early operation is that drainage of the abdomen can usually be avoided, whereas in delayed operations drainage is frequently necessary.

**Treatment.**—In patients with acute appendicitis operated upon within 36 hours of the onset, the mortality rate in the hands of competent surgeons is negligible, and since it is quite impossible to determine the course which any particular attack is going to take, there can be no doubt that when the diagnosis is definitely established, operation should be undertaken at once. Some surgeons are of opinion that when the patient is seen later than 48 hours from the onset and is tending to improve, *medical treatment should be undertaken until the attack has subsided and the appendix removed during the quiescent period*. Since operation in such cases is, with competent surgery, very little more difficult or dangerous than in early cases, such a view has little to recommend it, since it condemns the patient to two tedious periods of sickness instead of one, and there is in addition the risk of the patient's natural objection to an operation, when he feels perfectly well, overcoming the advice he has been given and leaving him exposed to all the risks of a further attack. When peritonitis or localised abscess formation has occurred, there are no two opinions as to the necessity of operation. If, for any reason, operation is impossible or refused, the patient should be kept in the Fowler position, should have nothing but water by mouth and may be given morphine to diminish both pain and intestinal movement, provided always that any question of operation has been finally and definitely decided. Chemotherapeutic and antibiotic agents should be administered. Under no circumstances should a purge be given, as there can be no doubt that far too frequently purgation is the direct cause of perforation.

Where an appendicular abscess has developed, it was formerly held that the abscess should be drained and the appendix removed subsequently. Modern surgical opinion is in favour of doing both at one operation and in the hands of an experienced operator this procedure is undoubtedly best, but where skilled surgical aid is not available, simple incision and drainage of the abscess meet the immediate emergency.

CHARLES DONALD.

## SUBACUTE APPENDICITIS

Recurrent attacks of subacute appendicitis are not rare, but true chronic inflammation of the appendix, as such, does not occur. For this reason, though recurrent infection with subsequent fibrosis and adhesions may be diagnosed with some assurance, the term chronic appendicitis should not be used.

**Symptoms and Diagnosis.**—Many patients suffering from colon spasm, constipation or other abdominal symptoms have their appendix wrongly removed, either without benefit or with actual aggravation of their symptoms. Diffuse caecal tenderness is so frequent a finding on physical examination that its presence is alone of very little diagnostic significance. Pain localised to the right iliac fossa, or in some cases of retro-caecal or retro-colic appendicitis to the right loin or right hypochondrium with localised tenderness on radiological examination may point to appendicular disease; in a few cases symptoms may simulate those of cholecystitis. In cases of recurrent appendicitis the symptoms are localised and not general, as in most neuroses; they may be made worse by physical exercise but are not relieved by food or alkalis. In rare cases, when the appendix is adherent to the rectum, there may be diarrhoea in the attacks. Nearly all cases of regional ileitis are at first misdiagnosed as chronic appendicitis, as is often ileo-caecal tuberculosis and carcinoma of the caecum.

Tuberculous mesenteric glands may also commonly cause local pain and tenderness in the right iliac fossa, usually with some persistent low fever and general ill-health. A few patients suffering from duodenal ulcer symptoms seem to be lastingly relieved by removal of a fibrosed and adherent appendix, but any true causal relationship is uncertain. It is exceedingly doubtful if the "kinked", long, or otherwise radiologically described "grumbling appendix" is ever the direct cause of indigestion or of digestive symptoms other than those indicated above.

## DISEASES OF THE LIVER

The liver is our largest glandular organ, and is essential for life, since it is concerned with the main processes of nutrition. It is often referred to as the seat of intermediate metabolism; after absorption through the intestinal wall the main products of digestion are at once conveyed by the portal vein to the liver, where many elaborate activities involving disintegration and synthesis take place.

Most of the common named diseases of the liver (excluding abnormalities, tumour growth and parasitic infestations) result from structural damage, and such damage would usually be serious and more often fatal but for two facts which have a fundamental bearing on all aspects of liver diseases, and especially prognosis and treatment: 1. We possess a large supply of liver tissue in excess of our essential needs. It is well known that the greater part of the liver may be replaced by carcinoma and yet the functions of the organ remain for the time unimpaired. 2. The liver has remarkable powers of regeneration and repair. Not only do surviving cells rapidly regenerate, often to form large masses (nodular hyperplasia), but the new cells come into perfect alignment with a completely efficient system of bile ducts.

## TESTS OF LIVER FUNCTION

The liver has so many functions that no single test can be expected to provide information about derangement of all of them. Moreover, the two facts already mentioned—the excess of liver tissue over normal requirements and the great capacity for repair—inevitably influence the results. On the whole the tests available demon-



strate disordered function readily in acute damage or disease, but do not tell what the clinician most wants to know, namely, the boundaries between adequate function and complete breakdown, especially in the more chronic diseases of the liver. In general, the correlation between liver histology as shown by biopsy and the results of biochemical tests of function is not close, and gross pathological changes may be obvious under the microscope whilst functional tests remain normal. In practice it is unwise to rely on any one biochemical test alone, the most useful information being obtainable by a combined series of tests, if possible repeated over a period of time.

**Liver biopsy.**—This technique was first described in 1895 and is now an accepted method of investigation. Various types of needle are used, and they may be inserted either below or just between the ribs; in the latter case the patient must co-operate by holding his breath. Good local anaesthesia is essential and the patient must remain in hospital for 12 hours after the test is completed. Among 10,000 biopsies the mortality was just over 0.1 per cent., and the incidence of complications 0.32 per cent. Liver biopsy is particularly useful in the diagnosis of chronic hepatitis, of hepatic enlargement of unknown nature, and as a guide to prognosis in cases of cirrhosis of the liver. It should not be performed in jaundiced patients unless the diagnosis remains uncertain after thorough physical and biochemical examination, as there is an increased risk of bleeding from the puncture in these patients. It may be of value in confirming a diagnosis of malignant metastases in the liver, sarcoidosis or of fatty infiltration. It demands considerable skill in its performance and should not be employed in cases where there are special risks of hæmorrhage.

The main *biochemical tests* of liver function are briefly described below.

**I. Tests based upon the formation and excretion of bile pigments.** *Van den Bergh Reaction: Urobilinogen in Urine.*—There are few hepatic diseases in which some increase in the urobilin content of the blood does not result, and estimation of the serum bilirubin by the van den Bergh test or, more roughly, by the icterus index, may give evidence of disease even when clinical jaundice is absent. In general, high values indicate severe liver damage, but the converse is not necessarily true. Repeated examinations of blood-bilirubin are often of great service in watching the waxing, waning and final recovery from disease. The amount of bilirubin in the plasma can be measured by a quantitative colour reaction, van den Bergh's test, which is given by Ehrlich's diazo reagent after adding alcohol. This test can detect variations in plasma level which are impossible to appreciate at the bedside. A sharp distinction was formerly drawn between reactions occurring before and after adding alcohol to the plasma, the "direct" and "indirect" reactions respectively, as it was believed that the former occurred only with obstructive jaundice and the latter with hæmolytic jaundice. It is now known that this is not consistently true, and as far as the differential diagnosis of most of the common forms of jaundice is concerned, the test is of little or no value.

**Urobilinogenuria.**—Some of the bile which normally reaches the intestine, after conversion in the large intestine to stercobilinogen is excreted in the urine as the colourless urobilinogen; this oxidises in light and air to the bright yellow urobilin. Damage to the liver or excessive formation of bile pigments as in hæmolytic jaundice leads to increased amounts of urobilinogen in the urine, whereas complete obstruction of the bile duct prevents bile reaching the intestine and so prevents any urobilinogen appearing in the urine. The presence of urobilinogen is detected by Ehrlich's aldehyde reagent, which gives a bright pink colour when 0.5 ml. is added to 5 ml. of urine.

**II. Tests based on the part played by the liver in carbohydrate metabolism.** *Lævulose and Galactose Tolerance Tests.*—Unfortunately pure lævulose is difficult to obtain and the test is so unreliable and of so little practical value that its use has been almost abandoned: the same is true also of the galactose test.

**III. Tests based on the detoxifying (toxiphylactic) function of the liver.** *Hippuric Acid Synthesis Test.*—Benzoic acid and its salts are conjugated in the liver with glycine to form hippuric acid which is excreted in the urine, and the test is carried out by giving sodium benzoate orally or intravenously. Renal disease, anemia, pneumonia and other diseases invalidate the results of this test which is time-consuming, unreliable and of little value in diagnosis.

*Bromsulphthalein Test.*—This test is of no value in the presence of jaundice and depends upon the ability of the liver to remove the dye from the blood. It requires an intravenous dye injection with subsequent collection of a blood sample after 45 minutes. In normal subjects all the dye should by then have disappeared from the blood, whereas in cases of liver disease such as cirrhosis, there is continued dye retention.

**IV. Tests based on the activity of the liver in the manufacture of the plasma-proteins.**—(a) *Total serum proteins and albumin-globulin ratio.*—Accumulating evidence points to the liver as the site of origin of the albumin and part of the globulin of the plasma-proteins. Changes, and especially diminution, occur in many other diseases but when the liver is known to be involved they have a special significance. Experimental hepatic injury and both acute and chronic hepatitis in man lead almost constantly to a fall in albumin and a rise in globulin. In liver disease the normal figures for total plasma protein of approximately 7 to 8 g. per 100 ml. may be reduced to 5 or lower, and the normal figures for albumin and globulin of 4 to 5.5 g. per 100 ml., and 1.2 to 3 respectively are reversed so that the former may fall to 2 or lower and the latter rise to 5 or higher. In acute hepatitis these changes are slight or moderate, but they become extreme if subacute necrosis develops. In cases of cirrhosis these changes may also be marked, and there is, as a rule, a close relationship between the level of plasma albumin and the functioning capacity of the liver, so that it may be of help in assessing prognosis. Inversion of the albumin-globulin ratio persisting in a jaundiced patient is a serious indication of continuing hepato-cellular damage.

(b) *Cephalin Cholesterol Flocculation Test.*—This test was originally introduced by Hanger in America and depends on an alteration in the relative levels of the serum proteins. It is usually positive in cases of parenchymatous liver disease and is a useful aid in differentiating hepatic from obstructive jaundice.

(c) *Thymol Turbidity Test.*—This test is also dependent upon the globulin fractions in the serum and is performed by adding thymol to serum and recording the degree of flocculation (turbidity) observed. The result is recorded in units, the normal being 0 to 4. This test is rapid and simple to carry out, and is the most useful and sensitive of all the flocculation tests at present in use, values above 8 being strong evidence of hepato-cellular disease. It is not increased in cases of obstructive jaundice.

(d) Other flocculation tests less frequently used are the Takata Ara, colloidal gold and colloidal red tests. They have no advantages over the thymol turbidity test.

**V. Tests based upon Lipoid Metabolism.**—In obstructive jaundice there is usually a rise in the total blood cholesterol above the normal level of 120 to 250 mg. per 100 ml.; when such rise is not found in a jaundiced patient, the cause is usually hepato-cellular disease. Moreover, in liver disease, the percentage of cholesterol in esterified form, which is normally 50 to 70 per cent., falls and this reduction in cholesterol esters is roughly proportional to the degree of liver damage. The test is thus of value in estimating the extent of hepatic disease and state of recovery, if repeated estimations are carried out. Unfortunately, a number of complicating factors lessen the reliability of the test.

**VI. Serum Alkaline Phosphatase.**—This enzyme is excreted in the bile and in cases of obstructive jaundice its level in the blood is increased. The test is of value

in helping to differentiate obstructive from hepatic jaundice and in conjunction with other tests gives most useful information. Normal values lie between 3 to 13 King-Armstrong units, and levels below 30 units in the presence of jaundice almost always indicate a hepato-cellular rather than obstructive cause, whilst values above 40 units strongly suggest obstruction.

**Summary.**—In practice the most useful combination of biochemical tests is the estimation of serum proteins and albumin-globulin ratio, the alkaline phosphatase and thymol turbidity tests and of bilirubin in the blood. Valid conclusions can never be drawn from a solitary test, and if possible multiple tests repeated at intervals with due appreciation of their wide range of variability should be carried out. In conjunction with the clinical history and examination they may then be of real value, particularly in the differential diagnosis of cases of chronic jaundice.

## JAUNDICE

**Definition.**—Jaundice is the condition caused by the presence of excess of bilirubin in the blood (bilirubinæmia) which manifests itself clinically by yellow colouration of the conjunctivæ and skin.

**Ætiology and Pathology.**—Many classifications of jaundice have been made, some of them based chiefly on ætiology and others on pathology. None of them is perfect, and for simple clinical purposes the best still appears to be a division into three groups, hæmolytic jaundice, toxic and infective hepatic jaundice and obstructive jaundice.

(a) **HÆMOLYTIC JAUNDICE.**—In hæmolytic jaundice bilirubin is produced in excess from hæmoglobin set free in the circulation by the destruction of red cells as a result of abnormal fragility, as in acholuric jaundice, or of the presence of hæmolytic toxins in the blood. The hæmoglobin is broken down in cells of the reticulo-endothelial system in the spleen, bone-marrow and elsewhere, and the bilirubin is carried to the liver for excretion. The excess of bile-pigment is thus formed quite independently of the glandular cells of the liver, and the condition is often referred to as a "disassociated jaundice".

(b) **TOXIC AND INFECTIVE JAUNDICE.**—This is by far the commonest variety, and is the result of damage or necrosis of liver cells which are unable completely to transfer the pigment from the blood to the bile-capillaries. Some pigment is therefore retained in the blood, but some passes through for excretion in amount depending on the extent of the damage and the stage of repair. Further, the bile-pigment which reaches the bile-ducts may again be obstructed (see below) by cholangitis. In this variety of jaundice therefore the excessive bile-pigment in the blood may be of two kinds—one which has passed through the glandular cells of the liver and one which has not done so.

(c) **OBSTRUCTIVE JAUNDICE.**—In obstructive jaundice bile excreted by the hepatic cells is reabsorbed by the hepatic blood capillaries, together perhaps with the lymphatics, owing to the rise in pressure caused by obstruction of the bile-ducts. The obstruction may occur (1) within the ducts, or it may be due to (2) changes in their walls or (3) pressure from without.

1. **Obstruction within the ducts.**—This is almost always due to gall-stones. In very rare cases a hydatid cyst ruptures into a duct, which becomes obstructed by a piece of membrane or a daughter cyst, or a round worm enters the common bile-duct from the duodenum.

2. **Obstruction due to changes in the walls of the ducts.**—Congenital obliteration of the bile-ducts is a rare cause of simple jaundice in infants (p. 699). An acquired stricture may result from accidental injury of the common bile-duct during operation. Infective and suppurative cholangitis lead to jaundice, but in some cases the obstruc-

tion to the ducts is associated with changes in the liver cells, which are in part responsible for the production of the jaundice. Jaundice is an early symptom of primary carcinoma of the hepatic and common bile-ducts and biliary papilla.

3. *Pressure on the ducts from without.*—Carcinoma of the liver and very rarely gummata and hydatid cysts give rise to jaundice by pressing on the intrahepatic branches of the bile-ducts; if some of the latter escape, bile still passes into the duodenum from other parts of the liver and the feces remain coloured. The tumour may also project into the portal fissure and give rise to jaundice with colourless stools by pressing upon the hepatic ducts or common bile-duct.

Enlarged glands in the portal fissure may cause jaundice by pressure upon the ducts. The most common cause is primary or secondary cancer of the liver, as these glands drain the liver, but not the other abdominal viscera or peritoneum; for the same reason they rarely become tuberculous. They are very rarely enlarged in Hodgkin's disease and glandular fever and never in syphilis.

Jaundice may occur in cancer of the stomach, even when no secondary deposits are present in the liver or in the glands in the portal fissure. This is due to the pressure of glands in the neighbourhood of the head of the pancreas, or to direct spread of the growth into the lesser omentum, where it compresses the common bile-duct and may invade its walls.

Jaundice is produced by obstruction of the common bile-duct when chronic pancreatitis occurs in an individual in whom the duct is embedded in the head of the gland. It is generally present in cancer of the head of the pancreas, but very rarely with a pancreatic cyst or calculus.

(a) **LATENT JAUNDICE.**—The recognition that bilirubin is always present in the blood and the development of tests such as the van den Bergh reaction, by which fairly accurate quantitative measurements can be made, have shown the existence of latent jaundice. This is important in a variety of hepatic diseases and also in other conditions such as pernicious anemia. Normally the bilirubin content of the blood is about 1 in 250,000 (0.4 mg. per 100 ml.) and except in hæmolytic jaundice the concentration must rise to 1 in 50,000 (2 mg. per 100 ml.) before bile pigment appears in the urine and the skin begins to be coloured.

In hæmolytic (or dissociated) jaundice, on the other hand, the renal threshold is much higher, and no bile pigment may be found in the urine in spite of a concentration greatly exceeding the normal in the blood.

**Symptoms.**—Jaundice appears first in the conjunctivæ and then successively on the face, neck, body and limbs. The mucous membrane of the lips and palate becomes yellow very soon after the conjunctivæ. In chronic obstructive jaundice the pigment in the skin becomes dark green. In a small proportion of very chronic cases xanthoma develops, but this condition is more common without jaundice (p. 784). The patches consist of cholesterol, which the blood in jaundice contains in excess. In chronic jaundice there is a tendency for telangiectases to develop over the body and face; they may disappear at the same time as the jaundice. Purpura and hæmorrhage from mucous membranes, especially the nose and gums, may occur as a result of deficiency in vitamin K.

The urine becomes bile-stained before the conjunctivæ and skin, the interval being sometimes as long as 24 hours, but it generally returns to normal before the yellow colour of the skin has disappeared. The urine may be yellow, olive, dark brown or even black. The colour can be distinguished from that in urobilinuria, hæmaturia and melanuria, and that produced by rhubarb, senna, santonin and chrysophanic acid by Gmelin's test for bile-pigment.

When obstruction to the bile-ducts is complete, no bile reaches the intestines and urobilin is absent from the urine; when the obstruction is incomplete, decomposition of the bile which reaches the intestines may occur and urobilinuria results. Bile-salts are present in the urine only for the first few days. Their dis-

appearance is due to the fact that they are produced in very small quantities, being constantly reabsorbed from the bowel and re-excreted; when the bile-ducts are obstructed the kidneys rapidly excrete all the bile-salts present in the blood. In chronic obstructive jaundice bile-stained casts are almost always present in the urine, and less frequently albuminuria occurs. The urine may reduce Fehling's solution owing to the presence of glycuronic acid.

The faeces are bulky and often extremely offensive. When the obstruction is complete they are clay-coloured, owing partly to the absence of stercobilin and partly to the presence of excess of fatty acids and soaps, which require the presence of bile for their complete absorption, and of neutral fat if the pancreatic duct is simultaneously obstructed (p. 701). Loss of weight results, and the excess of undigested food which reaches the colon is likely to cause excessive bacterial decomposition. This may lead to intestinal symptoms and toxæmia if the hepatic cells are damaged and their detoxifying action impaired.

The sweat may contain bile, which is also sometimes present in the tears and in the milk; but the saliva, cerebrospinal fluid and mucus of the alimentary canal are free from bile, although the salivary glands and other organs are deeply bile-stained. The sputum in pneumonia and the effusion in pleurisy and peritonitis contain bile-pigments. The blood plasma is tinged with bile. Coagulation is considerably delayed in obstructive jaundice owing to deficiency of prothrombin. This is a result of lack of fat-soluble vitamin K ("Koagulation vitamin"), too little of which is absorbed when bile is absent from the small intestine.

In jaundice of recent origin the pulse may be slow as a result of the presence of bile-salts in the blood. *Pruritus* occurs in about 20 per cent. of cases, especially when the jaundice is deep; it may be very severe and interfere with sleep. It is not directly due to the jaundice, as it may develop several days before the jaundice appears and continue after its disappearance. When present before the jaundice, it may subside with the onset of the latter. It may also disappear at a time when the jaundice is still as intense as ever. It is most frequently seen in obstructive cases.

The yellow vision or xanthopsia of jaundiced patients is less marked than that caused by santonin, and is rarely sufficiently obvious for the patient to mention it unless directly asked.

**Diagnosis.**—The importance of latent jaundice has already been referred to, but even when the conjunctivæ and skin are already yellow the diagnosis of jaundice may be completely missed if the patient is only seen in artificial light. This clinical point cannot be over-emphasised.

1. *Age, sex and history.*—Transient jaundice is common in the newly born (p. 746). Obstructive jaundice may result from congenital obliteration of the bile-ducts (p. 699) and congenital syphilis (p. 681). Severe jaundice in infants may be familial (p. 745). Mild infective jaundice may occur sporadically or in epidemics among infants; it is identical with the infective hepatitis of older children and adults.

Jaundice occurring in childhood or before the age of 30 is generally caused by infective hepatitis. After 30, gall-stones become a more common cause, especially in women, and after 40 cancer is the most common cause in both sexes. Jaundice developing in pregnancy should raise a suspicion of acute necrosis of the liver. When two or more members of a family are affected, an infective hepatitis, leptospiral jaundice or a toxæmia is the cause in acute cases. In chronic cases acholuric jaundice is probably present.

In jaundice of obscure origin the possibility of a toxic cause should be remembered, and enquiries made whether the patient has recently received treatment with organic arsenical preparations, Atophan or other hepatic poison. Serum jaundice (p. 666) is clinically indistinguishable from infective hepatitis except by the history of a probable cause at the material time-interval previously. Most cases of so-called arsenical jaundice are due to faulty sterilisation of syringes which have been contamin-

ated with traces of blood containing the icterogenic agent and not to the arsenic itself.

2. *Colour*.—In hæmolytic anæmia the skin has a characteristic lemon-yellow colour, though the conjunctivæ may be unaffected. In acute and subacute hepatic necrosis, such as the toxic jaundice caused by arsenobenzene, the skin assumes a very bright yellow colour, which is quite distinct from that of the jaundice caused by obstruction of the bile passages. A dirty or greenish-yellow colour occurs only in chronic and more or less complete obstructive jaundice.

3. *Course*.—Jaundice of very short duration is generally due to the passage of a gall-stone. If it lasts some days infective hepatitis is equally probable. Obstructive jaundice, which progresses until it becomes extremely deep, suggests cancer, whilst chronic jaundice, which varies from time to time, and intermittent jaundice are generally due to a stone in the ampulla of the bile-duct, but may also be due to cancer of the ampulla.

4. *Condition of the gall-bladder*.—Enlargement of the gall-bladder indicates obstruction of the cystic or common bile-duct, though the former is not likely to be associated with jaundice. The enlargement is present in over 90 per cent. of cases in which obstruction is due to causes other than gall-stones, but in only 20 per cent. of cases of calculous obstruction. The difference is due to the contraction of the gall-bladder caused by chronic inflammation in cholelithiasis, in which, moreover, the obstruction is often incomplete. This is known as Courvoisier's law, but as it has 20 per cent. exceptions it is no law, as Courvoisier (1890) well knew.

5. *Condition of the liver*.—Jaundice associated with great enlargement of the liver is generally due to growth if it is irregular, and to chronic obstruction of the common bile-duct if the liver is smooth; the irregular enlargement due to syphilis is less extreme, and, like that due to hydatid cysts or an abscess, is rarely associated with jaundice. The presence of ascites points to a growth or to cirrhosis, but the jaundice is generally greater in the former.

6. *Examination of the stools*.—The presence or absence of stercobilin in the stools shows whether the common bile-duct is incompletely or completely obstructed. Slight excess of fatty acid and soap without any striated meat fibres or starch occurs in uncomplicated jaundice; excess of neutral fat, as well as fatty acid and soap, together with striated meat fibres, points to obstruction of the pancreatic duct. Complete absence of both bile and pancreatic juice from the intestinal contents indicates obstruction at the ampulla of Vater.

7. *Pain*.—Constant pain suggests growth or, at the onset, infective hepatitis; attacks of pain gall-stones, and absence of pain acute or subacute necrosis. Many exceptions to this general statement occur. Chronic pancreatitis may be painless as may carcinoma of the pancreas, but more usually pain is present, often of severe degree.

8. *Syphilis*.—Active signs of syphilis or scars of old lesions indicate the possibility of a syphilitic origin, or of infection through an arsenical injection which a patient may be having for syphilis without his own doctor's knowledge.

*Treatment*.—The treatment of jaundice is the treatment of the condition which causes it. The subject, therefore, requires no further consideration here, except for the pruritus and tendency to hæmorrhage, which are results of the jaundice itself. Thyroid, gr.  $\frac{1}{2}$  three times a day, and fractional doses of calomel may give relief to the pruritus, which is also helped by a warm alkaline bath, or moistening the irritable parts of the skin with 1 in 40 carbolic acid, 1 in 50 ichthammol, or 1 in 70 solution of menthol in spirit. Sedatives should be used with caution in liver disease and especially the barbitones and opium derivatives, but if sleep is much interfered with, paraldehyde 3 to 10 ml. intramuscularly is safe and often successful. The antihistamine drugs are also of value in controlling the itching and should be tried in full dosage especially at night.

*Vitamin K*.—This vitamin has been prepared from alfalfa cereals and other sub-

stances, as well as a number of synthetic analogues under the names menaphthone (B.P.) and menadione (U.S.P.). Vitamin K causes a rapid rise in plasma prothrombin and is thus able to control considerably the hæmorrhagic tendency present in many cases of obstructive jaundice. When given by mouth it must be combined with bile salts (or it is not fully absorbed), and a dose of 5 to 10 mg. daily with gr. 5 of bile salts is sufficient to raise the prothrombin level to normal in 12 to 36 hours. Intramuscular injections of the synthetic products dissolved in oil are painful but act more certainly and more rapidly. Intravenous injections can also be given. Vitamin K should always be administered before an operation on any patient with obstructive jaundice, preparations such as Kapon, Synkavit (water-soluble) being suitable in doses of 10 mg. Also see p. 769.

### CHRONIC INTERMITTENT JUVENILE JAUNDICE

A number of writers have described a condition, seen predominantly in men between the ages of 15 and 25, in which intermittent periods of lassitude and jaundice occur over many years, and in which an hereditary basis can often be detected.

**Ætiology and Pathology.**—No definite cause is known but, as stated, an hereditary factor is often present, and attacks are especially brought on by external factors, such as alcohol, lack of sleep, overwork and mental anxiety. Liver biopsy has shown only slight fatty infiltration of the liver cells but no inflammatory changes or evidence of cirrhosis. Liver function tests are usually normal.

**Symptoms.**—Periodic lassitude, with slight jaundice and sometimes mild dyspeptic symptoms are the only complaints. There is never itching, and the yellow staining of the sclerotics is only faint, if in fact it is detected at all. The serum bilirubin is raised but fluctuates considerably, values between the normal and 35 for the icterus index being found at different times. The urine is normal in colour and bile pigments are not present.

**Diagnosis.**—The condition may be suspected in any case of a young adult showing barely detectable jaundice, varying in intensity but continuing for many years with periodic bouts of fatigue, but the malady can only be diagnosed for certain with the aid of the serum bilirubin estimation. There is no enlargement or tenderness of the liver, as occurs in infective hepatitis, and no signs of hæmolysis, or splenic enlargement as occurs in chronic hereditary hæmolytic jaundice.

**Prognosis and Treatment.**—The prognosis is uniformly good. As Meulengracht has written, the most important therapy that can be given is the diagnosis. No special dietetic or medicinal treatment is indicated.

### HÆMOLYTIC DISEASE OF THE NEWBORN (see p. 745)

#### ACHOLURIC JAUNDICE (see p. 741)

### CONGESTION OF THE LIVER

**Ætiology.**—When the outflow of blood from the hepatic vein is impeded as a result of right-sided heart failure, following primary disease of the heart or obstructive pulmonary disease such as emphysema, passive congestion of the liver may result. It is also produced by thrombosis of the hepatic veins, a rare condition generally secondary to some neighbouring malignant, syphilitic or inflammatory disease.

**Pathology.**—The sublobular and intralobular veins are dilated. The centre of each lobule thus appears as a dark spot, whilst the outer part is pale owing to fatty infiltration. The mottled appearance resembles the section of a nutmeg and has led to the name "nutmeg liver".

**Symptoms.**—In addition to the symptoms of the cardiac or pulmonary disease,

which has led to the right-sided heart failure, special symptoms result from the passive congestion of the liver. The capsule of the liver is stretched and pain results, especially if the enlargement is rapid. When the increase in size is more gradual, there is a feeling of fullness and weight in the right hypochondrium. The liver can be felt to extend considerably lower than normal, its size varying from time to time according to the condition of the heart. It is firm and tender, especially if the congestion is recent and acute. Distinct expansile pulsation can sometimes be felt by placing one hand in the loin and the other just below the right costal margin; which corresponds with ventricular systole if tricuspid regurgitation exists. It must be distinguished from the non-expansile pulsation transmitted through the diaphragm from the labouring right ventricle.

The congestion of the liver leads in turn to congestion of the organs which are drained by the portal vein. Anorexia, discomfort immediately after food, flatulent distension of both stomach and intestines from deficient absorption of the gas swallowed with the food or produced by fermentation, and constipation are commonly present. The combination of slight jaundice with cyanosis produces a characteristic dusky colour of the face. The jaundice is, however, often latent, a positive van den Bergh reaction being obtained with no pigmentation of the skin or conjunctivæ.

Ascites is common, but is rare in the absence of general œdema, being mainly due to the same causes; it is also in part a direct result of portal congestion and sometimes of chronic peritonitis. The spleen is very rarely enlarged in spite of the interference with the outflow of blood in the splenic vein by the hepatic congestion.

**Diagnosis.**—When cardiac or pulmonary disease is obvious, the diagnosis is easy. Sometimes, however, the most prominent symptoms are due to the congestion of the liver, and the diagnosis from cirrhosis may be difficult. In congestion of the liver the spleen is not enlarged, and the symptoms rapidly improve and the liver diminishes in size with rest and cardiac treatment. Moreover, hæmatemesis, though common in cirrhosis, very rarely occurs in passive congestion in spite of the engorgement of the gastric mucous membrane.

**Treatment.**—Diet has no effect on the flatulence, which can only be relieved by treatment of the cardiac condition. Digitalis and mercurial diuretics will do more to reduce hepatic pain and discomfort than any local application, but in some cases venesection may do good. Mild purgation with magnesium sulphate may also help to relieve the portal congestion.

## INFECTIVE HEPATITIS

Infective hepatitis, which was formerly designated catarrhal jaundice, has become increasingly common in the last 15 years, both in Great Britain and abroad, and in the War of 1939–1945 it was the most important infection in the British Army in Africa, the Near East and India.

**Ætiology and Pathogenesis.**—Data at present available show that an icterogenic agent is present in the blood-stream in cases of hepatitis, and may exist there before symptoms arise and before any evidence of liver damage can be detected. This agent is now known to be a living virus, and healthy volunteers given dried Seitz filtered extracts of urine and stools from jaundiced patients have developed hepatitis both when extracts were given orally and intra-nasally. Naso-pharyngeal washings taken from cases of hepatitis, however, have so far not been shown to transmit the disease, and there is at present no test known which will detect the presence of the icterogenic agent except observation of the result of transmission to man; no method of culture *in vitro* has yet been successful.

**Homologous Serum Hepatitis.**—Much of our knowledge of the causation of infective hepatitis has come through a study of the very closely allied, but almost certainly



not identical condition now generally entitled *homologous serum jaundice*, though more correctly it should be known as *homologous serum hepatitis*. Experimental work on this condition has shown that the causative agent will pass through filters which retain bacteria, is extremely resistant to heat and disinfectants, surviving storage at low temperatures for very long periods, and is probably very similar though not identical with that which causes natural infective hepatitis. Serum hepatitis differs from infective hepatitis in having an incubation period of between 60 and 150 days, and in having an appreciably higher mortality, even though the majority of the cases are mild.

Serum hepatitis may follow the transfusion of whole blood, serum or plasma; it has resulted from the injection of convalescent human serum used in the prophylaxis of measles and mumps; it occurs after the use of syringes contaminated by human blood and in this way accounts for cases of so-called post-arsphenamine jaundice; cases of "post-vaccinal jaundice" have followed the use of yellow fever and other vaccines, and in 1941 one series of yellow fever vaccines was responsible for over 23,000 cases in the U.S. Army with an incidence of over 5 cases per 100 doses of vaccine.

Post-transfusion jaundice was of serious importance during the War of 1939-1945, and in 1945 was for a time a major cause of death in U.S. hospitals in England; an incidence of 7.3 per cent. of cases of jaundice following transfusion with pooled serum or plasma was reported in 1946 among 2,040 patients transfused. In some series the mortality has been as high as 12 per cent. Experimentally the intensity of the hepatitis has shown no relationship to the amount of dried serum injected—as little as 0.1 ml. intravenously being enough to cause severe hepatitis, even of a serum stored for over 2 years.

*Epidemiology.*—Infective hepatitis most frequently affects those under 40 years of age. The main epidemics occur in the autumn, but sporadic cases are found at all times of the year. The incubation period is between 15 and 35 days and the mode of infection is both through stools and urine, and probably by air-borne droplets from the saliva and naso-pharyngeal secretions. The pre-icteric stage is said to be the most infective period but there is some evidence that the blood may remain infective for a considerable time after jaundice has actually disappeared. It is quite rare for cases to develop hepatitis from bed to bed contact unless sanitation is defective, and it is not essential to isolate the patient provided ordinary precautions are taken as for other excremental diseases. It is probable that cases may arise through careless contamination of food or drink with excreta of individuals in a household suffering from apparently simple gastro-enteritis without jaundice.

During the War of 1939-1945 the incidence was markedly higher amongst officers than amongst men, a fact which has been attributed by some to the immunity developed by the men owing to the repeated minor infections which they suffer and from which the officers are more protected owing to their better hygiene and feeding arrangements.

*Morbid Anatomy.*—Post-mortem examination in the numerous fatal cases occurring in the extensive epidemic in Scandinavia in 1926 and 1927, and in epidemics in Great Britain and in the British Army overseas in 1942 and 1943 always showed acute or subacute hepatic necrosis. Liver biopsy has demonstrated that the primary change is inflammatory, and that the necrosis is to a large extent the result of post-mortem autolysis. Inflammatory changes are invariably present in the connective tissue, the parenchyma shows irregular foci of necrosis and glycogen disappears from the cells. The lobular pattern is lost. With the disappearance of symptoms the inflammatory cells rapidly disappear and the lobular pattern is restored. The jaundice is in part a result of impaired functional activity of the hepatic cells, which normally take up the bile pigment from the undamaged reticulo-endothelial cells, and excrete them into the bile capillaries, and in part a result of disorganisation of the structure

of the lobules with consequent rupture of the intralobular bile capillaries. The interlobular and larger bile-ducts are unaffected, and the stomach and duodenum are normal. The pathological appearance of the liver in homologous serum hepatitis is indistinguishable from that found in hepatitis, and fatal cases show a massive hepatic necrosis.

**Symptoms.**—In all but a few mild cases jaundice is preceded by other symptoms. The mode of onset is usually very characteristic but certain other variable types may be described.

Most commonly there is a gradual onset over several days of severe anorexia, nausea, constipation and headache. Vomiting is often present but is less frequent than the almost continuous feeling of nausea, especially marked at any smell, sight or even thought of food. Epigastric discomfort is present in most cases, occasionally amounting to quite severe pain, but never colicky as in gall-stone attacks. Some pyrexia occurs during this pre-icteric period, which averages 3 to 4 days but may vary from 24 hours to 15 days or even longer. As soon as jaundice appears the symptoms and fever usually quickly improve, and appetite often returns with remarkable rapidity.

In about 20 per cent. of cases the onset is violent and sudden, resembling severe influenza, malaria or even meningitis; the temperature may rise to 105° F. with rigors, intense headache, general pains and prostration. The temperature may remain high for several days but jaundice often does not develop in these cases until the fifth or sixth day of the illness. Paradoxically such severe cases at the onset often recover exceptionally quickly and have a particularly good prognosis, perhaps partly because they are, as a rule, treated urgently and at once in bed when milder cases are not.

In a proportion of mild ambulatory cases, perhaps 10 to 30 per cent., there are no symptoms whatever of ill health and the only abnormality noticed is an icteric tinge in the eyes and skin. Jaundice is not deep and appetite is not impaired. In another group a mild coryzal illness, or a slight febrile "bilious attack" with vomiting, headache and vague abdominal discomfort occurs but no clinical jaundice ever develops. Such cases are not rare in epidemics of infective hepatitis and should always be borne in mind in such circumstances. It is probable that ambulatory non-icteric cases are an important cause of spread of infection, resembling in this way the non-paralytic cases of anterior poliomyelitis. Diagnosis of the mild sporadic cases is difficult and may be impossible, but in an epidemic, if this type of case is remembered the symptoms together with slight enlargement of the liver and sometimes a transient trace of bile in the urine should enable a fairly confident opinion to be given.

Pruritus is rare in cases of infective hepatitis, but general depression is common and considerable loss of weight and weakness may follow any but the mild cases. Dehydration may be pronounced at the onset if vomiting is at all severe. Mental symptoms are unusual except as a premonitory sign of beginning hepatic necrosis (*q.v.*) when delirium, mania, convulsions or coma may occur. On examination the jaundice may be very deep or only just detectable as a faint yellow tinge in the sclerotics. The pulse is often slow, 50 to 60, but this is by no means a constant sign or of much help in diagnosis, being usually rapid during the pyrexial period and tending to become slower at the later stage of the disease. The liver is almost always palpable, being in some cases much enlarged. Such enlargement may considerably precede the appearance of jaundice, and does not run parallel by any means to its intensity, persisting often for some time, after all signs of jaundice have disappeared. The liver is smooth, tender and firm but not hard; the lower edge may reach as low as the umbilicus, but in more than half the cases is only one or two finger-breadths below the costal margin; in about one-third of the cases it is not palpable at all. The spleen is slightly enlarged in less than one-fifth of the cases.

The bilirubin in the serum is increased above the normal value of 0.4 mg. per cent. to values between 2 and 40 mg. per cent., such excess often remaining in the blood for some time after apparent clinical recovery. The blood count may be normal but more usually shows a relative lymphocytosis with some leucopenia; leucocytosis does not occur, and there is no anaemia.

**Diagnosis.**—The diagnosis in the pre-icteric period is suggested by the characteristic triad of anorexia, nausea and fever. In older patients the distinction from jaundice due to carcinoma of the pancreas may be extremely difficult, but any severe pruritus should always arouse a suspicion of an obstructive jaundice due to growth or stone. Liver function tests are of some help in the differential diagnosis, and a markedly positive thymol turbidity test is very suggestive of hepatitis rather than a duct obstruction. The serum bilirubin is rarely raised until immediately before jaundice appears. No specific laboratory test for hepatitis has yet been discovered. Regular estimations of serum bilirubin are of considerable value in judging the progress of a case, and so helping in the distinction between obstructive malignant disease and severe hepatitis.

The possibility of Weil's disease must be remembered, and the presence of albuminuria together with positive serological tests (*q.v.*) will confirm the diagnosis.

**Prognosis.**—The average total duration of the illness is from 20 to 40 days, but in a number of patients a so-called "post-hepatitis syndrome" characterised by fatigue, anorexia, dyspepsia and a palpable liver may persist for many weeks, making convalescence very slow. These symptoms are in many cases psychogenic, and liver biopsies have not shown evidence of cirrhosis or other histological changes in the liver. Depression and intolerance to alcohol and fatty food are commonly noticed for a time after recovery. In others, however, the disease appears to remain active and a condition of chronic hepatitis with progressive liver cell degeneration and fibrosis results. Hepatic necrosis at the time of an attack may also later lead to cirrhosis of the liver with nodular hyperplasia and scarring. Such sequelae, though fortunately rare, are of very great importance and are particularly likely to occur in individuals who have lived on diets deficient in protein before acquiring hepatitis.

The mortality is low amongst healthy well-fed individuals, being not more than 1 or 2 per thousand, though varying somewhat in different epidemics; amongst undernourished or debilitated people, however, it may rise to 2 or 3 per cent.

Relapses occur in from 2 to 8 per cent. of cases and are usually mild, coming on from 3 to 6 weeks after recovery from the initial illness. Alcohol may undoubtedly precipitate such relapse, and also may appear to bring on jaundice in a patient incubating the disease. Second attacks though infrequent are by no means as rare as is generally believed, and exceptionally three or even more attacks at intervals apart may occur in the same patient.

**Treatment.**—**PREVENTION.**—The chief means of prevention lie in attention to personal hygiene and general sanitation. Care in washing and in the handling of food is especially essential during an epidemic and by those in contact with cases of supposed gastro-enteritis or undiagnosed fever. The use of gamma-globulin in a dose as low as 0.01 ml. per pound body weight injected intramuscularly has seemed to produce immunity, which has lasted several months or longer; some trials have suggested that this may be partly an active response conferring more than merely a temporary passive protection. Previous good nutrition and an adequate protein intake are almost certainly of importance in lessening the severity of an attack. During an attack patients should be kept completely in bed in the course of the earlier stages and, as a rule, it is wise to continue this until the jaundice has disappeared. If, however, the patient has no symptoms, feels well and is eating a full diet he may be allowed up in his room even though slight jaundice is still present, but this should rarely be allowed under 2 weeks from the onset of the illness. If the patient is able to eat normally, the diet should not be restricted and carbohydrates and proteins

especially should be given freely from the start. This is in order to maintain the glycogen deposits in the liver cells (carbohydrates) and the plasma proteins which are often lowered in liver disease (proteins). A low fat diet has no special merit, and fats need not be avoided unless they cause nausea and vomiting, or are so repugnant that the patient feels unable to eat them. If there is much vomiting it is essential to ensure that adequate fluid and glucose are given, either rectally or intravenously, and it is wiser to give 1 or 2 litres of glucose saline intravenously early than to wait until the patient shows signs of dehydration. As a rule sweet drinks containing glucose, jellies, biscuits, boiled sweets and stewed fruit with sugar are well taken, and iced skimmed milk is often tolerated well. The administration of amino-acids—cysteine and methionine—by mouth in doses of 3 to 5 g. daily have in some cases appeared to shorten the duration of the illness, but their use on the whole has proved disappointing.

The use of ascorbic acid, 100 mg. daily, and of vitamin K is advisable if any operative interference is needed during the illness or if any signs of hæmorrhage such as purpura occur. Drugs have no place in treatment, except symptomatically, but some benefit has been reported from the use of chlortetracycline. Aspirin may be given safely for headache, and various dyspeptic mixtures may be tried for the nausea and vomiting, rhubarb and soda sometimes seeming to act satisfactorily. Morphine is contraindicated in cases of hepatitis, and even the barbitones in small doses, e.g. phenobarbitone, gr.  $\frac{1}{2}$  two or three times a day, should only be ordered if there is very severe insomnia or itching.

During convalescence the avoidance of chilling is important and alcohol should be forbidden for several weeks or longer after recovery, according to the severity of the illness. In some cases alcohol tolerance is lowered for a long time, or even permanently, and strict teetotalism may be advisable. Signs of drowsiness, mental confusion, delusions or mania, or of reduction in the urine output with deepening jaundice and vomiting must be watched for, especially between the eighth and fifteenth days, as indicating liver failure from hepatic necrosis.

## ACUTE AND SUBACUTE HEPATIC NECROSIS

**Ætiology.**—Hepatic necrosis, previously often called Toxic Jaundice, may be caused by a large variety of toxins, but coincident infection either by natural infective hepatitis or by transmitted serum or "syringe" jaundice is often impossible to exclude. The vulnerability of the liver to toxins is dependent partly upon dietary factors, experimental work having shown that both carbohydrates and proteins—particularly the sulphur-containing amino-acids—increase the resistance of the liver to poisons such as chloroform and phosphorus. Too high an intake of fat on the contrary is harmful, by causing fatty deposition in the liver (see Cirrhosis) and by increasing the effect of many toxic substances which are more soluble in fat than in water.

(a) *Intrinsic toxins.*—An unknown toxin, which may develop in the later months of pregnancy—the toxic jaundice of pregnancy.

(b) *Extrinsic toxins.*—i. Acute alcoholic poisoning.

ii. Delayed chloroform poisoning.

iii. Delayed poisoning with bromethol (Avertin) and other basal anæsthetics.

iv. Carbon tetrachloride used in treatment of ancylostomiasis.

v. Trinitrotoluene, tetrachlorethane, and other chemical solvents used in industry.

vi. Arsenic: (i) acute in arseniuretted hydrogen poisoning; (ii) subacute in poisoning with arsenamine preparations used in the treatment of syphilis, though in many cases a "syringe-transmitted" virus infection is the cause.

vii. Phosphorus poisoning.

viii. Gold poisoning, a rare result of chrysotherapy for skin diseases and arthritis. It occurred in 8 per cent. of 1500 patients who were given gold for arthritis.

ix. Cinchophen (Agotan, Quinophan, Atophan); acetanilide.

x. Mushroom poisoning (p. 345).

xi. Infective hepatitis. In epidemics of infective hepatitis a small number of cases, usually less than 1 per cent., terminates in acute or subacute necrosis of the liver. Death does not often occur before the end of the third week. It is probable that some of the sporadic cases of acute hepatic necrosis which are otherwise unexplained are instances of fulminating infective hepatitis, but this cannot be regarded as established in the absence of tests for the presence of the virus.

**Pathology.**—Acute and subacute hepatic necrosis are caused by severe poisoning of the liver cells, the intracellular ferments of which are set free and produce autolysis. The necrosis may affect particularly the periphery of the lobules, or the centre, or it may be very diffuse. If extensive, death may ensue within a few days (acute necrosis). The old name of *acute yellow atrophy of the liver* is unsuitable, as the pathological change is necrosis and not atrophy. If a certain amount of liver tissue withstands the toxic onslaught, the patient may survive for some weeks or months, and *at necropsy the destroyed liver is found to have become replaced by cellular fibroblastic tissue*, the surviving islets of parenchyma being in a state of active proliferation. This is the stage of subacute necrosis. Finally some cases survive for many months or years, as the regenerated liver tissue compensates more or less adequately for what has been destroyed. When death occurs in such cases from the progress of the lesion or from some intercurrent disease, the liver presents the appearance known as multiple nodular hyperplasia, with numerous rounded nodules of regenerated functioning liver tissue separated by broad tracts of post-necrotic fibrosis. The stomach, duodenum and bile channels up to the smallest canaliculi are completely normal.

### 1. ACUTE HEPATIC NECROSIS

**Synonyms.**—Acute Yellow Atrophy of the Liver; Icterus Gravis.

Acute hepatic necrosis is a very rare and very fatal disease apart from the cases in which necrosis is the result of an extrinsic poison. It may occur at any age, but chiefly between 20 and 30. In adults, females are affected twice as often as males owing to the fact that pregnancy is one of the chief exciting causes, but the proportion is reversed in childhood.

**Symptoms.**—In the first stage jaundice is present with fever, malaise, vomiting, constipation and muscular pains. In about a third of the cases the patient suffers from general malaise for some time before the jaundice appears, and in rare instances jaundice is absent throughout. This first stage generally lasts for 5 or 6 days.

The second stage, that of hepatic failure, begins suddenly with drowsiness, headache, photophobia, restlessness and delirium with characteristic maniacal shrieking and wailing. Muscular twitching and occasionally general convulsions follow, and the patient may become violent. Transient squint is sometimes present, the pupils are generally dilated, and there is often an extensor plantar reflex. Retraction of the head may be present, and a lumbar puncture may be required to diagnose the condition from meningitis. Severe vomiting occurs, and the vomited material may contain altered blood. The tongue is dry and tremulous. The pulse becomes rapid and feeble, but the temperature is generally subnormal, though it often rises just before death. An erythematous rash is sometimes present and a moderate degree of œdema is usual. Purpura is common, and hæmorrhage may also occur from the gums, nose, kidneys, uterus and alimentary canal, and in the retina. The sulphurous smell of mercaptan may be noticed in the breath. Coma finally develops with Cheyne-Stokes respiration and incontinence of urine and fæces, the whole of the second stage lasting less than a week and often only 3 or 4 days.

The liver is often enlarged and tender in the first stage, but at the onset of severe

symptoms it rapidly diminishes in size, until the hepatic dullness disappears owing to the necrotic and flabby liver falling back and allowing the intestines to pass between it and the abdominal wall. The spleen is sometimes enlarged. Ascites is rarely detected during life, though it may be found after death. There is no anæmia, but there is moderate leucocytosis.

The urine contains bile and albumin, and casts are often present. There is no glycosuria. The percentage of nitrogen excreted as ammonia increases from the normal of about 5 to 20 owing to the acidosis, which causes ammonia to be fixed by organic acids before there is time for it to be converted into urea. Rounded discs of leucin and needle-shaped crystals of tyrosin derived from autolysis of the liver cells may be deposited in the urine when it cools, but they are sometimes found only after concentration and may be absent altogether, though they are subsequently discovered in the liver. They are also occasionally found in the urine in typhoid fever, erysipelas, small-pox and leucæmia, so that their presence is not pathognomonic of acute necrosis of the liver.

**Diagnosis.**—The diagnosis cannot be made with certainty without biopsy or necropsy, but depends upon the occurrence of severe general symptoms with intense jaundice and evidences of bleeding. The serum bilirubin is high—20 mg. per 100 ml. or higher—and the serum albumin is greatly reduced.

**Prognosis and Treatment.**—Acute hepatic necrosis is fatal in between 50 and 100 per cent. of cases, in spite of all treatment. Glucose must be given freely either by mouth or intravenously, or in both ways, from 10 to 15 oz. a day orally and 2 to 3 litres of 5 to 10 per cent. solution intravenously; 10 ml. of 10 per cent. calcium gluconate injected slowly intravenously is advised by some authorities, and a high fluid intake is essential. Insulin is not of value and may be harmful. The use of methionine, cysteine and choline, though justifiable experimentally have so far been of little demonstrable value in man.

## 2. SUBACUTE HEPATIC NECROSIS AND NODULAR HYPERPLASIA

If jaundice persists for more than 3 months after an attack of hepatitis it is probable that permanent damage has been done to the liver, and the longer the jaundice lasts, the more likely is this to be true. Other patients may make an apparent recovery from an attack of hepatitis but the jaundice returns and the illness pursues a relapsing course. In still other cases there is no clear history of an acute attack and the patient presents himself—or more commonly herself—with a chronic jaundice of insidious onset. In all such cases the structure of the liver has been so gravely disorganised that the normal connections of the portal venules and the biliary canaliculi cannot be re-established and the patient eventually succumbs from portal hypertension or cholæmia. The clinical picture is that of cirrhosis (pp. 674, 678), except that jaundice is more prominent. The differentiation of subacute hepatitis from obstructive jaundice may be difficult at the bedside but great help is usually obtained from biochemical tests. Diagnostic laparotomy should be avoided if possible in subacute hepatitis as operation is not well borne. The hepatic functions are much more gravely impaired than in obstructive jaundice and the hypoproteinaemia and reversal of the ratio of albumin and globulin in the plasma are of considerable diagnostic value. The prognosis is unfavourable and death may occur after a duration of a few months or years, but in some cases nodular regeneration is sufficient to maintain liver function for a normal length of life. Treatment should follow the same lines as for acute hepatic necrosis in the early phase of the illness and as for cirrhosis in the later.

## FATTY INFILTRATION OF THE LIVER

**Synonyms.**—Hepatosi; "Liverishness".

Individuals who habitually overeat and consume large quantities of alcohol and

carbohydrate, but take only small amounts of protein in their diet, are likely to develop fatty infiltration of the liver. The condition is frequent in the tropics where it is called "tropical liver" and is due to the above factors, combined sometimes with the effects of malaria, amœbiasis or enteric fever. Excessive consumption of alcohol does not seem by itself to cause the condition, provided the dietary protein intake is sufficient. The condition can be demonstrated by liver biopsy and is rapidly recoverable under conditions of rest and high protein feeding.

It is to be distinguished from a much more serious form of liver disease found in children in tropical countries, called serous hepatosis, which is also due to protein deficiency; in this condition there is œdema of the liver with exudation of an eosinophilic coagulum, fibrosis and later true cirrhosis.

**Symptoms.**—No close correlation between the degree of fatty infiltration and the clinical symptoms can be drawn, but enlargement of the liver is the most important and characteristic sign. It is usually tender and firm. Ascites is rare, but slight anæmia is frequent, which in a few cases may be macrocytic. Albuminuria occurs in fully half the cases. The patient complains of a feeling of discomfort, rarely amounting to pain in the right hypochondrium, and symptoms of alcoholic gastritis especially morning anorexia and nausea are often present. The complexion is often sallow and there is sometimes a slight degree of jaundice. He says he is "liverish" or "bilious", he is irritable and depressed, and complains of a feeling of general unfitness, headache and drowsiness. Gastric and intestinal flatulence may occur as a result of deficient absorption of gas secondary to slight portal obstruction.

Periods of comparative well-being may alternate with acute exacerbations or "liver attacks" which are generally caused by increased alcoholic excess, by over-eating and sometimes by exposure to cold. During such an attack the liver becomes larger and more tender, and the stretching of the capsule may cause acute pain. With suitable treatment an attack usually subsides within a fortnight and even in severe cases a month or 6 weeks is generally sufficient to restore the patient to good health. If he becomes teetotal complete recovery usually occurs, otherwise cirrhosis eventually develops in many cases.

**Treatment.**—The patient should be kept in bed on a high protein diet until all symptoms have disappeared and the liver is no longer tender. He should avoid alcohol permanently and reduce his weight if this is excessive by restricting both carbohydrates and fat. Additional vitamins and amino-acid preparations are of little proved value. It should be pointed out to the patient that his liver has become abnormally vulnerable, and that even small quantities of alcohol are dangerous to him and may eventually cause cirrhosis and death.

## CIRRHOSIS OF THE LIVER

**Synonym.**—Chronic Interstitial Hepatitis.

Cirrhosis of the liver is a condition in which the liver hardens as a result of the development of new fibrous tissue. The pathological picture varies considerably, but the primary feature is always a loss of hepatic glandular cells associated with an increase in fibrous tissue. New liver cells regenerate, and at this stage the liver is often uniformly enlarged; later scar-tissue is formed which by contraction distorts the liver, diminishes its size and twists the blood vessels and bile-ducts to an extreme degree. Fibrosis may be fairly uniform throughout the whole organ, or very irregularly disposed, according to the ætiological factors discussed below. Pathologists describe five main types, based on the histological picture; namely, the common portal or multilobular cirrhosis (p. 674), cirrhosis associated with nodular hyperplasia (p. 672), pericellular cirrhosis (in congenital syphilis, p. 681), biliary or perilobular cirrhosis (p. 679) and the very specialised form known as hæmochromatosis (pigmentary cirrhosis, bronzed diabetes, p. 680).

**Ætiology.**—Two main causes are postulated which between them may explain the majority or even all forms of hepatic cirrhosis—direct damage to the liver cells produced by viruses, microbic infections or toxic substances; and dietary deficiencies acting indirectly by interfering with the nutrition of the liver cells which gradually degenerate and die.

The first factor has long been accepted as important, but the recent work on infective hepatitis, particularly by the technique of liver puncture, has proved that not all acutely damaged livers recover but some progress slowly to the stage of typical cirrhosis. Toxic chemical substances may also produce the same effect.

Dietary factors in cirrhosis have been extensively studied experimentally, and it was found that in animals high fat diets induced fatty degeneration of the liver with subsequent cirrhosis; the inference was drawn that the excess of fat interfered in some way with the nutrition of the liver cells, which died and were replaced by fibrous tissue. It was also discovered that administration in adequate dose of two natural substances of the body, lecithin and choline, reduced the fat content of the liver and prevented cirrhosis. Casein, a natural protein, was equally effective; and its activity was proved to be due to the presence of the amino-acid methionine, an essential substance for the production of lecithin. Lecithin, in fact, appears to be an essential medium for the transport of fat in the body; and if lecithin or the methionine necessary for its manufacture are deficient, fat accumulates in the liver cells and degeneration follows.

Further experiments showed that rats fed on diets deficient in first-class protein also developed cirrhosis, and it was found that the critical deficiency in the low-protein diet which brought about necrosis was of the two sulphur-containing amino-acids, methionine and cysteine, the first being the more important.

It is probable that toxic and dietetic factors often act together in man and that the development of cirrhosis after acute hepatitis is far more likely to occur in individuals whose diets have been previously deficient in proteins than in others. Certainly the two main groups of post-infective and nutritional cases are not always easy to distinguish either clinically or histologically.

### PORTAL OR MULTILOBULAR CIRRHOSIS OF THE LIVER

**Synonyms.**—Portal or Multilobular Cirrhosis; Laennec's Cirrhosis.

**Definition.**—The portal or multilobular form of cirrhosis of the liver is so much the most common that it is generally described shortly as cirrhosis of the liver. It is a disease in which degeneration of the hepatic cells occurs in association with fibrosis spreading from the portal spaces to enclose various numbers of lobules.

**Ætiology.**—The general problems of ætiology have already been discussed. The disease is generally fatal about the age of 50, but a distinct group of cases occurs in childhood. It is three times more common in men than in women, but only slightly more so in boys than in girls. Cirrhosis is in rare instances familial, presumably as a result of an inborn defect of the liver cells which renders them abnormally vulnerable to toxins and liable to premature degeneration; this may then be associated with chronic lenticular degeneration. It is more common in individuals who follow a sedentary occupation than in those who lead an active life, and among the poor than the well-to-do.

The majority of patients with cirrhosis of the liver in Britain have indulged excessively in alcohol; it is three times more common among people connected with the liquor trade than among the general public. Cases occur, however, especially in India, Egypt and Dutch East Indies, and in children in which alcoholic excess can be excluded with certainty. Thus cirrhosis is not infrequent among Brahmans, the majority of whom indulge in large quantities of ginger, cardamom, red pepper and other spices, but never touch alcohol.



**Pathology.**—Cirrhosis never develops experimentally in animals as a result of chronic alcoholic poisoning, although fatty changes and occasionally necrosis with a slight degree of small-celled infiltration may be produced. It occurs in less than 3 per cent. of drunkards dying from the effects of alcoholism, though it is at least three times as frequent amongst inebriates as amongst the non-drinking public; its geographical distribution does not correspond with that of chronic alcoholism, and when excessive indulgence in alcohol leads to nervous changes, cirrhosis of the liver is rare.

It is probable that the main factor concerned is the low-protein diet which alcoholics often take, combined with their high calorie intake in the form of alcohol. There may also be deficiency of other essential food factors owing to the substitution of alcohol for ordinary food with consequent serious imbalance of the diet as a whole. Associated virus hepatitis, other infections such as malaria or amœbiasis and possibly some constitutional vulnerability of the liver may be additional factors concerned.

The size of the liver varies greatly; it may be much smaller or much larger than normal, depending upon the relative degrees of hyperplasia and fibrosis.

Its surface is irregular. The projections may be as small as those of a granular kidney, but more frequently they give rise to a hob-nailed appearance.

The obstruction to the intrahepatic branches of the portal vein produces a rise in pressure in its tributaries; this results in dilatation of the collateral circulation which normally exists between the portal and general venous systems. This compensatory circulation is carried out by the following groups of vessels.

1. An anastomosis may develop within the liver between the branches of the portal vein and the intralobular veins. Large branches pass from the liver and its capsule to the phrenic and intercostal veins, where the liver and diaphragm are uncovered by peritoneum. Occasionally a single large vein passes from the liver in the falciform ligament by the side of the obliterated umbilical vein to join the veins of the abdominal wall at the umbilicus; the subcutaneous veins around and above the umbilicus are consequently dilated, and a large bunch of dilated veins may form at the umbilicus (*caput medusæ*). In rare cases a loud venous hum may be heard with the stethoscope at this point or below the xiphisternum.

2. The gastric veins anastomose with the œsophageal veins, which open into the azygos veins; the veins in the œsophagus, especially its lower end, may become greatly dilated.

3. The inferior mesenteric vein communicates through the superior and middle hæmorrhoidal veins with the inferior hæmorrhoidal vein, which is a branch of the internal iliac vein. This might be expected to give rise to hæmorrhoids, but they are hardly more common among patients with cirrhosis than in individuals with healthy livers.

4. Additional veins unite the radicles of the portal veins in the intestines and peritoneum with the inferior vena cava and its branches. These include the retro-peritoneal veins, which are often greatly enlarged, especially in the neighbourhood of the kidneys.

**Symptoms.**—About 50 per cent. of patients with cirrhosis of the liver die from some intercurrent disease or accident. Such cases are generally described as latent. But in the majority symptoms due to the condition were probably present before death, and the fatal result of the intercurrent disease or accident was often due to the diminished power of resistance which results from cirrhosis. In some cases, however, the disease may be genuinely latent, owing to compensatory hyperplasia of the liver cells and to the development of an efficient collateral circulation between branches of the portal vein and systemic veins.

In a large majority of cases the symptoms caused by cirrhosis are preceded by those of fatty infiltration, which have already been described (p. 673), and alcoholic œsophagitis and gastritis have generally been present for many years. The patient

habitually wakes in the morning with a feeling of nausea and no desire for breakfast; violent retching often occurs, and he then vomits a small quantity of alkaline watery fluid, after which some bile-stained mucus may appear. A sense of uncomfortable fullness is also felt in the epigastrium after other meals, and the nausea and vomiting may recur. The appetite is poor, and there is a special repugnance for meat. When cirrhosis develops, the symptoms due to catarrh are exaggerated by the congestion of the gastric and intestinal mucous membrane caused by portal obstruction; this leads to the secretion of still more mucus, and by preventing absorption of gas leads to flatulence, which aggravates the feeling of distension already present. Flatulence is a constant early symptom and may be the earliest sign of portal congestion; it is "*le vent avant la pluie*".

The complexion is generally sallow and bloated with dilated capillary or arterial angiomas, especially over the nose and cheeks. In the later stages the face is drawn, the cheeks and eyes are sunken, and the conjunctivæ are congested and often slightly tinged with bile. The skin of the body is dry and inelastic; numerous spider angiomas appear on the face, neck and back as the disease progresses, and red or purple areas of skin may be produced by the uniform distension of small venules. Purpura and various forms of erythema may occur.

The tongue is flabby and furred, the gums readily bleed and pharyngitis is common owing to chronic irritation by alcohol. The breath is often offensive as a result of oral sepsis.

The patient is generally constipated, but attacks of diarrhœa often occur, especially during the last few weeks of life.

In a large proportion of cases the liver is enlarged when the patient is first seen. Its lower border can generally be felt below the costal margin in the right nipple line; but ascites and occasionally flatulent distension of the intestines or obesity may render it unpalpable. It is always hard; and its edge can consequently often be felt even when it is not enlarged. An enlarged liver can be observed to shrink as the disease progresses until it ceases to be palpable, and after death it may be found to be considerably smaller than normal. The irregular surface of the liver may be recognised by palpation, and in contrast with its tenderness in the pre-cirrhotic stage, is insensitive.

Discomfort is often felt in the right hypochondrium, but pain occurs only if the disease is complicated by an attack of perihepatitis.

In about 35 per cent. of cases jaundice occurs. It is generally slight and is often transient. In the absence of jaundice, excess of bile pigment may be found in the blood.

In 80 per cent. of cases the spleen is enlarged. Owing to its hardness it is easily felt unless it is obscured by ascites or intestinal flatulence. Discomfort or pain may result from stretching of the capsule if rapid enlargement occurs; more frequently it is due to perisplenitis. When both the liver and spleen are much enlarged, the left lobe of the former may overlap the latter.

Hæmatemesis occurs in about 25 per cent. of cases. It may be an early symptom, and is often the first indication of the presence of serious disease, though it is generally preceded by symptoms of gastritis. It is less common after ascites has developed. The hæmatemesis generally takes the form of a single large hæmorrhage, but sometimes a smaller quantity is vomited during several days. It is generally repeated only after a considerable interval. The blood collects slowly in the stomach and often passes into the intestine, causing melæna without hæmatemesis. When a considerable quantity has collected in the stomach, the distension causes it to be vomited; small quantities are not brought up unless vomiting occurs from some independent cause. Death directly from hæmatemesis is unusual in cirrhosis and accounts for less than 5 per cent. of the mortality. In the majority of cases the hæmorrhage is a result of rupture of varicose veins of the œsophagus, especially in the lowest 3 in.,

where they can often be demonstrated with the radiograph. The blood runs into the stomach, though in severe cases it may well up directly from the œsophagus. Hæmorrhage may also occur from minute erosions secondary to acute gastritis, sometimes associated with varicose veins. The erosions are very difficult to discover post mortem and possibly in some cases there is no actual loss of surface, the hæmorrhage corresponding with the bleeding which occurs from other mucous membranes. In very rare cases *melæna* may result from thrombosis of the portal vein or one of its branches (see p. 688).

Epistaxis is common. The hæmorrhage generally comes from a point on the anterior part of the septum. In the late stages oozing from the nose may occur, as well as from the gums, lungs, kidneys and uterus, as a result of the toxæmia caused by hepatic insufficiency and deficiency in vitamin K, and small hæmorrhages often occur under the skin. Hæmoptysis, however, is generally due to the cirrhosis being associated with pulmonary tuberculosis.

Ascites is present in most cases of cirrhosis which run their full course. It is a late symptom in uncomplicated cases, and is often absent if the patient dies from some independent cause or from hæmatemesis at a comparatively early stage. The onset is generally gradual, but it occasionally develops suddenly after a blow on the abdomen, a chill or an acute infection; it is also acute in portal thrombosis. It sometimes disappears spontaneously. It is partly due to portal congestion, as the intra-hepatic branches of the portal vein are compressed, some being completely obliterated; occasionally others are thrombosed, and in rare cases thrombosis of the portal vein itself occurs, but this is not the sole cause as the fluid may collect with extreme rapidity instead of *pari passu* with the changes in the liver, and it is often absent when the portal pressure is high as shown by the occurrence of hæmatemesis. In some cases it is secondary to chronic peritonitis. The ascitic fluid is clear and sometimes slightly bile-stained. Its reaction is alkaline, its specific gravity between 1.008 and 1.015, and a large proportion of the cells it contains are endothelial. When the ascites is due to chronic peritonitis the specific gravity is greater than 1.015, more albumin is present, flakes of fibrin may form on standing and polymorphonuclear cells are found. When 50 per cent. or more of the cells are lymphocytes, tuberculous peritonitis is probably present. In rare cases the ascites is chylous or chyliform; still more rarely it is hæmorrhagic.

Oedema of the ankles is frequent, but it is rarely severe, though occasionally it spreads up the legs to the abdomen and back. It often develops before or at the same time as the ascites, in which case it may be the result of hypoproteinæmia, but most frequently it follows it and is then often due to thrombosis of the inferior vena cava. Pressure from the ascitic fluid may play some part, since removal of this may lessen the oedema.

Muscular weakness and loss of energy may be the earliest symptoms; they are constant in the late stages. The muscles are flabby and atrophied, and marked wasting of the whole body occurs.

The rise in intra-abdominal tension caused by flatulent dyspepsia and later by ascites is frequently followed by the development of hernias.

The urine is diminished in quantity and the specific gravity is high. It is very acid and high coloured, and a large deposit of urates generally forms on standing. It contains excess of urobilin, but even when slight jaundice is present bile-pigment is often absent. In the late stages the percentage of nitrogen excreted as ammonia increases at the expense of urea; this is due to ammonia being required to unite with the excess of organic acids present, and not to inability of the liver to form urea, as ammonia given by the mouth is still excreted as urea. In the last days of life leucin and tyrosin crystals are sometimes found.

Albuminuria is occasionally present as a result of hepatic toxæmia, nephritis or congestion of the kidneys from heart failure. Glycosuria is rare, as the glycogenic

function of the liver is maintained to a certain extent even in advanced cases. The blood may be normal, but in a number of cases anæmia develops, due either to deficiency of iron, proteins, or to hæmorrhage from œsophageal or other enlarged veins. In some cases the anæmia is hyperchromic or macrocytic, but more usually it is hypochromic and normocytic.

The temperature is often raised in rapidly progressing cases apart from complications such as tuberculosis and urinary infection.

In the late stages of cirrhosis the toxæmia which results from hepatic insufficiency gives rise to restlessness, irritability, muttering delirium and finally to coma. Severe colitis with large amounts of blood and mucus in the stools is a frequent complication.

Nervous symptoms may also be present as a direct result of chronic alcoholism. Delirium tremens may follow a drinking bout and occasionally a hæmatemesis. Slight mental disturbance and muscular tremor are common, but neuritis is rare.

Active tuberculous disease is found more frequently in patients dying with cirrhosis of the liver than with other diseases. This is probably due to the diminished resistance to tuberculous infection caused by chronic alcoholism. The lungs are most often affected, phthisis being the cause of death in 15 per cent. of cases of cirrhosis, and tuberculous pleurisy is not uncommon. Either the cirrhosis or the phthisis may be completely latent and remain undiscovered until death. Tuberculous peritonitis is found in 10 per cent. of cases; the accompanying ascites is often thought during life to be due to the cirrhosis. The lungs are generally also involved. The majority of cases of tuberculous peritonitis in adult males are associated with cirrhosis.

**Diagnosis.**—An enlarged, hard liver in an alcoholic individual is generally the result of cirrhosis. The occurrence of hæmatemesis, enlargement of the spleen or slight jaundice makes the diagnosis still more probable. The enlarged hard liver, which is produced by chronic venous congestion in heart failure, may be difficult to distinguish from cirrhosis if the patient is seen when the heart is no longer failing. A history of heart failure with pain in the hepatic region and any evidence of existing heart disease point to congestion.

The diagnosis from syphilis and from malignant disease of the liver is discussed elsewhere (p. 687).

The symptoms in the last stages are often indistinguishable from those of uræmia, and the diagnosis may be very difficult in the absence of a full history. But a much increased blood urea with high blood pressure, albuminuric retinitis or the presence of a large quantity of albumin with casts in the urine would prove that uræmia is present.

**Prognosis.**—If an individual with alcoholic cirrhosis becomes completely teetotal in the pre-ascitic stage, there is a good chance that the disease will not progress and that his symptoms will disappear. Even the damage done to the liver can be repaired to some extent by hyperplasia of its cells, a large liver being therefore a favourable sign, and the danger of hæmatemesis, together with the other ill effects of portal congestion, may be overcome by a sufficient development of the anastomoses between the portal and general venous systems.

Much, therefore, depends upon the patient's character, as, if he is unable to control his desire for alcohol, the disease is certain to advance to a fatal issue. The younger the patient the more chance there is for functional compensation to occur, but the prognosis is always bad in children. However completely latent the disease may become, much of the damage to the liver is, of course, permanent, and the patient's power of resisting acute infections and other diseases is materially reduced.

Fever is a serious symptom, as it indicates rapid advance of the disease or the presence of some complication. The development of jaundice, and particularly of ascites, are of serious significance.

In rare cases the disease runs a subacute course, death occurring within a few months of the onset of symptoms. Such cases are most frequent in comparatively

young adults who are heavy drinkers. The liver is painful and tender, fever is present, emaciation is rapid, and multiple hæmorrhages are likely to occur.

**Treatment.**—As has been indicated, the real treatment of cirrhosis must be prophylactic, but considerable alleviation and prolongation of life can often be achieved by treatment even when the disease is fully established. Alcohol must be absolutely prohibited for the rest of the patient's life, and no medicine containing alcohol should be prescribed.

The diet in the early stages should be that required for the treatment of the associated chronic gastritis, and curries, pickles, ginger, all highly seasoned food, vinegar, mustard, pepper, high game must be restricted. In the late stage, when symptoms of hepatic insufficiency are present, the diet should consist of milk, milk foods, vegetable purées and fruit; a quarter of a pound of dextrose in a pint of lemonade or other fruit drink should be given daily. High protein feeding is certainly important as a preventive and should be carried on throughout treatment, milk concentrates being useful when meat proteins are badly tolerated. When ascites is present rigid sodium restriction and a low fluid intake, combined with the use of mercurial diuretics may be most effective and completely relieve the fluid distension. A course of whole liver injections given intramuscularly daily for 2 to 3 weeks provides vitamins and lipotropic factors and may also lead to improvement. The bowels should be kept regular by means of Epsom salts. No other drugs are required in uncomplicated cases. The treatment of the gastritis, ascites and hæmatemesis is considered in detail elsewhere.

**Surgical Treatment.**—Many types of operation have been devised to try and relieve portal hypertension in cirrhosis of the liver. Most of these operations have aimed at shunting the portal blood into the systemic circulation either by a porto-caval or a lienorenal anastomosis. Ligation of the hepatic artery has also been carried out on the assumption that the pressure in the hepatic artery is directly communicated to the portal system through sinusoidal connections between the two systems.

These operations have a high operative mortality and in many cases have proved no more successful than medical treatment. In general they may be expected to help patients who have bled from œsophageal varices rather than those suffering from ascites.

## BILIARY CIRRHOSIS

There has been much discussion whether it is justifiable or desirable to separate this form of cirrhosis from others, but it makes for clearness to do so. Two forms are described.

### PRIMARY HYPERTROPHIC BILIARY CIRRHOSIS

**Definition.**—A chronic disease of the liver occurring in childhood and early adult life, accompanied by persistent jaundice, with great enlargement of the liver due to fibrosis surrounding the smaller bile-ducts and striking splenomegaly.

**Ætiology.**—Quite unknown, but thought to be primarily an inflammation of the small bile-ducts. This was Hanot's view, and the disease was formerly often described under his name. It is seen most commonly between the age of 20 and 30 years, but also occurs in children. An hereditary and familial incidence have been noted.

**Pathology.**—The liver is very large, smooth and coloured deep green from the chronic jaundice. Microscopically dense fibrosis surrounds the small bile-ducts and spreads out to surround the lobules, often single lobules, but the liver cells remain unaltered. In the later stages the lobules are invaded by the fibrosis, and the pathological picture is then almost identical with ordinary portal cirrhosis. It is chiefly for this reason that many writers refuse to separate this form of cirrhosis. The spleen,

however, is generally much larger than in portal cirrhosis, and may occasionally even exceed the liver in weight.

**Symptoms.**—The onset is slow, and jaundice which waxes and wanes but persists until death is the most obvious clinical feature. Abundant bile pigment is present in the urine throughout. Reasonable health may be maintained for years, interrupted by occasional crises of abdominal pain and fever. The abdomen is often greatly distended by the very large liver and spleen, and there is much flatulence. In the later stages hæmorrhages are not infrequent, and the patients become very thin and poorly nourished.

**Prognosis** is bad. The average duration is about 5 years, and unless intercurrent disease supervenes the termination is from gradual hepatic failure ending in coma.

**Treatment.**—As for portal cirrhosis.

#### SECONDARY OBSTRUCTIVE BILIARY CIRRHOSIS

**Definition.**—A chronic fibrosis of the liver spreading from the larger bile-ducts which have been obstructed and often infected (cholangitis) by previous disease.

**Ætiology.**—Obstruction of the larger bile ducts, with cholangitis and often pericholangitis, due to gall-stones, carcinoma or other obstructive disease. This condition is seen more often by surgeons than physicians.

**Pathology.**—The liver is at first enlarged, but never so large as in the hypertrophic variety of biliary cirrhosis. Jaundice is constant, and in section the liver is dark green with obvious dilated large bile-ducts filled with inspissated bile. The fibrosis spreads out quite irregularly from the ducts as in portal cirrhosis, and the liver cells are damaged and necrosed: there is considerable new bile-duct proliferation. The spleen is sometimes normal, sometimes enlarged, but never of the size found in the hypertrophic variety.

**Symptoms**—are those of the primary disease obstructing the bile-ducts, followed only later by those of cirrhosis.

**Prognosis**—depends on recognition of the primary cause and whether it can be relieved before cirrhosis has occurred.

**Treatment**—is essentially surgical and preventive. Once cirrhosis is fully established, the treatment is the same as in portal cirrhosis.

#### HÆMOCHROMATOSIS

**Synonyms.**—Pigmentary Cirrhosis; Bronzed Diabetes.

**Ætiology and Pathology.**—Hæmochromatosis is a rare disease, in which large quantities of hæmosiderin, an iron-containing pigment, are deposited in various parts of the body, especially the liver, upper abdominal lymph glands, pancreas, suprarenal glands and skin, but very little in the kidneys and spleen. The deposition of pigment is associated with ordinary multilobular cirrhosis of the liver and cirrhosis of the pancreas, and the latter, by involving the islands of Langerhans, may give rise to diabetes mellitus. It occurs in about 7 per cent. of cases of cirrhosis of the liver in males and hardly ever in females. There is no excessive hæmolytic. The quantity of iron deposited is much greater than in hæmolytic anæmias, in which the excess of iron is chiefly in the liver and kidneys, whereas in hæmochromatosis it is chiefly in the liver, pancreas and abdominal glands, to which it passes from the liver and pancreas. The condition appears to be due to some abnormal and excessive absorption of iron from the alimentary tract and since the body is unable to excrete this iron to any extent, it is stored in the liver, where it causes degeneration of the liver cells. In advanced cases, 40 g. of iron may be deposited in the body compared with the normal 2 to 4 g. Multiple blood transfusions may similarly lead to excessive iron deposition as may some forms of hæmolytic, but true cirrhosis is only very rarely

produced in this way. The disease is extremely chronic. Primary carcinoma of the liver occurs in hæmochromatosis somewhat more frequently than in simple cirrhosis of the liver.

**Symptoms.**—The symptoms are those of cirrhosis and diabetes associated with pigmentation. The liver and spleen become progressively larger. Ascites may occur and the subcutaneous veins are sometimes enlarged. The skin is generally pigmented a slaty colour, especially in the exposed parts of the body, and has a wrinkled parchment-like appearance. The lesion of the suprarenal cortex may give rise to symptoms of Addison's disease, the pigmentation of the skin being sometimes due to melanin and not to hæmosiderin, and pigmentation of the buccal mucous membrane may occur. In the rare cases in which no pigmentation is present a diagnosis can be made only after death. In most cases symptoms of severe diabetes with acidosis appear suddenly, but they may be absent to the end. Genital hypoplasia and loss of secondary sex characteristics are commonly found.

**Diagnosis.**—The disease can be diagnosed with certainty only when pigmentation, diabetes and cirrhosis are associated together. When two of these conditions are present alone, a definite diagnosis is impossible. It can, however, be made with a considerable degree of probability if well-marked bronzing is associated with cirrhosis, even in the absence of diabetes. The serum iron level is raised, normal = 80 to 180 µg. per 100 ml., and it can be shown that the iron binding capacity of the serum proteins is completely or almost completely saturated. In doubtful cases biopsy of a pigmented area of skin settles the diagnosis.

**Prognosis.**—So long as no diabetes is present the prognosis is not worse than that of uncomplicated cirrhosis, but the onset of diabetes is always serious. With insulin, however, a normal life can generally be led for several years, death being finally caused by the cirrhosis. Heart failure, due to involvement of the myocardium, is the cause of death in a number of patients.

**Treatment.**—The treatment is that of cirrhosis and diabetes. The latter requires large doses of insulin, with the aid of which the diet can be balanced without special difficulty. Repeated venesections to remove iron from the body have been tried with success and it is possible that the monthly loss of iron occurring with menstruation is the reason why the disease so rarely affects women.

### CONGENITAL SYPHILIS OF THE LIVER (PERICELLULAR CIRRHOSIS)

**Ætiology and Pathology.**—The liver is affected in 50 per cent. of infants with congenital syphilis. This great frequency is probably due to the *Treponema pallidum* passing through the placenta and the umbilical vein direct to the fetal liver, which is the first organ it reaches, and which is consequently found to contain it in larger numbers than any other organ.

Congenital syphilis produces diffuse changes in the liver very different from the focal lesions of acquired syphilis, except in rare cases occurring in later childhood, in which caseous gummata are found. The liver is smooth and uniformly enlarged and is firmer and paler than normal. The changes are due to pericellular cirrhosis, the result of diffuse infiltration with embryonic connective-tissue cells between the individual liver cells. These may be associated with small collections of round cells, or miliary gummata, which resemble tubercles when seen by the naked eye.

The spleen is generally enlarged and hard. Diffuse small-celled infiltration or fibrosis may be found in the kidneys, pancreas, testes, suprarenal glands and lungs.

**Symptoms.**—Symptoms pointing to disease of the liver are not often present in infants with congenital syphilis, but on examination the liver and spleen are found to be enlarged and abnormally firm. The liver normally extends farther down in young children than in adults owing to its relatively larger size and the more horizontal position of the ribs. Only definite enlargement and abnormal hardness of the

liver can, therefore, be regarded as important in the absence of other evidence of congenital syphilis. Jaundice is rare; it may be present from birth or, less frequently, it develops a few weeks later.

**Diagnosis.**—The diagnosis is generally easy owing to the well-marked signs of congenital syphilis present in other parts of the body together with a positive Wassermann reaction. In the absence of such signs the diagnosis must be made from rickets, tuberculosis and gastro-intestinal infection, and, when jaundice is present, from the other more common causes of icterus neonatorum (p. 746).

**Prognosis.**—The prognosis depends upon the general condition of the infant. It is less favourable in delayed congenital syphilis than in acquired syphilis owing to the changes being generally more widespread.

**Treatment.**—The treatment is that of congenital syphilis.

## ACQUIRED SYPHILIS OF THE LIVER

1. *Secondary syphilis.*—Jaundice formerly occurred in about  $\frac{1}{4}$  per cent. of cases of syphilis at the same time as the roseola and enlargement of glands, but it is now almost unknown. Rapid recovery generally followed treatment with mercury, but occasionally death occurred from acute hepatic necrosis. It must, of course, be distinguished from the jaundice following treatment with organic arsenical preparations (p. 229).

2. *Tertiary syphilis.*—**Ætiology.**—Gummata of the liver are becoming increasingly uncommon; but in more than half of the cases in which other active syphilitic lesions are found at necropsy the liver is affected.

Syphilis affects the liver three times as frequently in men as in women. The disease is generally discovered between 10 and 20 years after infection, but in rare instances it has occurred within a year.

**Pathology.**—In the early stages a mass of pink syphilitic granulation-tissue, sharply separated from the healthy liver, is found; necrosis soon occurs in the centre, which becomes yellowish-white. The caseous mass is later surrounded by a fibrous capsule; as this contracts, the liver becomes more and more deformed. The capsule of the liver in the neighbourhood of a gumma is thickened, and adhesions often develop between it and the adjacent organs, the diaphragm and anterior abdominal wall. Unless they are very large, gummata, which are generally multiple, are slowly absorbed till they may finally be represented by nothing more than scars, from which fibrous tissue radiates into the capsule. Much less often a large part of the liver is diffusely infiltrated. Gummata are often associated with some degree of diffuse syphilitic hepatitis, which produces cirrhotic changes in long-standing cases, especially if the patient is alcoholic or has been treated with arsphenamine derivatives.

**Symptoms.**—Gummata and cicatrices are sometimes found after death without having led to any symptoms. The nature of the symptoms they produce depends upon the size, extent and position of the lesions. Before any localising symptoms appear the patient may complain of general ill health, which is often associated with gastro-intestinal symptoms. The first symptom pointing to disease of the liver is generally pain in the right hypochondrium, the result of perihepatitis over a gumma. The pain may radiate to the right shoulder and is sometimes associated with local tenderness.

Irregularities on the anterior surface of the liver produced by gummata and by the contraction of cicatrices are easily palpable. The diagnosis from malignant disease can be made by the presence of a positive Wassermann reaction and the rapid disappearance of a gumma with antisymphilitic treatment; jaundice and ascites are much more common in malignant disease, in which the constitutional symptoms are generally more severe, and there may be evidence of a primary growth in some



other situation. In hydatid disease the liver is smooth apart from the tumour itself, but in syphilis it is often irregular, owing to the contraction of cicatrices. The presence of eosinophilia points to hydatid disease. A gumma near the gall-bladder or in the left lobe of the liver may simulate a growth of the gall-bladder or of the stomach respectively.

Irregular fever sometimes occurs, disappearing with antisyphilitic treatment. In rare cases an infected gumma may break down, when the symptoms and sequelæ do not differ from those of other forms of hepatic abscess.

Jaundice is infrequent in syphilis of the liver, but it is occasionally produced by the pressure of a gumma or of a syphilitic cicatrix; in very rare cases this is associated with attacks of pain indistinguishable from biliary colic due to gall-stones.

Ascites is uncommon, but may result from pressure of gummata or cicatrices on the intrahepatic branches of the portal vein or less frequently on the vein itself in the portal fissure, in which cases thrombosis is likely to occur.

When a gummatous liver is associated with amyloid disease, the clinical aspects of the latter may be so prominent that the presence of a gumma is overlooked. The liver and the spleen are enlarged, ascites and œdema are present, and the urine contains albumin and casts.

**Diagnosis.**—The possibility of syphilis should always be remembered in obscure hepatic disorders. Apart from a history of infection and the presence of other syphilitic lesions, the Wassermann reaction should always be tested in doubtful cases. As, however, infection with syphilis does not prove that every lesion present is syphilitic, the final proof of the nature of the disease is obtained only if great improvement or complete recovery results from antisyphilitic treatment. The diagnosis from cirrhosis of the liver is suggested by the greater irregularity in the enlargement of the liver. Hæmatemesis, dilated veins on the abdominal wall, jaundice and symptoms of gastritis and hepatic insufficiency are much more common in cirrhosis, and the nutrition suffers at an earlier stage.

**Prognosis.**—The prognosis of syphilitic lesions of the liver is good if treatment is actively carried out at an early stage. In the rare cases in which the symptoms are due to pressure exerted by cicatrices and not by gummata little or no improvement can occur.

**Treatment.**—As soon as the possibility of syphilis is recognised a full course of penicillin should be given. Large doses of iodide should then be ordered and ill results rarely follow the administration of as much as gr. 40 of sodium iodide every 6 hours; a patient is more likely to suffer from iodism if the dose is gradually increased from a small quantity than if full doses are given at once. Mercury should also be given, but no organic arsenical preparation because of the danger of hepatic necrosis occurring as a result of its action on the already damaged liver cells.

## AMŒBIC HEPATITIS AND HEPATIC ABSCESS

This is dealt with under Amœbiasis (see p. 279).

## HYDATID DISEASE OF THE LIVER

**Ætiology and Pathology.**—Hydatid disease is caused by swallowing the ova of the echinococcus or hydatid worm (p. 324). The infection often dates from childhood, even when the disease is not recognised till middle life. The ova are conveyed by the fingers from playing with a dog, the skin, paws or muzzle of which have been contaminated with infected fæces. Infection may also result from contaminated water, salads, watercress or uncooked vegetables. The disease occurs in many countries, and is common in Australia and New Zealand, where with a population of 1½ millions there are 150,000 dogs, of which about a third are spreading myriads of hydatid

eggs about the country homesteads every day. It also occurs in England, but is rare in North America.

When the eggs are swallowed, the embryos set free by digestion of the egg-shell pass through the walls of the stomach or small intestine into the radicles of the portal vein, by which they reach the liver, where they are generally arrested. The embryo now forms a small cyst, with an internal, nucleated, protoplasmic layer (the endocyst) and an external "cuticular membrane". The reaction in the surrounding tissues results in the formation of a fibrous capsule. After a time a dozen or more buds project from the endocyst, and develop into daughter cysts, identical in structure with the mother cyst; these soon separate from the endocyst of the mother cyst and become free.

The fluid in the cyst is clear or very slightly opalescent, with a specific gravity between 1.005 and 1.011. It contains chlorides, phosphates, traces of sulphates and succinates, and some unknown toxic substances, but only occasionally traces of albumin or sugar. Hooklets and less often hydatid heads may be found in the fluid.

The liver is involved in 60 per cent. of cases of hydatid disease in man. A single cyst is generally present, but there are occasionally multiple cysts, or single ones may develop in more than one organ.

**Symptoms.**—The patient remains in good health until the weight of the cyst, its pressure on surrounding parts, or the occurrence of a complication, such as rupture or suppuration, causes symptoms. A hydatid cyst of the liver may remain latent and be discovered only after death or in the course of a routine examination of the abdomen in a patient without abdominal symptoms.

The increasing size of the liver may give rise to a sensation of weight and fullness in the right hypochondrium, and pain may be felt in the right shoulder. Jaundice caused by pressure on the bile-ducts, œdema of the legs and scrotum by pressure on the inferior vena cava, and ascites by pressure on the portal vein, may all occur in exceptional cases.

A small cyst may rupture into the biliary passages: intense jaundice results, and the patient generally develops suppurative cholangitis. A large cyst may burst into the general peritoneal cavity, especially after a blow on the abdomen, when shock and collapse may follow. Symptoms of an allergic character may result, especially severe urticaria, erythema and pruritus. Less frequently there may be diarrhœa and vomiting, and dyspnœa, sometimes of an asthmatic character. In rare cases convulsions, collapse and cardiac failure may occur and end fatally. Rupture into the stomach or intestines may lead to spontaneous recovery.

The upper part of the right side of the abdomen and lower part of the thorax become prominent when the cyst is large. If the cyst reaches the front of the liver it becomes palpable in the hypogastrium. When it projects from the under surface, the liver is pushed forward and it may simulate a large gall-bladder or a renal tumour. A cyst near the convexity pushes the diaphragm upwards and may compress the lung and simulate a pleural effusion. In such cases the irregularity in the upper surface of the liver can be recognised with the radiograph. When deeply embedded in the liver, it produces a more general expansion and no local tumour is palpable. The tumour is generally tense and elastic. In rare cases percussion of the middle finger, when the left hand is placed flat over the cyst, produces a peculiar vibration—the hydatid thrill—which is pathognomonic.

Bacteria may invade the fibrous capsule and multiply between it and the cuticular membrane, with the result that the nutrition of the hydatid is impaired and the parasite dies. Its death results in a change in the cuticular membrane, which, when healthy, is impervious to bacteria and leucocytes, but now allows them to pass into the fluid, which acts as an excellent culture medium and gradually becomes filled with pus cells. Symptoms of hepatic abscess are present, and the abscess may finally rupture into the general peritoneal cavity, stomach or intestines.

**Diagnosis.**—The discovery of a tumour of the liver should lead to a consideration of cancer, syphilis and hydatid cyst. The general health is greatly affected in the first, comparatively little or not at all in the second and third. In cancer and syphilis the tumour is likely to be irregular and multiple; in hydatid it is a uniform round swelling, and most frequently only one can be felt. The two former are hard and obviously solid, while the latter is elastic, and in rare cases the characteristic hydatid thrill can be felt. The Wassermann reaction is positive with a gumma and generally negative in the other diseases. Eosinophilia is frequent in hydatid, but in no other liver disease, and may rise as high as 75 per cent. The intradermal injection of sterile hydatid fluid produces a positive cutaneous reaction in 90 per cent. of cases (Casoni test). Once the skin has become sensitised it may remain so permanently in spite of removal of the cyst. The complement fixation and precipitin tests are less reliable. Radiography may show the outline of a hydatid cyst if its wall has become partly or wholly calcified.

**Prognosis.**—A cyst may continue to grow for 20 or 30 years, but the possibility of suppuration or perforation is a constant danger. When it dies, the cuticular membrane folds on itself and may become calcified; its contents dry up and form a mass containing gritty material. It can then cause no further trouble.

**Treatment.**—In places where hydatid disease is common, dogs should never be fed on raw offal. They should be treated periodically with the vermifuge, arecoline, and not petted unless the hands are carefully washed afterwards.

Hydatid cysts were formerly treated by tapping, but such methods have now been completely superseded by an open operation, in which the fluid is evacuated and as much of the cyst wall as possible is removed. In some cases the latter is very loosely attached and can be pulled out intact. The operation should be performed whenever a hydatid cyst is diagnosed, even if it causes no symptoms, as there is always a danger of serious complications.

## CARCINOMA OF THE LIVER

**Ætiology and Pathology.**—(a) **PRIMARY GROWTHS.**—Primary carcinoma of the liver is found only about once in each thousand necropsies, and primary sarcoma is considerably rarer. Primary carcinoma may be derived from the liver-cells (hepatoma) or, much less frequently, from the bile-duct cells (cholangioma); 90 per cent. of the former and 50 per cent. of the latter occur in cirrhotic livers. Primary cancer occurs in about 7 per cent. of patients with cirrhosis, the incidence being many times as great as among patients without cirrhosis. The incidence is very high in the Dutch East Indies owing to the great frequency of non-alcoholic cirrhosis among the natives and to a special tendency of this form of cirrhosis to undergo malignant degeneration. It accounts for some 10 per cent. of all malignant tumours in some Asiatic countries such as Japan and the Malay States.

Primary cancer of the liver readily invades the portal vein, along which it spreads in both directions from the point of entry, forming a tree-like cast of the affected part of the portal system. On section the growth-distended vessels give the appearance of a tumour of multicentric origin, and dissemination to other parts of the liver often occurs through the portal system. In 40 per cent. of cases extrahepatic metastases are present. Spread by lymphatics may involve glands in the portal fissure, which press upon the portal vein and bile-ducts, as well as glands elsewhere in the abdomen and chest, and malignant emboli may pass by the hepatic veins to the lungs. The symptoms may be indistinguishable from those of cirrhosis, the liver being normal in size or considerably enlarged. In the latter case, nodules can sometimes be felt on the surface. The spleen is often enlarged, and ascites develops owing to portal obstruction. Pain in the right hypochondrium and jaundice are more common than in uncomplicated cirrhosis.

(b) **SECONDARY GROWTHS.**—Secondary carcinoma of the liver is about thirty times as common as primary carcinoma; it is ten times as common as secondary sarcoma. It occurs most frequently after the age of 50. It is more common in women than men because it frequently follows carcinoma of the breast and female genital organs, and is rare in carcinoma of the lip, mouth and tongue, which are much more common in men than women. The most common seat of the primary disease is the stomach, and then in order the colon, breast and uterus. Cancer of the gall-bladder, extrahepatic bile-ducts and the stomach may invade the liver by direct continuity.

**Symptoms.**—The liver is almost always palpable, as it is enlarged and abnormally hard. It becomes progressively larger until it may be so enormous that it appears to fill the whole abdomen, the right lobe being generally most affected. It is irregular in shape, and individual nodules of growth are often depressed in the centre—"umbilicated". Deposits may be felt at the umbilicus and in the falciform ligament near the linea alba.

Persistent pain is generally felt in the right hypochondrium and in the back; it may pass to the right shoulder and occasionally down the arm. It is in part due to stretching of the capsule of the liver, especially when it grows rapidly, but the most severe pain is due to perihepatitis, the presence of which can sometimes be confirmed by feeling and hearing a rub. Deep-seated growths may cause no pain throughout the illness.

Progressive and persistent jaundice is present in 50 per cent. of cases owing to pressure on the main bile-ducts within the liver by the growth or on those in the portal fissure by glands. The fæces sometimes retain their colour, as the jaundice may be due to pressure on the intrahepatic bile-ducts, one or more of which escape.

Ascites develops in 50 per cent. of cases, generally as result of malignant peritonitis or perihepatitis. It may also be caused by pressure on the capillaries when the liver is extensively infiltrated with growth and by portal thrombosis following invasion of the portal vein. The fluid is generally serous, and when jaundice is present it is bile-stained. Extravasation of blood into a superficial nodule may cause it to be hæmorrhagic. In rare cases it is chylous owing to obstruction of a main lymphatic, but more frequently it is chyloform. Perforation of the organ primarily involved or infection without perforation may cause it to become purulent. Oedema of the ankles is present in the late stages as a result of toxæmia, hypoproteinæmia and cardiac weakness. More widespread dropsy may be caused by pressure upon or thrombosis of the inferior vena cava or some other large vein.

In the late stages the patient becomes rapidly weaker. The appetite is lost, and there is often a special distaste for meat. The body weight falls progressively, but occasionally the loss of weight due to the general emaciation is more than counterbalanced by the increase in weight of the liver and the accumulation of fluid in the abdomen. The skin is inelastic and sallow, and secondary anæmia develops. It is often possible to see the liver moving up and down with respiration through the wasted abdominal wall. Fever is often present, especially in rapidly advancing cases, quite apart from that caused by infection of the primary growth or of a necrotic secondary deposit. Suppurative cholangitis may be caused by the infection of obstructed ducts.

The large liver and the ascites may push the diaphragm up and compress the bases of the lungs, which are then likely to become congested, but the main enlargement is always downwards. The growth may spread through the diaphragm and cause hiccough and cough; pleurisy generally develops and often gives rise to a blood-stained effusion, but empyema is rare.

Finally the patient becomes somnolent and sometimes delirious. Coma is generally present during the last few days of life. Respiration becomes gradually more shallow, and death comes imperceptibly.

**Diagnosis.**—A painful, tender and irregular enlargement of the liver is most frequently due to a growth, and the probability is increased if general symptoms of

malignant disease are present. If there is evidence of a primary growth elsewhere or a growth has been removed by operation within the last 5 years, the diagnosis can be made with certainty.

The tumour produced by cancer of the liver must be distinguished from one produced by syphilis and hydatid of the liver. The shape of the liver often helps in the diagnosis, and umbilication of a nodule is conclusive evidence of cancer. The general health is much more impaired and the patient is generally older in cancer than in syphilis and hydatid disease. A history of syphilis or evidence of its effects in other parts of the body points to a gumma, and unless a primary growth is discovered the Wassermann reaction should always be tested. Whenever hydatid disease is possible, a differential blood count should be made, as eosinophilia is frequently present, but not in the other conditions. When there is ascites it may be impossible to diagnose between cirrhosis and cancer, especially if the patient is slightly jaundiced. The abdomen should be tapped so that the liver can be palpated; the irregularities of the cirrhotic liver are so much less marked than those in cancer that they are often not recognisable through the abdominal wall. The spleen is generally large in cirrhosis, but normal in size in cancer, and the liver is rarely very large in cirrhosis. Pain is generally much greater in cancer, and jaundice, when present, is more profound.

In secondary cancer of the liver the primary disease is often latent, especially when it is situated in the stomach, colon, tail of the pancreas, prostate or lung. But when a thorough investigation fails to reveal a primary growth elsewhere in the body, if jaundice and ascites are absent and emaciation is slight, a single, rapidly growing tumour of the liver is more likely to be primary than secondary. In doubtful cases liver puncture may provide a conclusive diagnosis, but an exploratory laparotomy may often be of more value as it enables a biopsy to be done if needed, and satisfies both physician and relatives that no possible further therapeutic steps are possible. Peritoneoscopy, though regularly practised in some clinics, has had little general support as a diagnostic procedure (see p. 723).

**Prognosis.**—Cancer of the liver is always fatal. The course of primary cancer is very rapid, as it rarely lasts more than 4 months, and death may occur even within 4 weeks of the onset of symptoms. The duration of the illness in secondary carcinoma of the liver depends upon the primary disease, death being often due to the latter. If the primary disease has been removed by operation or is latent, death may not occur for a year or even longer after the disease of the liver is discovered; but most cases prove fatal within 6 months. The disease generally advances steadily, but it may remain almost stationary for a time and then rapidly progress to a fatal issue.

**Treatment.**—It is rarely justifiable to operate when it is known that a growth of the liver is present; but if during an operation for cancer of the stomach or gall-bladder the liver is found to be involved only in its immediate neighbourhood, an attempt should be made to remove the affected part. Moreover, the presence of one or more small nodules in the liver does not contraindicate partial gastrectomy or colectomy for the primary growth, as the operation may be followed by a period of a year or more of complete freedom from symptoms. Much care and thought must be given to the psychological handling of the individual patient; though no general rule can be laid down it is, in general, unwise to inform him that he has an inoperable and fatal disease. If it is decided to tell him the truth, some form of treatment should, if possible, be given him at the same time in order to provide some slight hope even if this is plainly stated to be small.

The medical treatment of cancer of the liver is purely palliative, but by means of morphine the patient should be spared pain throughout the illness. An injection of morphine should be given whenever pain is felt, and the dose should be increased as the disease progresses and the patient becomes accustomed to the drug. With adequate dosage patients can be kept drowsy but free from pain and not to the end. The bowels should be kept regular by drugs, the dose of which

requires to be increased as more morphine is given. The patient should be allowed to eat and drink exactly what he likes, and no restrictions should be made on account of the supposed indigestibility of certain articles of food, nor should large quantities of food be forced upon a patient who has no appetite. When the diagnosis has once been made with complete certainty, frequent examinations of the abdomen distress the patient without doing any good.

## NON-SUPPURATIVE PYLEPHLEBITIS AND PORTAL THROMBOSIS

**Ætiology and Pathology.**—The stagnation of blood caused by cirrhosis of the liver accounts for about 30 per cent. of cases of portal thrombosis, but the latter is so rare that it occurs in less than 5 per cent. of cases of cirrhosis. Malignant disease of the liver, stomach or pancreas is the next most common cause; invasion of the veins of the affected organ leads to thrombosis, which spreads to the portal vein. Syphilitic changes in the walls of the portal vein and non-suppurative pylephlebitis caused by spread of infection from neighbouring parts may cause thrombosis.

Portal thrombosis may extend throughout the vein and its branches, but more frequently it is localised to the main trunk and one or more intrahepatic branches or extrahepatic tributaries.

**Symptoms.**—In the presence of cirrhosis of the liver or intra-abdominal growth, especially if ascites is present, there may be no indication that portal thrombosis has occurred. If, however, the patient is in comparatively good health, sudden occlusion of the portal vein may lead to the rapid development of ascites, hæmatemesis and melæna, and the spleen becomes enlarged. When the splenic vein is occluded, the splenic enlargement is rapid and considerable. When mesenteric veins are suddenly involved, hæmorrhagic infarction results and leads to intestinal paralysis with severe melæna and early death.

## SUPPURATIVE PYLEPHLEBITIS

**Ætiology.**—Suppurative pylephlebitis is almost always secondary to some intra-abdominal inflammatory disease, generally associated with the presence of pus under pressure. Acute appendicitis accounts for nearly half of the cases.

**Pathology.**—The veins leading from the source of infection to the liver, together with the trunk and intrahepatic branches of the hepatic vein, may all be involved, but the disease is generally less extensive and may be confined by firm clots to a part of the portal vein or one of its branches. The affected veins contain pus and broken-down blood clots. Their walls are acutely inflamed and may give way, leading to the formation of abscesses. Thus a large abscess may develop in the mesentery or behind the pancreas. The liver is almost always involved by extension to the intrahepatic portal branches, or by secondary abscesses formed from infective emboli from the part of the vein primarily affected. Innumerable minute abscesses are present, many of which may coalesce to form a honey-combed appearance or large abscesses. Superficial abscesses may rupture and lead to general or local peritonitis, which may also result from the primary disease. The infection is generally caused by *Bact. coli*, streptococci or staphylococci, and very rarely by *Salm. typhi* or *Sh. dysenteriae*.

**Symptoms.**—The onset is generally sudden, the symptoms due to the primary disease being complicated by the occurrence of a rigor or pain and tenderness over the liver. The clinical picture is eventually a composite one of the symptoms of the primary disease, sepsis and liver disease, with the frequent addition before death of

pneumonia, pulmonary abscesses or empyema, generally on the right side. Evidence of portal obstruction is rarely present. The patient looks anxious and ill. He is sallow and in about half the cases is slightly jaundiced. Fever is continuous, intermittent or remittent, leucocytosis is present, and the pulse and respiration are rapid. Rigors with profuse sweating are common, especially in the early stages. Uniform enlargement of the liver occurs in about 60 per cent. of cases. Pain and tenderness are generally present, and a rub may be heard over the liver. The spleen is only occasionally enlarged. Vomiting is common and diarrhoea may occur. Blood cultures are generally sterile.

**Diagnosis.**—The development of a septic state with rigors and enlargement and tenderness of the liver in a patient with appendicitis or other intra-abdominal disease is suggestive of suppurative pylephlebitis, but a correct diagnosis is rarely made. In *amoebic abscess of the liver* there is generally a history of dysentery, the progress of the disease is less rapid, and there may be signs of a single abscess instead of a uniform enlargement of the liver. A history of gall-stones is much more common in suppurative cholangitis than in pylephlebitis, and jaundice appears earlier and is deeper. The diagnosis from a sub-diaphragmatic abscess secondary to appendicitis may be impossible, and the two may be present together. Acute infective endocarditis with enlargement of the liver and spleen without cardiac murmurs closely simulates suppurative pylephlebitis.

**Prognosis and Treatment.**—The disease is almost always fatal, and no treatment is of real avail, though massive doses of antibiotics and sulphonamides should always be tried.

THOMAS HUNT.

## DISEASES OF THE GALL-BLADDER AND BILE-DUCTS

### CHOLECYSTITIS

**Ætiology and Pathology.**—Cholecystitis results from infection of the gall-bladder most frequently with *Bact. coli*, but also with *Salm. typhi* and *paratyphi*, streptococci and staphylococci. The mere presence of bacteria in the bile does not necessarily lead to cholecystitis, just as bacilluria may occur without causing pyelitis. Organisms which normally inhabit the colon and lower part of the ileum might theoretically gain access to the gall-bladder by four different channels.

(1) Typhoid bacilli pass from the intestines by the lacteals to the mesenteric glands, from which they are conveyed by the lymphatics to the thoracic duct and thence into the general circulation, a typhoid septicæmia being thus produced. The bacilli are excreted from the blood into the bile by the liver and in the urine by the kidneys probably in every case, but cholecystitis and pyelitis develop in only a comparatively small proportion. There is no doubt that *Bact. coli* can pass through the healthy bowel wall, but under ordinary conditions it reaches no farther than the lymphatic glands, which act as a very efficient filter, and there is no evidence that cholecystitis is ever preceded by a *Bact. coli* septicæmia.

(2) The portal vein would seem a likely channel for the passage of *Bact. coli* to the liver and thence in the bile to the gall-bladder without gaining access to the general circulation. But the portal blood is normally sterile and remains so even when the wall of the bowel is damaged, and bacteria injected into the portal vein of animals are not excreted in the bile.

(3) It has been suggested that cholecystitis is the result of infection with strains of streptococci having a special affinity for the gall-bladder, which are conveyed to

it by the cystic artery from infected teeth, tonsils and other foci. But infection of the gall-bladder with streptococci is much less common than with *Bact. coli*, and later investigations have failed to confirm the experiments upon which this theory was based.

(4) Cholecystitis might be due to an ascending infection from the duodenum, and though this is normally sterile, in achlorhydria large numbers of *Bact. coli* and streptococci are often present, and achlorhydria is found in about 30 per cent. of cases of gall-stones. In the acute gastritis which occurs in food poisoning and influenza and other infections achlorhydria is generally present, and it is possible therefore that the duodenum may be infected during the temporary achlorhydria resulting from acute gastritis, and last sufficiently long for ascending infection of the gall-bladder to occur. It is in fact not uncommon for patients with chronic cholecystitis to date their symptoms from an attack of food poisoning or an acute infection, which may have been accompanied by achlorhydria, even if the gastric secretion when the patient comes under observation is normal.

Infection of the gall-bladder first leads to inflammation of the mucous membrane, the external appearance of the gall-bladder remaining normal. The inflammation subsequently spreads to the deeper tissues; the walls become thick and inelastic and the cystic lymphatic gland enlarged and inflamed.

Cholecystitis may be acute, subacute or chronic from the onset. Acute and subacute cases may become chronic, and suppuration or gangrene may occur in a chronically inflamed gall-bladder if a stone becomes impacted in the mouth of the cystic duct. The contents may become purulent in the course of an acute infection without gall-stones, but necrosis is very rare in their absence.

#### ACUTE CHOLECYSTITIS; EMPYEMA OF THE GALL-BLADDER

**Ætiology and Pathogenesis.**—Acute cholecystitis occurs in about 1 per cent. of cases of typhoid and paratyphoid fever. Apart from this it is rare unless the cystic duct is obstructed by an impacted gall-stone. Bile is generally present in the gall-bladder only if the contents are examined within a few days of the onset. The wall is thickened and obviously inflamed, and the cystic lymphatic gland is enlarged. When the cholecystitis is secondary to an impacted gall-stone suppuration or gangrene is likely to occur. Suppuration leads to empyema of the gall-bladder: if adhesions have previously formed as a result of chronic cholecystitis the empyema may rupture into the duodenum or colon; otherwise localised or generalised peritonitis results. Necrosis may be localised or general. When localised it is generally secondary to ulceration at the neck of the gall-bladder following impaction of a stone; rupture into the duodenum or the production of a local abscess commonly follows. The whole wall of the gall-bladder may become gangrenous as a result of over-distension from obstruction of the cystic duct or less commonly of the common bile-duct, especially in elderly people in whom the blood supply is deficient; unless cholecystectomy is promptly performed, general peritonitis is then certain to develop.

**Symptoms.**—Acute pain in the right hypochondrium is the most constant symptom. It often radiates to the angle of the right scapula and less frequently to the right shoulder. The gall-bladder may be felt as an extremely tender tumour, but more frequently the rigidity of the right rectus makes deep palpation impossible. Jaundice occurs only if there is a stone in the common bile-duct or the cholecystitis is part of a general infection of the biliary passages. Pyrexia with polymorphonuclear leucocytosis is always present.

The *défense musculaire* often involves the right dome of the diaphragm as well as the right rectus, and signs of œdema and congestion of the base of the right lung may be present.

In mild cases recovery takes place after a few days, but symptoms of chronic



cholecystitis may develop at a later date. In suppurative or gangrenous cholecystitis fatal complications rapidly occur unless an early operation is performed.

**Treatment.**—The patient should be kept strictly at rest with a lacto-vegetarian diet and the local application of heat. The effect of sulphonamides and full doses of antibiotics should be tried but if suppuration or gangrene is suspected, an operation should be performed without delay.

### CHRONIC CHOLECYSTITIS

**Symptoms.**—Chronic cholecystitis is a common cause of chronic dyspepsia. The patient complains of intractable indigestion of an irregular character, in striking contrast with the clock-like regularity of the pain in duodenal ulcer. The time of onset and the severity of the pain vary greatly from meal to meal and from day to day; it sometimes begins immediately after food, and at other times it may not come until 2 or 3 hours after a meal, or it may occur only in the early part of the night. It is unaffected or only incompletely relieved by taking food and by alkalis. In most cases the patient complains of what he calls flatulence, but this is really only a sensation of fullness, which is not associated with increased fermentation, and with eructation only when it gives rise to aerophagy by causing the patient to make repeated but futile efforts to belch in the hope of relieving his discomfort.

Nausea is common. It may occur on waking, when it is sometimes associated with vertigo, cold sweats or headaches, in which case migraine may be simulated, though the headache is not unilateral. It may be relieved by breakfast, unless eggs are eaten, when it is often aggravated. It is sometimes followed by vomiting, which gives much less complete relief than in ulcer.

Patients with ulcer generally lose all their pain in 2 or 3 days if put to bed on a strict diet, but improvement is less likely to follow in cholecystitis; the dyspepsia may, however, rapidly improve if fried food and other indigestible fatty foods are prohibited. Constipation is generally present, but in some cases intermittent or continuous diarrhoea of a mild grade occurs, and in rare instances profuse, watery diarrhoea heralds the onset of an acute exacerbation.

If attacks of biliary colic, whether of the abortive or acute variety, occur in association with symptoms of cholecystitis, gall-stones are probably present.

The discomfort after meals is generally in the mid-epigastrium, but it often extends to the right and may be confined from its onset to the right hypochondrium. It is frequently associated with pain at the angle of the right scapula.

Tenderness of the gall-bladder is the most characteristic sign of cholecystitis. It is best elicited with the patient lying relaxed on his back; the fingers are then pressed beneath the right costal margin in the region of the gall-bladder. The pain is much increased when the fingers are brought into still more intimate contact with the gall-bladder by deep inspiration, which is then sharply arrested.<sup>1</sup> The pain produced in this way is in striking contrast with the absence of tenderness when deep pressure is exerted under the left costal margin or a short distance to the inner or outer side of the gall-bladder under the right costal margin, though it is not uncommon for a slighter degree of tenderness to be observed over the whole of the lower border of the liver, especially in the immediate neighbourhood of the gall-bladder. Pressure on the gall-bladder may also cause nausea.

The upper part of the right rectus abdominis muscle is often tender and rigid; tenderness and rigidity of the lowest intercostal muscles may cause impeded respiration and a stitch in the right side of the chest. Tenderness is also sometimes present over the third to the tenth dorsal spines, the muscles to their immediate right and the end of the eleventh rib.

<sup>1</sup> This sign was first described by Naunyn in 1892, but is often incorrectly ascribed to Murphy who described it ten years later.

In chronic cholecystitis there is generally no pyrexia, but occasionally the temperature rises to between 99° and 100° F. each evening or during exacerbations of the inflammation accompanied by more marked symptoms. Jaundice rarely occurs unless there is biliary obstruction due to a calculus, but in some cases an associated hepatitis leads to slight icterus and marked excess of urobilinogen in the urine.

**Diagnosis.**—The healthy gall-bladder can be visualised by cholecystography. After a preliminary film of the right upper quadrant of the abdomen has been taken, a dose of pheniodol or Telepaque is swallowed in the evening and no further food or drink is taken until the next morning. Films are then taken at 12 to 16 hours after swallowing the dye and, if no good shadow is seen, again at 18 and 20 hours. When a sufficiently clear picture has been obtained a fatty meal, consisting mainly of buttered eggs is eaten and films are taken at hourly intervals to show the gall-bladder contractility and rate of emptying. If no shadow is seen at all, the test is repeated the next day using a slightly larger dose of the radio-opaque dye. Pheniodol and similar compounds have now in general replaced the earlier tetraiodophenolphthaleine first used by Graham and Cole in 1924. Most of the substances now used contain over 60 per cent. of iodine and are contraindicated in renal disease and in gastro-intestinal disorders such as pyloric stenosis, which prevent absorption from the alimentary tract. Liver disease need not be regarded as a contraindication. The method depends upon the substance used containing atoms of sufficient atomic weight to throw a radiographic shadow, and upon its proper absorption in the alimentary tract and secretion into the bile by the liver. In this way it reaches the gall-bladder via the cystic duct where, as a result of absorption of nine-tenths of the water of the bile by the mucous membrane, it becomes sufficiently concentrated to throw a shadow of the gall-bladder, which can be seen on the screen, and a cholecystograph taken. A normal gall-bladder gives a homogeneous shadow with a regular outline; it is not tender when directly palpated, and it is freely movable, being quite independent of the shadow of the duodenal bulb, which can be seen simultaneously by giving a small opaque meal. The normal gall-bladder is found to have contracted and evacuated the greater part of its contents an hour after the fatty meal. If no shadow of the gall-bladder is obtained this may be due either to the dye not having entered the gall-bladder or to its not being concentrated by it sufficiently to give a radio-opaque shadow. The former may occur in liver disease, especially if jaundice is present, or if a calculus or adhesions obstruct the neck of the gall-bladder at the cystic duct, and the latter if the mucous membrane of the gall-bladder is unable to concentrate the bile—as in cholecystitis—whether gall-stones are present or not. Variations in shape, position and density of shadow and emptying after a fatty meal are difficult to interpret, but may indicate cholecystitis; when the mucous membrane is at all seriously diseased no shadow is seen. In some cases of cholecystitis the visualised gall-bladder is tender, or may be in an unusual position or deformed by adhesions even when contracted after the fatty meal; it may then be impossible to separate the shadow of the gall-bladder from that of the duodenal bulb. It must be pointed out, however, that poor technique in radiography, bad preparation of the patient, vomiting of the dye, overlying gas shadows, and a few rare congenital abnormalities all make the interpretation of cholecystograms a matter requiring considerable experience.

When the diagnosis is uncertain, an attempt may be made to obtain some of the contents of the gall-bladder for pathological examination. A sterilised duodenal tube is swallowed up to the 23-in. mark first thing in the morning before the patient has had anything to eat or drink. The stomach is emptied and washed out with sterile water. The tube is then slowly paid out up to the 28½-in. mark, which allows sufficient length for the duodenum to be reached. Samples are aspirated periodically until the comparatively abundant, acid, turbid and colourless fluid present in the stomach is replaced by the very small quantity of neutral or alkaline, clear and generally bile-stained fluid present in the duodenum, which generally occurs within 1 or

2 hours. Radiographic control of the position of the tube is advisable, if means are available. The duodenum is washed out with sterile water, and 25 ml. of a 25 per cent. solution of magnesium sulphate are injected through the tube. This causes the gall-bladder and the bile-ducts to contract and the sphincter of the common bile-duct to relax. An abundant flow of pure bile, first pale from the common bile-duct and then dark from the gall-bladder, rapidly appears; this is aspirated, and the tube is withdrawn. In the absence of disease the gall-bladder bile contains no pus cells, and only a few epithelial cells, pigment granules and rarely cholesterol crystals; it is generally sterile, but a few bacteria may be present if the duodenum has not been sufficiently washed out, especially in cases of achlorhydria. In cholecystitis the quantity of mucus is greater than normal, and degenerated columnar epithelial cells, pigment granules and, less frequently, pus cells are present; the bile contains bacteria, most commonly an aberrant form of *Bact. coli* in pure culture, and rarely streptococci or staphylococci. In rare cases *Salmonella typhi* may be isolated many years after the original typhoid fever. The combination of cholesterol crystals with pigment granules suggests the presence of gall-stones, especially if large cholesterol crystals with the corners broken or rounded are found.

**Treatment.**—Some early cases of cholecystitis can be cured by medical treatment, and great improvement often occurs even in very chronic cases. Sulphonamide drugs are excreted in the bile in a concentration sufficient for bacteriostatic effects as judged by the levels required for this purpose in the blood. Unfortunately, since they reach the gall-bladder via the cystic duct and not through the blood-stream, they are not excreted in the bile in significant amounts if either liver disease or cystic duct obstruction is present. The same applies to both penicillin and streptomycin; nevertheless a trial of chemotherapy is justified provided there is no clear evidence of either of these complications, and good results may certainly follow a course of sulphadiazine in a few cases. There is some evidence that part of this drug may reach the gall-bladder wall directly through the blood.

Hexamine has been widely used as a biliary disinfectant and must be given with alkalis to avoid risk of damaging the kidneys. It is excreted unchanged in the bile and is given in doses of gr. 60 increasing up to gr. 120 with an equal amount of sodium bicarbonate. It must be taken on an empty stomach and should not be followed by food which will cause the gall-bladder to empty itself rapidly. Daily treatment must be continued for a number of weeks, but results are difficult to assess.

Biliary drainage should be stimulated by giving a concentrated solution of magnesium sulphate when the stomach is empty an hour before breakfast. The correct dose is the largest quantity the patient can take without producing diarrhoea when no other aperient is used. The salts cause the gall-bladder and bile-ducts to empty their contents into the duodenum through the relaxed sphincter of the common bile-duct. Half an ounce of olive oil should be taken three times a day half an hour before meals, as it has the same effect as magnesium sulphate on the gall-bladder. Bile salts are the most effective of all stimulants of bile excretion and they also play an essential part in keeping cholesterol in solution. The sodium salt of dehydrocholic acid (Dehydrocholin) should be given three times a day in a dose of gr. 3 to 5.

There is no clear evidence that food containing cholesterol has any appreciable effect on the quantity of cholesterol in the blood or bile. Consequently a cholesterol-free diet cannot be regarded as a means of preventing gall-stones. When, however, a patient with cholecystitis is aware that the less digestible forms of fatty food give him discomfort, they should, of course, be avoided. If, however, he is able to tolerate fats they should be included in the diet, as they stimulate gall-bladder emptying.

If achlorhydria is present, gastric lavage may be practised in the hope that normal secretion will be restored, and hydrochloric acid should be given before breakfast and with lunch and dinner.

The only indication for surgery in chronic cholecystitis is the failure of medical

treatment which has been thoroughly carried out for an adequate time. If it is likely that gall-stones are present, it is generally useless to delay operation. In all cases cholecystectomy should be performed in preference to cholecystostomy.

## GALL-STONES

**Synonym.**—Cholelithiasis.

**Ætiology.**—Clinically gall-stones occur about twice as frequently in women as in men, but they are found post mortem about five times more often in women than men. They are very rare before the age of 15; 75 per cent. of clinical cases occur between 30 and 60, 40 to 45 being the most common age. The incidence is greatest post mortem about 20 years later. Gall-stones occur in about 20 per cent. of all women and 7 per cent. of all men dying after the age of 25. There is a definite tendency for gall-stones to be familial, and they are often associated with obesity and overeating.

**Pathology.**—(a) *Infection.*—Infection of the gall-bladder leads to cholecystitis. The agglutinated bacteria, precipitated mucus and cellular debris may form the nucleus of gall-stones if excess of cholesterol or bile-pigment is present in the bile, especially if the flow from the gall-bladder is less free than it should be. The nature and the path of infection have been discussed in connection with cholecystitis (p. 689). Stones may form very rapidly, but when they have once formed, the infection frequently dies out, and the bile, stones and wall of the gall-bladder may be sterile, though the latter still shows signs of old inflammation. In other cases the organisms commonly found in cholecystitis are still present. The "strawberry gall-bladder" is probably the result of low-grade infection. In this condition, also called cholesterolosis of the gall-bladder, cholesterol esters are formed in the wall of the gall-bladder and appear on the inner surface as multiple yellowish granules visible to the naked eye giving, on the congested and reddened mucous membrane, the appearance of an unripe strawberry.

(b) *Excess of Cholesterol in the blood and bile.*—The majority of gall-stones contain a considerable proportion of cholesterol. Normal blood contains cholesterol, which comes from endogenous and exogenous sources. The endogenous cholesterol is produced by the constant activity of the cortex of the suprarenal glands, and by the periodic activity of the corpus luteum at each menstrual period. During pregnancy the corpus luteum produces a very large quantity of cholesterol, so that the percentage in the blood gradually increases to nearly double and that in the bile to four times the normal. The exogenous cholesterol comes from certain articles of diet; it is abundantly present in eggs and to a less extent in cream, and in liver, kidney, sweetbread and brain. The importance of hypercholesterolemia in the pathogenesis of gall-stones has, however, been exaggerated. Accurate post-mortem statistics show that the greater incidence of gall-stones in females is not due to pregnancy, as the proportion of women with gall-stones who have borne children to those who have not is the same as the proportion among those who have no gall-stones. But there is no doubt that a biochemical factor must be present to explain the development of the large, solitary, pure cholesterol stones, which are occasionally found in perfectly healthy and sterile gall-bladders, and it is probable that some constitutional peculiarity in connection with cholesterol metabolism is an important predisposing cause.

(c) *Biliary stasis.*—A stone is especially likely to form in the presence of infection and excess of cholesterol in the bile if biliary stasis is also present. In some cases there appears to be a congenital or acquired abnormality of the anatomical relations or of the neuro-muscular mechanism of the bile channels, which impedes the evacuation of the bile (see p. 661). Deficient exercise also leads to biliary stasis.

By examining sections of gall-stones it is generally possible to get some idea of

the history of their formation. Thus the centre of most is white and consists of pure cholesterol; only after the stone has reached a certain size is there, as a rule, any deposit of pigment and lime salts resulting from a period of infection. Then there may be a further layer of cholesterol caused by hypercholesterolaemia, possibly the result of pregnancy; then another stratum of pigment and lime salts may form, and so on. A pure cholesterol stone corresponds to a pure oxalic acid or uric acid stone in the kidney, and the presence of pigment and of lime salts corresponds to that of phosphates in a urinary stone. Pure pigment stones are frequently found in cases of acholuric jaundice, when they are secondary to excessive production of bile-pigment by haemolysis.

**Symptoms.**—Gall-stones may be completely latent. More frequently their development is preceded and accompanied by continuous or intermittent dyspepsia. These "inaugural symptoms" are sometimes referred to as gall-stone dyspepsia: they are really due to cholecystitis (pp. 690, 691) and not to the presence of stones. Abortive attacks of biliary colic may occur independently of or associated with gall-bladder dyspepsia. Typical attacks of severe colic are less frequent and are uncommon in the absence of previous symptoms.

Many patients who suffer from gall-bladder dyspepsia and a few who have no such symptoms complain of short attacks of severe pain, which may occur at any time of the day or night with or without any obvious cause, such as an indiscretion in diet: occasionally an attack is the direct sequel of a long railway journey, a drive in a motor car on a bad road, or violent exercise. Attacks may occur daily or at long intervals, or there may be a series close together followed by a long spell of freedom. The patient may shiver during an attack, although his temperature never rises greatly and often does not rise at all. When the pain is acute, it is impossible to take a deep breath, the attempt producing a "catch" in the right side of the chest, which is very similar to that felt in pleurisy.

Attacks of biliary colic most frequently result from impaction of the stone in the neck of the gall-bladder close to or at its junction with the cystic duct. They often occur in the night. The attack begins with extremely sudden acute pain high in the epigastrium or in the region of the gall-bladder or both; it may pass through to the angle of the right scapula; it is often continuous and not of colicky type. The violent pain is accompanied by great restlessness, in contrast to the motionless state of a patient with a perforated ulcer or acute appendicitis. Some relief may be obtained by pressing upon the abdomen. The patient feels cold, but sweats profusely. Slight inspiratory distress is common, but the presence of definite dyspnoea or faintness, when the pain is high in the epigastrium or still more so if it is substernal, should raise the suspicion of coronary thrombosis as an alternative diagnosis. Nausea almost always occurs; the presence of vomiting generally indicates that the stone has passed from the gall-bladder into the cystic or common bile duct. Aerophagy is generally present. The pain commonly disappears with absolute suddenness. The sudden onset and sudden cessation are specially characteristic of gall-stone obstruction in the cystic duct. The temperature may rise a degree or two during the attack, and there may be a slight temporary leucocytosis. Constipation is complete.

Jaundice occurs only when a stone reaches the common bile-duct. Repeated attacks without jaundice are generally caused by a stone of some size becoming impacted in the neck of the gall-bladder. Repeated attacks with jaundice, which may be very evanescent and sometimes completely latent and only recognisable by a temporary rise in the serum bilirubin indicate the passage of small stones down the cystic and common bile-ducts into the duodenum, numerous stones being generally still present in the gall-bladder. The slightest yellow tinge of the conjunctivæ or a trace of bile in the urine is strong evidence that an attack of pain of doubtful origin is due to gall-stones.

If a small stone, having traversed the cystic duct and passed down the common

bile-duct to reach the ampulla of Vater, remains there owing to the smallness of the lumen of the sphincter, a special group of symptoms appears. In two-thirds of the cases one or more stones are still present in the gall-bladder. A stone in the ampulla acts as a ball-valve causing intermittent attacks of colic with incomplete jaundice. Pain is variable; it is occasionally the only symptom. Vomiting is common in the attacks, which are accompanied by fever with chills or severe rigors in 50 per cent. of cases. The jaundice is rarely complete and persistent; it is occasionally absent, but in such cases serum tests generally show that hyperbilirubinæmia is present; in rare cases it is unaccompanied by pain. In the intervals between attacks the patient may appear to be quite well, though a slight degree of jaundice or some residual pain in the gall-bladder region may be present. Sooner or later ascending cholangitis is likely to develop; there is then constant pyrexia with repeated rigors and polymorphonuclear leucocytosis. If the condition is of long duration, the liver becomes enlarged and hard as a result of biliary obstructive cirrhosis; the spleen is palpable in about one-third of the cases.

Small gall-stones are rarely recognised in the stools and larger ones are very rarely passed. It is important to distinguish gall-stones from concretions produced by drugs or by the administration of large quantities of olive oil. The majority of gall-stones consist of cholesterol and can, therefore, be recognised by being very light and inflammable. The rarest form of stone to be passed is a very small rounded one, which has probably traversed the normal passages during an attack of colic; as it may be the only one, a cure may result. More frequently faceted stones are passed; even if large numbers are found, it is very unlikely that all have left the gall-bladder. Lastly one, or less frequently two or three large stones, which may be formed by the agglomeration of several smaller ones, may be passed after traversing a fistulous communication between the gall-bladder and duodenum or colon. The fistula may develop very slowly without symptoms after chronic cholecystitis has led to the production of adhesions. More frequently the perforation appears to be sudden and takes place during or after an attack of colic. In other cases the fistula may be caused by the perforation of an empyema of the gall-bladder into the bowel. In rare cases a large stone may cause acute intestinal obstruction, generally near the end of the ileum. Occasionally the pain in the neighbourhood of the umbilicus or the right iliac fossa disappears spontaneously as the stone passes onwards; pain may be subsequently felt below the umbilicus and finally in the rectum, from which the stone may have to be dislodged by the finger. The complete passage may take from 1 to 8 days.

It is generally impossible to palpate the gall-bladder during an attack of acute pain owing to the rigidity of the abdominal muscles, but when the attack passes off the tenderness generally becomes localised to the gall-bladder itself. In some early cases the gall-bladder is found to be enlarged owing to distension with clear fluid, especially if the stone is impacted in the cystic duct. It gradually contracts on the stone or stones within it, probably after temporary dilatation, so that in long-standing cases it is rarely palpable. Even if a gall-stone passes into the common bile-duct, the gall-bladder does not often become enlarged; thus a large gall-bladder in a case of chronic jaundice generally indicates chronic pancreatitis or a growth of the head of the pancreas or of the common bile-duct, rather than stone (Courvoisier's law).

Pure cholesterol gall-stones are never visible with the radiograph, but when lime salts are present, especially in thin patients, they often throw a characteristic "ring" shadow. The shadow must be distinguished from that produced by a renal calculus, a calcified tuberculous focus in a kidney, a calcified tuberculous gland or a calcareous deposit in a costal cartilage. This can be easily done by means of cholecystography. This method also makes it possible to photograph transparent stones, as they may then appear as pale areas surrounded by the dark shadow formed by the dye filling the rest of the gall-bladder. Failure to visualise the gall-bladder on two successive

occasions, especially in the presence of a good shadow of the liver, which proves that the dye has been absorbed from the intestines, indicates that the cystic duct is obstructed, probably by an impacted stone, that the lumen of the gall-bladder is entirely occupied by stones, or that its mucous membrane is so damaged that it is incapable of absorbing water and so producing the concentration of the bile necessary for the production of a shadow.

In doubtful cases valuable information can often be obtained by examination of the bile obtained through a duodenal tube (p. 692). Failure to obtain dark bile on injecting magnesium sulphate would confirm a diagnosis of gall-stones suggested by absence of a gall-bladder shadow after cholecystography.

**Complications.**—Cholecystitis is always present before gall-stones develop, except with the rare solitary sterile cholesterol stone. If the mouth of the cystic duct becomes obstructed suppuration or gangrenous cholecystitis may develop (p. 690). In some cases inflammation may spread up the hepatic ducts or down the common bile-duct; in the latter case the pancreatic ducts may become infected and chronic pancreatitis develops. In rare cases glycosuria or actual diabetes follows. Primary cancer of the gall-bladder makes up not more than 1 per cent. of all cancers, but between 5 and 10 per cent. of people over 40 with multiple-faceted gall-stones ultimately develop cancer of the biliary tract. It is probable that it is the chronic cholecystitis which is associated with the carcinoma rather than the gall-stones since the relationship does not appear to exist in the case of single metabolic cholesterol stones. Biliary fistulae may develop between gall-bladder and duodenum or colon, or peritonitis may result from perforation of the gall-bladder into the abdominal cavity.

**Diagnosis.**—Gall-bladder dyspepsia must be distinguished from that due to peptic ulcer. An onset of duodenal ulcer symptoms after the age of 45 and especially in a woman, is much in favour of gall-stones, and relief from food and alkalis is rarely as definite in gall-stones as in ulcer. Symptoms due to colon spasm and constipation often cause difficulty in diagnosis, especially as a spastic colon and cholelithiasis often exist together in the same patient. The pain of coronary infarction is usually sub-sternal and often spreads to the neck and arms, but may be exceedingly difficult to distinguish from that of gall-stones. The distinction from other forms of colic—renal or intestinal—is usually not difficult. When gall-stones are associated with persistent jaundice the diagnosis from hepatitis, carcinoma of the head of the pancreas, or cirrhosis of the liver, may be very difficult; loss of weight occurs in all four, but a distended gall-bladder in the presence of jaundice almost always means a growth. The biliary obstruction due to growth is complete whilst that due to stone is often only partial and frequently intermittent.

**Treatment.**—During an attack of biliary colic the pain should be controlled by the injection of morphine (gr.  $\frac{1}{4}$ ) with atropine (gr.  $\frac{1}{80}$ ). Slight attacks may be relieved by 1 or 2 tablets of glyceryl trinitrate (gr.  $\frac{1}{100}$ ) placed under the tongue. The latter experimentally relaxes spasm of the sphincter of Oddi, whilst morphine increases it, but in practice the latter is always effective if enough is given, whilst nitroglycerine often fails.

The early recognition and thorough treatment of cholecystitis can be regarded as a true method of prophylaxis of gall-stones, and attention to obesity, exercise and drug treatment especially with bile salts, as given on p. 693, is often successful in relieving dyspepsia and preventing colic.

However, if the symptoms point definitely to the presence of gall-stones, and especially if repeated attacks of biliary colic have occurred, surgery should be advised, unless on account of obesity or renal or cardiac complications the patient is too bad a subject for operation. Myocardial disease is not, however, a contraindication, as the cardiac condition frequently improves after cholecystectomy, and patients with impaired hearts often stand the operation remarkably well. Fat patients should be strictly dieted for 2 or 3 months in order to bring their weight down before

operation. If there is evidence of active cholecystitis preliminary treatment with one of the sulphonamide drugs is advisable. The liability to complications or the recurrence of symptoms is reduced by the regular use of magnesium sulphate to prevent stagnation of bile after the operation. Whenever feasible cholecystectomy should be performed in preference to cholecystostomy, and the common bile-duct should always be explored for stones even if there has never been any jaundice. Pre-operative preparation of the patient is of supreme importance and a high protein diet, extra glucose and treatment with vitamin K are measures which do much to lessen risks of operation. The operative mortality for uncomplicated cases in experienced hands is less than 2 per cent.

## BILIARY COLIC WITHOUT GALL-STONES

It occasionally happens, especially in otherwise healthy young adults of both sexes, that typical attacks of slight or severe biliary colic, generally unaccompanied by jaundice, occur in the absence of gall-stones. During an attack and for a short time afterwards the gall-bladder is tender. The bile obtained through a duodenal tube from the gall-bladder is normal in every way. Cholecystography occasionally reveals some abnormality in the cystic duct in the form of acute angulation with or without dilatation of the proximal segment, and pressure upon the visualised gall-bladder, especially in a direction from its vertex towards its neck, causes pain; the gall-bladder is sometimes unusually large.

On abdominal exploration the gall-bladder looks healthy, but it may be tightly distended. Examination may show some abnormality in the anatomy of the cystic duct, or an accessory cystic artery may be present, which might cause kinking when the gall-bladder is in certain positions. The condition is analogous to Dietl's renal crises. Cholecystectomy in such cases is sometimes followed by permanent cure, even though neither macroscopical nor microscopical examination shows any abnormality in the gall-bladder wall or contents.

When no anatomical abnormality is discovered, the condition is comparable to that which gives rise to attacks of biliary colic after cholecystectomy for gall-stones or cholecystitis, and which leads to the assumption that a stone has been left in the common bile-duct, though at operation no stone or other cause of organic obstruction is discovered. The attacks are probably due to spasm of the sphincter of the common bile-duct, and are often called biliary dyskinesia. When the gall-bladder has been removed, the common bile-duct often dilates to form a reservoir, which to some extent takes its place, and it may take a long time for the neuro-muscular mechanism of the common duct and its sphincter to adapt itself to the conditions present after cholecystectomy; during this period attacks of pain may result from temporary obstruction by the closed sphincter when the dilated common duct is unable to empty itself.

**Diagnosis.**—This condition must be considered when attacks of biliary colic are associated with definite tenderness of the gall-bladder, cholecystography shows that no stone is present, and the bile obtained from the gall-bladder is normal. Between attacks the tenderness over the gall-bladder disappears, whereas in cholecystitis it rarely goes completely. The condition is most frequent in nervous and anxious individuals and may be associated with general symptoms of nervous origin. When attacks of colic occur after cholecystectomy has been performed for gall-stones, one or more stones has probably been left in the bile-ducts, but spasm of the sphincter is a possible alternative diagnosis, and treatment for this should be tried before advising further surgery.

**Treatment.**—Regular contraction of the gall-bladder and ducts and relaxation of the sphincter can be promoted by giving magnesium sulphate when fasting in the



morning and olive oil half an hour before meals. Before resorting to morphine, an attempt to relieve attacks with 1 or 2 glyceryl trinitrate tablets (gr.  $\frac{1}{15}$ ) placed under the tongue should be tried. If attacks persist laparotomy should be advised, the bile-ducts explored and the sphincter of Oddi dilated. A fibrous stricture may be found or the sphincter much hypertrophied. If all the findings at operation are fully normal to the naked eye it is usually unwise to remove the gall-bladder.

## CARCINOMA OF THE GALL-BLADDER

*Carcinoma of the gall-bladder is a rare disease, which occurs three times more often in women than in men, and generally after the age of 50. Calculi are present in about 75 per cent. of cases (p. 697).*

**Symptoms.**—In about 50 per cent. of cases there is a long history of repeated gall-bladder attacks. This is followed by a short phase of constant pain, accompanied by progressive weakness, anorexia and loss of weight, but no anæmia. The pain is situated in the right hypochondrium and often radiates to the right scapular region. Flatulence, nausea and vomiting are common. A tumour can generally be felt; it may at first be smooth, but later becomes hard and irregular. It is generally not very tender, and there is less muscular rigidity over it than is commonly the case with an inflamed gall-bladder.

After a time secondary deposits lead to symptoms, and in some cases these are most prominent throughout, the primary disease remaining latent. Thus the liver is often large, hard and irregular and jaundice may occur as a result of extension to the bile-ducts or compression by enlarged glands; it is occasionally remittent or intermittent, when it is generally due to cholangitis or a gall-stone in the common bile-duct.

Ascites is present in about a quarter of the cases as a result of malignant peritonitis or pressure of glands on the portal vein. Septic complications, such as suppurative cholecystitis or cholangitis, or local or general peritonitis, may occur. Death generally supervenes within 6 months of the development of definite symptoms apart from those due to the preceding cholecystitis or gall-stones.

**Diagnosis.**—The diagnosis is often exceedingly difficult, but the presence of a hard irregular tumour in the region of the gall-bladder with pain, anorexia and loss of weight in a middle-aged or elderly individual, especially if there have been symptoms pointing to cholecystitis or gall-stones, is suggestive of a growth of the gall-bladder.

**Treatment.**—It is rarely possible to remove a growth of the gall-bladder owing to the difficulty in making an early diagnosis. The operative mortality is high, and a very large proportion of cases recur within 6 months. The presence of early carcinoma is occasionally discovered on microscopical examination of a gall-bladder removed on account of chronic cholecystitis with or without gall-stones; permanent recovery may then follow.

## CONGENITAL OBLITERATION OF THE BILE-DUCTS

**Ætiology.**—This rare disease occurs rather more frequently in male than female infants. It is occasionally familial and is not associated with congenital syphilis.

**Pathology.**—Some unknown toxin probably passes from the mother by the umbilical vein to the fœtus. Part of the toxin reaches the liver direct and causes multilobular cirrhosis. The rest passes into the general circulation and reaches the liver by the hepatic artery; it is excreted in the bile and gives rise to unilobular cirrhosis and inflammation of the small and large ducts and gall-bladder, which, being extremely small at birth, become more or less completely obliterated. The

disease is thus a combination of portal and biliary cirrhosis with obstruction of the ducts.

**Symptoms.**—Jaundice is generally present at birth, but may not appear for 2 or more weeks. The meconium is normal, but the stools are free from bile from the first, and the urine is deeply bile-stained. The liver and spleen are large and hard. The infant is often remarkably well till the terminal stage, when deficiency in vitamin K results in purpura and hæmorrhages from the mucous membranes and umbilicus, and convulsions may occur.

**Diagnosis.**—Deep jaundice in a new-born infant, with a large liver and spleen and hæmorrhages without any early evidence of infection, is generally due to this disease.

**Prognosis.**—Life may last from a few days to as much as 11 months.

**Treatment.**—No treatment is of any value.

## CARCINOMA OF THE BILE-DUCTS

**Ætiology.**—The incidence of carcinoma of the bile-ducts is about half that of carcinoma of the gall-bladder. It is associated with gall-stones in about 50 per cent. of cases.

**Pathology.**—The growth arises most frequently in the ampulla of Vater, where a papillomatous projection into the duodenum develops. The common hepatic duct and the common duct are next most affected; a growth of either of the two hepatic ducts is very rare. Primary growths of the cystic duct can rarely be recognised, as at the time of death they are likely to have spread either to the gall-bladder or to the junction with the hepatic duct.

**Symptoms.**—The first symptom is generally jaundice, which develops gradually and is often intermittent; though the fæces are clay-coloured, they generally contain a little stercobilin. Apart from loss of weight and strength the symptoms are those of obstructive jaundice, but pain may be felt in the epigastrium or right hypochondrium, and attacks of colic may occur. In rare cases the symptoms resemble those of duodenal ulcer and there may be no jaundice if ulceration of the growth destroys the sphincter. Occult blood is present in the stools, and the patient may become extremely anæmic. The gall-bladder and less frequently the liver is enlarged. The primary tumour is never palpable. Ascites may occur as a result of secondary malignant peritonitis or of pressure of glands on the portal vein. The course of the disease is sometimes remarkably slow, some cases living for over 2 years after the first attack of jaundice.

The diagnosis from carcinoma of the pancreas, chronic pancreatitis and a stone in the common bile-duct is discussed on p. 705.

**Treatment.**—Life may be rendered more bearable as well as being considerably prolonged by cholecystenterostomy if the obstruction is in the common bile-duct. In spite of the technical difficulties of the operation it is sometimes possible to excise a growth of the ampulla of Vater, but recurrence is almost invariable.

THOMAS HUNT.

## DISEASES OF THE PANCREAS

### THE INVESTIGATION OF DISEASES OF THE PANCREAS

The pancreas produces an external secretion—pancreatic juice, and an internal secretion—insulin. The two functions are entirely independent, and in the diseases affecting the former, which are alone considered in this section, glycosuria due to deficient insulin is rarely present.

The pancreatic juice reaches the duodenum by the large pancreatic duct and a small accessory duct. The former runs by the side of the common bile-duct for a short distance and then joins it to form the ampulla of the bile-duct, a small cavity in the wall of the descending part of the duodenum, which opens in the biliary papilla, the end of the duct being kept closed by the tonic action of the sphincter of Oddi. In most individuals the pancreatic and common bile-ducts are quite separate, but in some 30 per cent. of normal people the two ducts are united terminally and have a common passageway. The accessory pancreatic duct discharges through a small papilla a short distance nearer the pylorus, but in 30 per cent. of normal individuals it is not patent or is too small to perform the functions of the main pancreatic duct if the latter is obstructed. The common bile-duct is completely surrounded by the head of the pancreas in 62 per cent. of bodies; in the remainder it lies in a more or less deep groove in the gland. It is clear from these anatomical facts that deficient pancreatic digestion may occur owing to failure of the pancreatic juice to reach the intestine either as a result of diffuse disease of the pancreas, which inhibits the activity or actually destroys the secreting cells, or as a result of obstruction caused by a pancreatic or gall-stone in, or a growth of, the ampulla of the bile-duct occurring in an individual with an incompetent accessory pancreatic duct. In most cases of chronic inflammation or cancer of the head of the pancreas jaundice will result, but if the accessory duct is incompetent, jaundice accompanied by deficient pancreatic digestion may also be due to obstruction of the ampulla of the bile-duct without disease of the pancreas.

*The stools in deficient pancreatic digestion.*—The stools are bulky and pale owing to excess of fat, the proportion of which in the dried faeces may be increased to 60 to 80 per cent. from the normal of 15 to 25 per cent. The pallor is still more marked in the presence of jaundice, as stercobilin is then absent or reduced in quantity. The fat is present chiefly in its neutral form, whereas normally only about 10 per cent. is unsplit; in rare cases it separates as oil, which solidifies on cooling. Microscopically oil droplets are seen, together with crystals of fatty acids and soaps, which are formed by bacterial decomposition of the undigested fat, but the proportion of neutral fat to fatty acids and soaps remains high, in contrast with the excess of the latter and small proportion of the former in the fatty diarrhoea of the sprue syndrome (p. 612). Fragments of undigested meat can sometimes be recognised with the naked eye, especially if the presence of excess of fat is prevented by giving a fat-free diet. Striated muscle fibres are always recognisable with the microscope, but there is often no excess of undigested starch. In severe diarrhoea associated with rapid passage through the small intestines the stools may contain some excess of undigested fat, meat and starch in the absence of pancreatic disease; conversely the irritating products of bacterial decomposition of undigested fat and meat may themselves give rise to diarrhoea, in which case excess of mucus is often present.

*Pancreatic ferments in the duodenal contents, faeces and urine.*—The duodenum normally contains trypsinogen, which is converted into active trypsin by the enterokinase of the intestinal juice, amylopsin (diastase) and steapsin (lipase). Under the conditions already described, in which no pancreatic juice reaches the intestine, the ferments cannot be isolated from the duodenal contents obtained through a tube. But it is impossible to recognise with certainty a simple reduction in the quantity present, owing to the great variations which normally occur and the technical difficulties in the quantitative estimation of the ferments. The same is true with regard to their presence in the stools, and only a very rough estimate of the quantity of pancreatic juice secreted can be made by measuring the tryptic activity of the faeces. On the other hand, by giving pure secretin intravenously the pancreatic secretion can be stimulated and readily collected through a duodenal tube; the volume, bicarbonate content and enzyme activity can then be measured. The rate of secretion normally lies between 2 and 5 ml. per minute; both the volume and bicarbonate

content are reduced in pancreatic disease, but the enzymes are more difficult to estimate, and being under vagus control their variations in disease are less fully understood. The amounts of lipase and amylase in the blood may readily be determined and are of much value in diagnosis. The former is the more difficult to estimate and in consequence the serum amylase test is more often employed. This ferment is excreted in the urine, though only in small amounts if renal disease is present and the urinary amylase estimation is also of some value in diagnosis. In acute hæmorrhagic pancreatitis the amounts of amylase in the serum are greatly increased. The normal value is defined by units, each of which represents the amount of enzyme which will fully hydrolyse 1 mg. of 2 per cent. starch solution at pH of 7. In acute pancreatitis the serum amylase value may be as high as several thousand units in comparison with normal values of between 100 and 180. This estimation is of great value in the differential diagnosis of the "acute abdomen" as it is almost invariably high in pancreatitis, is never raised in coronary thrombosis and is only very rarely raised in cases of perforated ulcer.

*Carbohydrate metabolism.*—Although the secretion of insulin is rarely much affected in the diseases of the pancreas considered in this section, a rise in the blood sugar with or without glycosuria is sometimes observed, and the glucose tolerance test may show some deficiency in carbohydrate metabolism. In doubtful cases this is a strong point in favour of pancreatic disease.

In very rare cases an adenoma or carcinoma develops from the cells of the islands of Langerhans and gives rise to hyperinsulinism with symptoms of hypoglycæmia, indistinguishable from those produced by an overdose of insulin; the condition must be considered as one of the possible causes of epileptiform convulsions.

## ACUTE NECROSIS OF THE PANCREAS

**Synonym.**—Acute Hæmorrhagic Pancreatitis.

**Ætiology.**—The pressure under which bile is secreted is considerably higher than the maximal pressure attained in the pancreatic duct after a meal, when pancreatic secretion is most active. Bile is not, however, forced into the pancreas, as the resistance offered by the sphincter of the common bile-duct is overcome by a smaller pressure. But when the mouth of the common bile-duct is obstructed, the bile may be forced into the pancreatic duct. Normally this may cause no ill effects but if the bile is very concentrated or it is infected, it may activate the pancreatic zymogens: the trypsin causes necrosis with secondary hæmorrhage of the pancreas, and the steapsin causes fat necrosis. If the bile is infected, but not otherwise, suppuration of the pancreas occurs simultaneously.

The obstruction is caused by a gall-stone in 50 per cent. of cases, and in very rare instances by a pancreatic calculus or a round worm. When the lumen is free, the obstruction is probably caused by spasm of the sphincter of the common bile-duct. Necrosis may also follow hæmorrhage caused by a direct injury to the pancreas. It is believed that in some cases acute congestion, œdema and even necrosis of the pancreas may result from intense reflex stimulation of the splanchnic nerves.

Very rarely infection reaches the pancreas by way of the blood-stream in pyæmia and infective endocarditis, and abscesses may result from retrograde thrombosis in suppurative pyelophlebitis. Acute pancreatitis is a rare complication of mumps, but suppuration and necrosis never occur (see p. 174).

**Pathology.**—Necrosis, hæmorrhages and suppuration are present in varying proportions in the pancreas. Opaque white areas of fat necrosis are found in the fat of the pancreas, the retroperitoneal tissue, omentum and mesentery, and also occasionally in that of more distant parts, such as the pericardium, to which the pancreatic lipase has been conveyed by lymphatics. Bacteria, especially *Bact. coli* and strepto-

cocci, can generally be isolated from the pancreas and often from the gall-bladder. The peritoneal cavity often contains blood-stained fluid, especially in the lesser sac; in the later stages this fluid is infected and suppurative peritonitis may be present.

**Symptoms.**—Without any warning a sudden very violent pain is felt in the epigastrium. It continues without intermission, but paroxysms of still more severe pain occur from time to time. Severe pain across the back is often present. After a short time vomiting begins and is repeated at frequent intervals; the gastric contents are first ejected, and after a time the vomit contains bile. Flatus may be passed, but the bowels are not opened, and no sounds indicating gastro-intestinal activity can be heard on auscultation. The abdomen soon becomes distended; it is very tender on palpation, but the muscles are often not correspondingly rigid. The tenderness and rigidity begin in the epigastrium, but before long become general. In rare cases the enlarged pancreas can be felt, but the rigidity of the abdomen generally makes this impossible. Slight jaundice is occasionally present as a result of pressure of the swollen pancreas on the common bile-duct. The patient soon becomes collapsed with a weak and rapid pulse and slight cyanosis; he appears more severely ill in the first few hours than is generally the case in acute peritonitis. Occasionally he is dyspnoeic. The temperature is not greatly raised and may be subnormal, and leucocytosis is generally absent. The symptoms of vasomotor collapse are due to the absorption of protein-breakdown products which are produced by the proteolytic (tryptic) ferments escaping from the obstructed pancreatic ducts. Glycosuria is rare, possibly because death occurs too rapidly, as the diabetes produced in animals by the removal of the pancreas often does not develop until some days have elapsed.

**Diagnosis.**—The possibility of acute pancreatic necrosis should be considered in all cases of acute symptoms in the upper part of the abdomen in adults, especially if the patient is an elderly obese, alcoholic individual, who has previously suffered from symptoms which might have been due to gall-stones or gastro-duodenitis. A carefully taken history may reveal the fact that the patient has previously had one or more similar, but much slighter attacks, probably due to acute but localised necrosis from which complete recovery took place. The symptoms may closely resemble those following perforation of a gastric or duodenal ulcer, but in the latter there is generally a history pointing to the presence of an ulcer before the onset of acute symptoms; vomiting is continuous in pancreatitis, but occurs only at the onset or not at all in perforation, and the hepatic dullness does not alter in pancreatitis, but often disappears owing to the escape of gas through a perforated ulcer; and the abdominal muscles are generally less rigid in pancreatitis than in perforation. In other cases acute intestinal obstruction is simulated, but flatus generally continues to be passed, the abdomen is less distended, and intestinal sounds disappear at once instead of being unusually loud at first. Severe cases with much shock may be confused with coronary infarction. At the operation the discovery of fat necrosis at once makes the diagnosis clear. The serum amylase test is of great value in diagnosis, figures of 200 units per 100 ml. of blood or higher being almost pathognomonic of acute pancreatitis, the normal levels lying between 80 and 150.

**Prognosis.**—The most acute cases are usually fatal and the initial shock may even result in sudden death. Some cases run a subacute course, especially if one or more localised abscesses form.

**Treatment.**—The severe shock associated with acute pancreatic necrosis makes immediate operation a procedure of extreme risk. For this reason the first step in treatment must be to correct the fluid and salt balance and the hæmoconcentration which is usually present. Intravenous saline, and plasma should be given at once and if possible the serum chloride and protein estimated. Morphine, complete rest and restriction of all fluids or food by mouth to prevent vomiting must be maintained, and in most cases improvement is rapid. Provided the diagnosis is certain, non-operative treatment on these lines is the safest procedure and operation should only

be considered if signs of increasing peritoneal irritation or the development of jaundice with a rising serum amylase figure make it imperative. At laparotomy any associated gall-bladder disease should be treated, and the abdomen drained, but incision of the pancreas itself is not to be advised unless a localised abscess is found. Permanent deficiency of pancreatic secretion may follow due to a chronic interstitial pancreatitis. The mortality for cases requiring operation lies between 15 and 30 per cent., but the recovery rate in less severe cases treated by intravenous fluids is as high as 90 per cent.

## SUBACUTE NECROSIS OF THE PANCREAS

**Pathology and Symptoms.**—Necrosis may occur in small areas of the pancreas as well as in the generalised form just described. This condition is frequently associated with gall-stones and with penetrating gastric or duodenal ulcer. It gives rise to recurrent attacks of mid- or left-sided epigastric pain, which tends to radiate round the left costal margin or to bore through to the muscles immediately to the left of the lower dorsal spine, when it may simulate renal colic. It may spread upwards to the left shoulder and downwards to the left iliac fossa and even to the left thigh and leg. The attacks generally occur 2 or 3 hours after food, when the functional activity of the pancreas is at its height. The pain may be associated with deep tenderness, but there is little or no rigidity, and the abdomen is often much distended. The patient may be perfectly well in the intervals between attacks. As in acute pancreatic necrosis, the attacks may be associated with cyanosis and a weak, though not specially rapid, pulse. The stools are generally normal, and there is no constant glycosuria, but there may be temporary hyperglycæmia and glycosuria during the attacks.

**Diagnosis.**—Attacks of left-sided pain occurring in cholelithiasis and after cholecystectomy are often caused by subacute pancreatic necrosis, which may also account for pain boring through to the back in gastric and duodenal ulcer, though severe pain of this kind may occur in which the ulcer at operation is found to be free from adhesions and the pancreas healthy. The sudden violent abdominal pain, with tenderness, rigidity and leucocytosis, which may occur in an attack of diabetic coma, is probably of similar origin.

**Treatment.**—The recurrence of attacks may be prevented if a diet is given which affords as complete rest as possible to the pancreas. The patient should be starved for 3 days and then given carbohydrates alone for 3 days. After that a more liberal diet is allowed, but fats and meat should be given sparingly in spite of the fact that the stools show no evidence of pancreatic insufficiency.

In severe attacks the question of operation requires consideration: gall-stones, if present, should be removed and cholecystectomy performed.

## CHRONIC PANCREATITIS

**Ætiology and Pathology.**—Chronic pancreatitis is generally due to infection spreading up the pancreatic duct. This may be the result of stagnation of pancreatic secretion owing to the presence of a gall-stone in the lower end of the common bile-duct. In rare cases the duct is obstructed by a pancreatic calculus, but this may itself be secondary to infection of the pancreatic ducts. Cancer of the head of the pancreas, and obstruction of the mouth of the common bile-duct by cancer of the ampulla or of the duodenum, are generally complicated by chronic pancreatitis.

When no obvious obstruction is found to account for chronic pancreatitis, the disease may have been due to a gall-stone which has been passed, or infection may have ascended from the duodenum, or descended from the upper biliary passages,

as non-calculous cholecystitis is sometimes present. When a chronic gastric or duodenal ulcer erodes the pancreas, the neighbouring part of the gland becomes chronically inflamed.

In chronic pancreatitis the inflammation and secondary fibrosis are mainly interlobular, coarse bands of connective tissue, often visible to the naked eye, separating the lobules of the gland from each other. The head of the pancreas is generally most affected. It is hard and somewhat enlarged.

**Symptoms.**—In chronic pancreatitis the normal functions of the pancreas must be more or less disturbed, but in many cases it is entirely latent, as the inflammation may not be sufficiently severe and widespread to interfere seriously with pancreatic digestion. It is often found accidentally during an operation for gall-stones, or at necropsy if the primary disease proves fatal. In an individual in whom the pancreas completely surrounds the common bile-duct, jaundice is likely to develop. It may be the only symptom, and chronic painless obstructive jaundice, developing insidiously may be due to chronic pancreatitis as well as to carcinoma. The gall-bladder is dilated, but it is generally difficult to recognise by palpation, and the liver is often enlarged and abnormally hard, but not tender. In cases in which pancreatic deficiency occurs, the stools contain excess of fat and undigested meat (p. 701) and diarrhoea may result; the deficient digestion causes emaciation with increasing weakness; steatorrhœa may be severe with much diarrhoea, extreme emaciation and anorexia.

Diabetes rarely results from chronic pancreatitis, but it may occur in very chronic cases if the inflammation invades the islands of Langerhans.

*Chronic pancreatitis may be painless, but in the majority of cases periodic attacks of pain occur, lasting from 1 to 5 days and recurring every few weeks or months—chronic relapsing pancreatitis. The pain is often severe and tends to radiate along the left costal margin and to bore through to the muscles immediately to the left of the lower dorsal spine and to the angle of the scapula. The pain is often worse lying down than sitting up and usually requires morphine for its relief. Left-sided pain of this kind in gall-bladder disease should suggest the possibility that the pancreas is involved, and in chronic gastric and duodenal ulcer that penetration into the pancreas has occurred.*

**Diagnosis.**—It is rarely possible to determine with certainty whether chronic pancreatitis is present as a complication of gall-stones or of the other conditions with which it may be associated. If hyperglycemia with or without glycosuria develops in such a case, it is extremely probable that the pancreas is becoming affected. The changes in the faeces, which result from the absence of pancreatic digestion, do not prove that the pancreas is affected in a case of chronic jaundice, as obstruction of the ampulla of the bile-duct may prevent the pancreatic juice as well as the bile from reaching the duodenum although the pancreas is healthy.

The possibility of chronic pancreatitis should be considered in all cases of chronic jaundice in which the cause is doubtful. Attacks of pain, even in the absence of a characteristic history, makes the presence of gall-stones probable. In the absence of such attacks, especially if the gall-bladder be enlarged, either chronic pancreatitis or a growth is probably present. A growth is much more commonly associated with chronic pain, and emaciation and weakness develop more relentlessly than with chronic pancreatitis. It is often impossible, however, even at an operation, to distinguish between a growth of the head of the pancreas and chronic pancreatitis. Only when a patient recovers completely and permanently is it possible to be certain that the condition was inflammatory. The periodic attacks of chronic relapsing pancreatitis are often mistaken for those of duodenal ulcer, but there is less vomiting and loss of weight in ulcer and the pain during attacks is more continuous in pancreatitis. In some cases the pain of pancreatitis may simulate a coronary infarction and diverticulitis of the colon may also have to be considered in the differential diagnosis.

**Prognosis.**—The prognosis depends upon that of the primary condition in

secondary cases, and the presence of chronic pancreatitis does not alter the outlook in operations for gall-stones. In cases of apparently primary pancreatitis recovery has taken place after an exploratory operation in which nothing was done. Chronic pancreatitis causes death only in the presence of complications. Morphine addiction is not uncommon, and the continued attacks of pain and loss of weight may lead to serious secondary neurosis.

**Treatment.**—It is only necessary to consider the treatment of those cases which appear to be primary, as when the pancreatitis is secondary no treatment beyond what is necessary for the primary disease is required. If the jaundice does not abate within 3 months, or a shorter period if the patient rapidly loses weight and strength or tests show that the functional efficiency of the liver is becoming impaired, an operation should be performed. A cholecystenterostomy will cure the jaundice, remove one source of irritation of the pancreas by draining the infected bile, and prevent the development of secondary infection and necrosis in the liver. In chronic cases without jaundice the diet should be kept low in fats, alcohol avoided and full doses of pancreatin given after each meal. Hexamethonium salts are sometimes effective in relieving pain, probably by their action in depressing vagal action and so reducing pancreatic secretion. Various forms of surgical treatment have been suggested, including division of the sphincter of Oddi, thoracolumbar sympathectomy and even excision of the pancreas, but results have been uncertain.

## FIBROSIS OF THE PANCREAS IN INFANTS

**Synonym.**—Fibrocystic Disease of the Pancreas.

**Ætiology and Pathology.**—This disease was first described in 1905, but it was not until 1938 that it was fully recognised as a clinical and pathological entity. It is frequently familial and is by no means so rare as was believed, being found in between 1 and 2 per cent. of routine admissions to children's wards and in approximately 3 per cent. of all necropsies in infants. The main changes are found in the pancreas, lungs and intestine. In the pancreas the acini and small ducts are blocked by inspissated eosinophilic secretion with resulting atrophy of the acini and gradual replacement by fibrous tissue: the islands of Langerhans are not affected. Similar changes to those occurring in the pancreas are found in the lungs and intestine, and it is probable that the condition is a generalised disease of mucus-secreting glands throughout the body, due to some nutritional deficiency. Broncho-pneumonia is almost always present, with bronchiectasis, fibrosis and abscesses of the lungs, except in infants dying in the very early neonatal period.

**Symptoms.**—Symptoms generally appear soon after birth. Extreme emaciation occurs in spite of a very good appetite owing to the absence of all pancreatic ferments from the intestines. The abdomen is distended. Diarrhoea is common and the stools are often large, pale and offensive, but much of the fat is split owing to bacterial action in the colon. A chronic cough is present from an early age and signs of pulmonary infection appear. Clubbed fingers and cyanosis with purulent offensive sputum usually develop later and dominate the clinical picture.

**Diagnosis.**—The disease should be suspected in all cases of chronic respiratory infection and nutritional deficiency in children; a clinical diagnosis is often possible from an accurate history and examination alone, but may be confirmed by the finding of a high fat content in the stools, together with an absence of pancreatic ferments in the duodenal juice. If death occurs in the first few months of life, the condition is rarely distinguished from many disorders causing chronic wasting with terminal broncho-pneumonia, but if the illness lasts longer, coeliac disease is simulated; in this case the pulmonary symptoms should arouse suspicion of fibrocystic disease.

**Treatment.**—The results of treatment are disappointing. The diet should be



low in fats but high in carbohydrates, proteins and vitamins. Protein hydrolysates are a valuable addition to the feeds, if they can be tolerated and full doses of pancreatin, 1 to 2 g. per meal, should also be given.

Therapy with antibiotics usually fails to control the pulmonary infection completely, but should be given a full trial. Death from broncho-pneumonia is the rule, but the prognosis, though bad, is not quite hopeless, and a few patients survive for a number of years or even exceptionally appear to make a full recovery.

## SYPHILIS OF THE PANCREAS

The pancreas is affected in 20 per cent. of cases of congenital syphilis in the newborn; in most cases the liver is simultaneously affected, and somewhat less frequently the spleen, bones, lungs and other organs. The gland is enlarged and hard owing to proliferation of the interlobular connective tissue; the gland-cells atrophy, but the islands of Langerhans escape. Acquired syphilis occasionally gives rise to gummata of the pancreas.

**Symptoms.**—The symptoms are those of chronic pancreatitis or carcinoma of the pancreas. The tumour may be palpable, and it may lead to obstruction at the pylorus or duodeno-jejunal flexure with persistent vomiting. The occurrence of diabetes in a syphilitic patient should suggest that the pancreas may be affected. The Wassermann reaction should always be tested in cases of suspected chronic pancreatitis and carcinoma of the pancreas, whether the diagnosis is made clinically or at an operation, and in diabetes, and anti-syphilitic treatment instituted if it is positive.

## PANCREATIC CALCULI

**Pathology.**—Diffuse calcification in the parenchyma of the pancreas is found by radiography in about 10 per cent. of cases of chronic pancreatitis, but true pancreatic calculi occurring in the ducts themselves are rare. When present they may be single or as many as two or three hundred. They are white, yellow or brown, and vary in size from mere sand to smooth or irregularly shaped masses, an inch or more in length. They consist of tribasic calcium phosphate or of an amorphous debris mixed with calcium carbonate. Even though pancreatic juice normally contains no calcium carbonate, this is the chief constituent of the calculi, which consequently, on radiographic examination, throw much more definite shadows than gall-stones. Calculi never form in a healthy pancreas; they result from infection of the ducts and stagnation of the secretion. The ducts behind the calculi are dilated, and chronic pancreatitis is present, but suppuration is very rare. The condition may be associated with gall-stones.

**Symptoms and Treatment.**—In 30 or 40 per cent. of cases calculi are completely "silent" but when they cause symptoms they are those of the associated chronic pancreatitis; the attacks of pain begin and end more abruptly if a stone is present. If the presence of definite calculi can be proved in contrast to the irregular calcification of chronic inflammation, surgical exploration is justified when it may be possible to remove one or more stones even though others may still remain.

## PANCREATIC CYSTS

**Ætiology and Pathology.**—Simple obstruction of the pancreatic duct leads to atrophy of the secreting tubules and not to the formation of cysts. When chronic

pancreatitis is also present retention cysts may develop. Hydatid cysts may occur in the pancreas, and congenital cystic disease, generally associated with cystic disease of the kidneys, may occur.

Single large pancreatic cysts, the origin of which is unknown, may contain as much as 14 pints of fluid. Multiple cysts of various sizes, often quite small, may occur in the absence of pancreatitis. The contents are generally turbid and dark reddish-brown or yellow. The fluid is alkaline, slightly viscid and albuminous and may contain altered blood. Microscopically degenerated epithelial cells, leucocytes, and occasionally crystals of cholesterol and rarely of leucin and tyrosin are found. The pancreatic ferments are often absent, especially in old cysts.

A large proportion of so-called pancreatic cysts are really collections of fluid in the lesser sac of the peritoneum, the foramen of Winslow having been occluded by peritonitis. About a quarter follow an injury to the pancreas, which causes the escape of blood and pancreatic juice into the lesser sac with secondary peritonitis. In the remaining cases serous fluid collects slowly as a result of local peritonitis secondary to pancreatitis, the condition being analogous to a pleural effusion following pneumonia.

**Symptoms.**—The tumour is generally discovered by chance before the development of any symptoms. Sometimes attacks of epigastric pain, which may radiate to the left shoulder, occur; they are sometimes accompanied by vomiting, wasting and jaundice. Diabetes rarely develops.

The tumour is generally in the centre of the upper part of the abdomen, but it often extends farther to the left than the right. It does not move on deep respiration and is only very slightly movable in any direction. As it grows it extends farther down and may finally appear to fill the entire abdomen. It is smooth, rounded and elastic; a thrill is often produced on striking it.

Its relation to the stomach and colon can be readily determined by means of radiography after a barium meal and enema. It is first behind the stomach, but as it enlarges it generally reaches the anterior abdominal wall between the stomach above and the transverse colon below. Less frequently it comes forward above the stomach or below the transverse colon between the leaves of the mesocolon. It generally grows very slowly, but sudden enlargement may result from hæmorrhage into it.

**Diagnosis.**—There should be no difficulty in diagnosing a pancreatic cyst from ascites and from a hydronephrosis, enlarged gall-bladder, ovarian cyst or distended bladder. It is impossible to distinguish a true pancreatic cyst from a pseudo-pancreatic cyst clinically; even at an operation the distinction may be impossible. Mesenteric cysts are generally more movable than pancreatic cysts.

**Treatment.**—The cyst should be emptied and drained by operation. No attempt should be made to remove it because of the dense adhesions which often fix it to its surroundings. The immediate results of operation are very satisfactory, but a recurrence is not uncommon.

## CARCINOMA OF THE PANCREAS

**Ætiology.**—Primary carcinoma of the pancreas is found in about 3 per cent. of all patients dying of cancer, and occurs approximately three times as frequently in males as in females. The pancreas may also be invaded by direct spread of a growth of the stomach. Less frequently secondary deposits are found when the primary disease is situated in some distant situation.

**Pathology.**—The growth nearly always arises from acinar or duct epithelium and the head of the pancreas is involved in 75 per cent. of cases. The duct is obstructed and may become dilated, occasionally forming retention cysts. The stasis of the pancreatic secretion frequently leads to chronic pancreatitis and very rarely a pan-

creatic calculus. Secondary deposits are often found in the neighbouring lymphatic glands, the liver and peritoneum, and less often in more distant organs.

**Symptoms.**—When the head of the pancreas is involved, jaundice is generally present owing to pressure on the common bile-duct, but the latter may escape if it is not embedded in the gland. The jaundice increases until it is very intense, bile being then completely absent from the *fæces*. The gall-bladder is almost always distended and is generally palpable; the liver is also generally large and hard. When the growth is confined to the body or tail of the pancreas there is no jaundice unless the duct is compressed by a secondary deposit, and neither the gall-bladder nor liver is enlarged. Pain is present in 80 per cent. of cases; in 65 per cent. it is the first symptom. The patient complains of a dull, gnawing, aching pain deeply situated in the upper abdomen and extending to the back. It is constantly present, and unrelated to meals or bowel actions. In some cases it is paroxysmal. It is generally bilateral, but occasionally confined to the left, especially with growths of the tail, and tends to be worst at night. The pain may simulate that produced by a spinal tumour, when it is probably caused by involvement of the *cœliac* plexus. Wasting is rapid in almost all cases, and the patient becomes progressively weaker. If the head of the pancreas is involved, the stools may have the characteristics described on page 701, and diarrhoea is likely to occur, but typical fatty stools are passed in only a small minority of cases. *Glycosuria* is only occasionally present but impaired glucose tolerance is more frequently found. A growth of the body or tail does not interfere with digestion, but loss of appetite is very characteristic.

A tumour of the head of the pancreas is not often palpable, as it is deep-seated and likely to be hidden by the enlarged liver and the ascites, which often develops as a result of malignant peritonitis or pressure on the portal vein. A tumour of the body or tail of the pancreas is more frequently palpable, especially shortly before death when emaciation is extreme. It forms a hard, fixed mass extending across the abdomen on a level with the umbilicus, especially to the left, and is generally not tender. A pancreatic tumour can sometimes be seen as an indefinite shadow by radiography in the lateral position, and with a barium meal the duodenum may appear as a thin distended arc due to pressure from the enlarged head of the pancreas.

Insomnia, depression, anxiety and restlessness may be so prominent and so out of proportion to the abdominal pain, which may for a time be absent, that a neurosis may at first be diagnosed.

**Diagnosis.**—Chronic jaundice due to carcinoma of the head of the pancreas must be diagnosed from chronic pancreatitis, subacute hepatitis and cirrhosis of the liver, a gall-stone in the ampulla of the bile-duct and carcinoma of the ampulla. In carcinoma pain is more continuous and the loss of appetite greater than in chronic pancreatitis and the general deterioration in health is more steady. Liver function tests are usually abnormal in chronic hepatitis. A gall-stone rarely reaches the ampulla and causes jaundice without a preceding attack of colic, whereas jaundice is often the first symptom in carcinoma of the head of the pancreas; the jaundice in the former is often incomplete and intermittent instead of complete and permanent, pyrexia is common, and rigors may occur owing to infection of the bile passages. In carcinoma of the ampulla the jaundice which is accompanied as in carcinoma of the pancreas by dilatation of the gall-bladder, is less complete and more intermittent than might be expected; it can sometimes be recognised with the radiograph by the characteristic filling defect it produces in the duodenum, and it always leads to the presence of occult blood in the stools.

The possibility of a growth of the tail of the pancreas should be considered in a patient without jaundice whose general condition suggests that he is suffering from cancer, but in whom no evidence of disease can be found in the organs most commonly affected. The possibility is converted to a probability if he complains of severe pain boring through to the left side of the back or a fixed tumour becomes palpable. A

normal diastase index and stools showing no deficiency in fat or meat digestion do not militate against the diagnosis.

**Prognosis.**—Death generally occurs within 6 months of the onset of symptoms and is rarely delayed beyond a year.

**Treatment.**—A cholecystenterostomy should be performed in all cases of obstructive jaundice in which a growth of the pancreas is the probable cause. By relieving the jaundice, any itching already present is overcome and the almost intolerable itching which is likely to develop at a later stage is prevented. Moreover, pain and diarrhoea may become less severe and the progress of the disease appears to be delayed, some patients remaining free from symptoms and regarding themselves as completely cured for 6 to 18 months after cholecystenterostomy performed for the relief of jaundice. Moreover, in other cases permanent recovery may follow the operation when performed for a supposed growth of the pancreas, the surgeon having mistaken chronic pancreatitis for a growth. In rare instances a localised growth of the pancreas has been successfully removed. Total pancreatectomy has been successfully performed in many cases and a number of 5-year cures are reported. The mortality of the operation is high and, if successful, a maintenance dose of insulin of about 40 units a day is permanently required, with very large doses of pancreatic extracts after food.

## VISCEROPTOSIS

The position of the viscera in the abdomen varies widely in different individuals and extreme variations are compatible with perfect health and normal digestion. In many normal subjects the stomach, colon or other organs are found to lie low in the abdomen, but this is no indication that they have "dropped" to this position, and such terms as gastropptosis or colopptosis should, therefore, not be employed. Even when any true ptosis develops, as after pregnancy or following severe loss of weight, it is doubtful if it causes any significant symptoms or interference with function. Many patients who in the past were thought to suffer from visceroptosis were, in fact, overweight and the post-prandial discomfort of which they complained was due to a heavy pendulous abdomen and to over-eating. There is no good evidence that a colon lying low in the pelvis is ever for this reason a cause of constipation or presents any special danger of kinking or obstruction, and there is no place for surgery in fixing or altering the position of any of the digestive organs, as a therapeutic measure; it is indeed doubtful whether the term visceroptosis should not now be given up altogether and it is only in the case of the kidney that ptosis is a matter of importance when it can be shown to give rise to Dietl's crises (g.v.). Undue mobility of one or other part of the colon particularly the sigmoid due to a long mesentery, may be a factor in the causation of volvulus but this is in no way due to abnormal ptosis of the organ.

## GASTRO-INTESTINAL ALLERGY

When short, recurrent attacks of abdominal pain, vomiting and diarrhoea, either separately or in any combination, are not obviously the result of food poisoning, intestinal obstruction, or biliary or renal colic, the possibility of abdominal allergy should be considered. The onset is sudden, and the attacks terminate abruptly after a period lasting for a few minutes to 24 or 48 hours. The pain may occur in any part of the abdomen, but especially in the centre, and its situation may vary in different attacks. It may be extremely severe and only partly relieved by morphine. It is often associated with vomiting and diarrhoea, or either, especially diarrhoea, may occur alone. The diarrhoea generally consists of the passage of a single watery stool, which may contain mucus, in which are occasionally found many eosinophil cells and less frequently red blood corpuscles. The stools passed before and after

such a watery stool are generally quite normal. The patient has no abdominal symptoms of any kind in the intervals between the attacks, which may occur almost every day or not more than once or twice a year. Nothing abnormal is found on examining the abdomen between the attacks, and during the attacks there is little or no rigidity and generally little or no tenderness. Erythematous or urticarial rashes may sometimes occur, either during or after attacks.

The patient often gives a family history of asthma, hay fever, eczema, urticaria or migraine, and he is often himself a sufferer from one or other of these conditions. In some cases the vomiting or diarrhoea is often or always preceded by rhinorrhœa. The abdominal attacks generally occur, however, during periods of complete freedom from other allergic manifestations, so that the frequent presence of slight eosinophilia is an important help in diagnosis. Still more characteristic is the complete relief obtained by injecting 5 to 10 minims of adrenaline (1 in 1,000), as this drug has no effect on any other form of abdominal pain.

Cutaneous reactions may show that the patient is sensitive to certain articles of food, especially wheat, milk and eggs in the case of children, and pork or other pig food, cabbage, potatoes and chocolate in adults, but the absence of such reactions does not exclude an allergic origin of the symptoms, nor does their presence prove with certainty that the articles consumed must be excluded from the diet. Sensitiveness to foods frequently consumed is rarely recognised by the patient, who is, however, generally aware of an idiosyncrasy to such articles of diet as strawberries, tomatoes, onions, spinach, cucumber, melon, shell-fish and turtle. Gastro-intestinal allergy occurs at all ages, but is most common in infants and children. In rare cases attacks are brought on by foreign proteins absorbed by the nasal mucous membrane.

*Abdominal migraine.*—In some cases of migraine the headache appears to be entirely replaced by abdominal pain and in others by a persistent migrainous dyspepsia which resembles chronic cholecystitis but is not due to any organic disease of gall-bladder or liver.

*Treatment.*—The patient should avoid any articles of food which he has found give rise to attacks, and also any which give a strongly positive cutaneous reaction. As in asthma, this rule must be applied with great caution in the case of wheat, milk and eggs in children, as the malnutrition following deprivation from these foods may more than outweigh the questionable improvement which may occur in the allergic attacks. If attacks continue to be frequent, the effect of ephedrine hydrochloride, gr.  $\frac{1}{2}$  three times a day before meals should be tried. Nocturnal or early morning attacks may be prevented by taking gr. 1 to 2 of phenobarbitone at night with an additional dose of ephedrine. The patient should learn to give himself adrenaline, and at the first sign of an attack he should inject the smallest dose which experience shows prevents an attack: generally 3 to 5 minims are sufficient. The injection can be repeated at intervals if the attack does not at once completely disappear.

*Various elimination diets may be tried in the detection of food sensitisation, but are difficult to carry out efficiently and for this reason often give unsatisfactory results.*

THOMAS HUNT.

## DISEASES OF THE PERITONEUM

### ACUTE PERITONITIS

*Definition.*—Peritonitis results from infection of the peritoneum with bacteria. When it is dubbed acute, the acuteness refers usually to a condition which becomes severe in a short space of time, commonly a matter of several hours. Because of the large area of the peritoneum and its great powers of absorption the results may be grave; because of its intimate relationship to the alimentary canal and to viscera,

the risks of such infection are high. The inflamed peritoneum loses its lustre from œdema and produces both a serous and fibrinous exudate.

**Ætiology.**—Infection may reach the peritoneum (1) from without; (2) by the blood-stream and (3) from the contained organs.

1. Infection from without is possible in the case of wounds, but is of infrequent occurrence. Severe abdominal wounds commonly implicate the contained viscera, and the consequent peritonitis is usually the result of this.

2. Infection by the blood-stream is an occasional though uncommon mode of infection. In streptococcal and staphylococcal septicæmia, peritonitis may occur as a terminal event; it frequently gives rise to so few symptoms, however, that its existence is unrecognised during life. When pneumococcal peritonitis complicates pneumococcal lesions elsewhere the infection is undoubtedly blood borne.

3. Infection from contained or neighbouring organs is by far the commonest cause of peritonitis. The majority of cases depend more or less directly on the passage of bacteria from within the alimentary canal owing to changes in its walls. The appendix is the most frequent seat of the primary condition. Where there is no actual breach of continuity in the organ, bacteria escaping through its damaged walls are generally contained by a local plastic reaction in which omentum and neighbouring bowel, viscera and parietal peritoneum, singly or together, adhere to the inflamed organ and to one another through a fibrinous exudate. This protective structure usually resolves completely if the infection spontaneously subsides; where the infection is more severe a localised abscess forms inside it. When, however, the infection is particularly virulent or the patient's resistance unusually poor, a sufficient local reaction does not take place, and spreading diffuse peritonitis results. This is commonest in children and in the old; it may be brought about, even when the local reaction has been good, by unskilful operative interference. Diverticulitis and acute cholecystitis are occasional causes of this type of acute peritonitis, but are more commonly restricted by local adhesive changes. Peritonitis complicating typhoid fever in the absence of perforation, and pneumococcal peritonitis when associated with pneumococcal enteritis, have a similar origin.

In intestinal obstruction and strangulated hernia the changes which occur in the bowel wall speedily permit the passage of organisms through it to the peritoneum. The organisms present are usually *Bact. coli* with streptococci and staphylococci.

Perforation of a hollow viscus into the peritoneal cavity is responsible for some of the most virulent and widespread cases of peritonitis; the lower the perforation in the bowel, the more virulent will the resulting infection be. The appendix is the commonest source, gangrene or a perforating ulcer leading to a sudden peritoneal infection before any gradual passage of organisms has had time to produce a local peritoneal reaction. Perforating ulcers of the stomach and duodenum come next in order of frequency; less common causes are perforating ulcers of the ileum, the most important of which is the typhoid ulcer, rupture of the gall-bladder or bile ducts, and perforating wounds of any of the hollow organs, or leakage from surgical anastomoses. Abscesses of the liver, appendix, gall-bladder or Fallopian tubes occasionally burst into the general peritoneal cavity. Infection of the peritoneum may also result by direct spread from neighbouring parts. This type is particularly common in women, spread taking place either directly through the Fallopian tubes or by lymphatic permeation of the uterine walls. Peritonitis is a very rare sequel to infections of the lung and pleura, although the reverse is far from unusual. In the infant an infection of the thrombosed umbilical vein may lead to peritonitis by direct spread.

**Symptoms.**—As acute peritonitis is almost invariably a secondary condition, its symptoms and course are subject to very considerable variations, depending not only on the nature of the primary lesion from which it arises and on the nature and virulence of the infecting organism, but also on the general condition of the patient.

1. *Acute fulminant generalised peritonitis.*—This is usually associated with the

perforation of a hollow organ or the sudden bursting of an abscess into the peritoneum, and owes its chief characters to the sudden flooding of the peritoneal cavity with infective material. The patient may have been free from any symptoms of ill health and is suddenly seized with acute abdominal pain, accompanied sometimes by a sensation of something having given way. The pain may at first be localised in position and thus help in the diagnosis of the actual lesion, but it speedily spreads to the whole abdomen and is followed almost at once by a feeling of syncope or collapse. Within a few minutes the patient becomes cold and pale; his features are pinched and betray the most intense anxiety; beads of sweat stand out upon the skin, and the pulse may be almost imperceptible. He complains of nausea, but does not often vomit, and his respirations are shallow and quickened. In a short time some improvement takes place; the pulse, though rapid, is of better volume, and the pain may take on an intermittent colicky character. The abdomen is absolutely rigid, and is usually retracted; it is very tender on pressure. The liver dullness is usually absent, but this is only important if an abdominal examination made at the onset of the attack revealed a normal area of dullness. These symptoms may be sufficiently severe to lead to death by themselves; more usually they gradually merge into the symptoms of the consequent acute peritonitis itself. The latter are reactive in nature and are due to nature's attempts to limit the process.

If not relieved by operation at an early stage, the patient's condition usually worsens rapidly. He becomes anxious and restless. Vomiting is now frequent and, due to this and to other loss of fluid by sweating and exudation into the peritoneal cavity, the subcutaneous tissues become shrunken and give the patient the so-called "*facies Hippocratica*". The tongue is dry and furred and the teeth become covered with sordes. The pulse increases in rate and becomes thready and later running in character, and the temperature, which at first may be subnormal, rises. The abdomen presents a uniformly board-like rigidity and is extremely tender. It is held immovable, respiration being entirely thoracic, and the patient lies with his knees drawn up to relieve the abdominal tension. There is usually absolute constipation and the intestinal sounds are absent. Gradually the paralytic intestine becomes dilated and the abdomen distended. Vomiting becomes more frequent. The vomited matter is usually only small in quantity; it speedily becomes exceedingly foul, though it is rarely faecal, and the breath is extremely offensive. The urine is scanty and may contain traces of albumin, and its passage may produce a paroxysm of pain.

The pulse-rate rises still more, the restlessness increases, the features become more pinched, the limbs become cold from peripheral circulatory failure, the skin takes on a cyanotic hue and the patient dies, his consciousness usually unimpaired until near the end.

Such is the picture, rarely seen nowadays, of fulminant general peritonitis, with death occurring in from 24 to 48 hours. Its outstanding features are those of profound shock and toxæmia, measures of the high grade of peritoneal absorption. In the aged, and in patients with Bright's disease, the symptoms may be atypical; pain may be but little marked, and vomiting and tenderness may be absent, while the bowels may act freely throughout. The great restlessness, the condition of the tongue, the pulse and the ultimate meteorism will, however, usually indicate the true nature of the condition.

**2. *Acute spreading peritonitis.***—In this variety there is no sudden flooding of the peritoneal cavity with infective material. Instead there is a gradual, but usually quite rapid, spread of the infection from some focus which has not been limited by the protective screen referred to above. It accompanies many cases of appendicitis, and is a sequel of intestinal obstruction if unrelieved for a sufficiently long period. The peritoneal reaction is intense, and the coils of intestine become glued together with a sticky exudate, while pockets of pus form between them. The pain is at first localised to the region of origin, but as the infection spreads it extends until it

may become generalised over the whole abdomen. It is, however, never so intense as in the preceding variety, and may be distinctly spasmodic in character. The general abdominal symptoms are also less severe, the tenderness, rigidity, meteorism and constipation being of varying grade. The aspect of the patient betokens a profound septic infection, the tongue is furred and dry, the pulse rapid and the temperature of the hectic type. Rigors and sweats are not uncommon, and if left alone the case may terminate with fatal septicæmia or suppurative pyelophlebitis; in rare cases the pus may accumulate and burst either externally in the region of the umbilicus or into one of the hollow viscera. Sometimes the condition subsides to be followed by the swinging temperature suggestive of a localised collection of pus. Such collections are most common in the subphrenic spaces and in the pelvis.

3. *Acute localised peritonitis*.—Here the infection has been prevented from spreading far from such a focus as, for example, the appendix or gall-bladder, by a plastic adhesion of adjacent structures. The initial symptoms are those of the causal condition, e.g. acute appendicitis, acute cholecystitis. The features of the circumscribed peritonitis are those of rigidity of the adjacent abdominal wall and tenderness on deep pressure. All the structures concerned in the walling-off process swell with œdema, and a mass, of greater or lesser size, forms. This may be palpable from about the third or fourth day after the onset. Thereafter it either slowly disappears in the course of a week or so, during which time it becomes less tender, or it gradually enlarges to form an acute abscess, characterised by the tender mass and accompanied by fever and leucocytosis.

4. *Pneumococcal peritonitis*.—This presents certain fairly characteristic features, which in many cases enable the nature of the infection to be correctly diagnosed from the clinical picture alone. It is far more frequent in children than in adults, and in girls than boys in the proportion of nearly 7 to 3. It occurs in a diffuse and in an encysted form, depending probably on the resistance of the patient. In many cases there exists a definite pneumococcal enteritis, the organisms penetrating the wall of the bowel and so infecting the peritoneum. The predominance of the disease in girls is probably due to the female genitals being a source of infection, as the pneumococcus has been cultivated from the vagina in some instances. In the majority however, the peritonitis is part of a pneumococcal septicæmia; thus, when it is secondary to pneumococcal disease of the middle ear, local pneumococcal abscesses or pneumococcal arthritis, the blood-stream appears to be the route of infection, and it probably is so also in those cases which follow pneumonia or empyema.

There is a striking resemblance between the symptoms of most forms of pneumococcal infection, a resemblance which strongly supports the view of their origin in a septicæmia. The onset is usually sudden, often accompanied by a chill and a high temperature, the pain is violent and persistent, and the prostration severe. The patient has the characteristic flush, the respiratory rate is raised and the accessory muscles of respiration are called into play. Vomiting is frequent, and tenderness and rigidity are marked; but in place of the usual absolute constipation there is frequently profuse diarrhœa, which, associated with the other symptoms of acute peritonitis, is often almost diagnostic. In the diffuse form, unless operation is undertaken, death takes place early; but if the patient lives long enough there may be a sudden fall of temperature about the seventh day, as in pneumococcal pneumonia.

The encysted and more common variety of pneumococcal peritonitis is less severe and shows a remarkable tendency for pus to collect in the lower abdomen. There is the same acute onset as in the diffuse variety but the patient then appears to improve for a few days. Later, however, he gets gradually worse, the abdomen becomes distended, the diarrhœa changes to obstinate constipation and an abscess forms in the lower abdomen and finally, if unrelieved, bursts at the umbilicus. The exudate in these cases is a greenish, odourless pus, which is sufficiently characteristic to enable the infection to be diagnosed when it is discovered at operation.



5. *Gonococcal peritonitis*.—Gonococcal peritonitis is rare; it occurs both as an acute diffuse affection of the peritoneum and as a localised pelvic inflammation. It is commoner in females than in males, owing to the ready channel for infection through the Fallopian tubes, and when it occurs in males it is usually secondary to epididymitis. The infection is generally a mixed one, the more fragile gonococcus being readily overgrown, and some cases of unexplained peritonitis, which on culture show only *Bact. coli*, are possibly gonococcal in origin. The symptoms do not differ in the diffuse cases from those of other forms of acute peritonitis, although the primary focus usually gives rise to symptoms. The prognosis is, however, good, and the majority of patients, even those presenting severe symptoms, recover without operation.

6. *Streptococcal peritonitis*.—Peritonitis due to the streptococcus is occasionally secondary to lesions of the alimentary canal; but much more frequently it is a sequel of puerperal infections. It occurs commonly after a first delivery, and is frequently associated with retained products. Infection takes place along the lymphatics of the damaged uterus or through the Fallopian tubes, and may be localised in the pelvis but more often produces peritonitis. The symptoms are characteristic and are associated with evidence of a marked septicæmia. The abdominal wall, being already greatly stretched, does not show the usual rigidity, and extreme distension occurs rapidly. Diarrhœa is commoner than constipation, and a high temperature with rigors is usual. The uterine discharges are offensive, the milk secretion is suppressed and the patients frequently die within the first week. This type of infection is more fulminant than any other, except certain cases of perforative peritonitis.

**Diagnosis.**—The diagnosis of acute peritonitis is not usually difficult, except where the severity of the causal condition is so great that it masks the peritoneal response, or where the peritonitis occurs in a patient already so severely ill that no response is possible. Sometimes it is difficult to make a correct diagnosis of the lesion to which the peritonitis is secondary, and this may only be possible after laparotomy. The most valuable signs of acute peritonitis are the severe pain and tenderness, the rigid abdomen, the small, rapid and thready pulse, the dry tongue, vomiting and constipation, and the absence of sounds of gurgling on auscultation. Any of these symptoms may, however, be absent, and a diagnosis must be based on their occurrence in combination. In post-operative cases there is sometimes a remarkable absence of both pain and rigidity, and early recognition of the condition in these patients is often one of much difficulty.

Peritonitis is most likely to be mistaken for lead colic or acute intestinal obstruction. From the former it can be distinguished inasmuch as the abdomen in peritonitis is usually extremely tender, while, in colic, pressure often, though not invariably, relieves the pain; in lead colic a blue line on the gums is present, and the red corpuscles show punctate basophilia, the pain is intermittent and there is usually no vomiting and less extreme rigidity. From acute intestinal obstruction the diagnosis is often far more difficult. In the early stages of obstruction, before peritonitis has developed, the intermittent nature of the pain, the absence of great tenderness or rigidity, the copious nature of the vomit and the evidence of increased peristalsis from inspection or auscultation should help to distinguish the two conditions.

In acute pancreatitis the pain is more definitely epigastric, the patient is usually over middle age and collapse is extreme. The menstrual history, the typical pallor and the results of vaginal examination usually serve to indicate a ruptured tubal pregnancy, and in other acutely painful abdominal conditions the localised nature of the pain and the absence of any extreme general tenderness help to distinguish the condition from peritonitis.

The gastric crises of tabes are seldom likely to be a source of error; but the comparative absence of severe symptoms in tabetics, the subjects of peritonitis, is apt to lead to a mistaken diagnosis.

Basal pneumonia and diaphragmatic pleurisy may lead to acute abdominal symptoms. The temperature and pulse, the raised respiration rate and a routine examination of the chest in all cases should prevent a mistake being made.

**Prognosis.**—The prognosis of acute peritonitis is always grave, even with early surgical treatment. Without operation no case of acute perforative peritonitis can be expected to recover; such exceptions as have been recorded must be regarded as medical curiosities.

In diffuse spreading peritonitis the outlook is still grave unless operation is undertaken; but the process is less rapid, and a small proportion of patients undoubtedly recover without surgical aid. These cases occasionally merge into a form of chronic fibro-purulent peritonitis, characterised by the progressive formation of collections of pus between neighbouring viscera, and by repeated outbursts of symptoms as other parts of the peritoneum become successively involved. This condition usually terminates in fatal septicæmia, with infections in the pleura, pericardium or endocardium. The prognosis in pneumococcal cases is considerably better, as even without operation a fair proportion recover, either with or without the formation of a hypogastric purulent collection. In the rare gonococcal cases recovery is the rule, and the fatal cases recorded have almost invariably followed operation.

In forming a prognosis chief reliance must be placed on the degree of toxæmia and the severity of the intestinal paralysis, and to a less extent on the degree of meteorism and the frequency of the vomiting. Spontaneous bowel actions or their induction by enemata make the prognosis relatively more favourable.

The rate of rise of the pulse-rate and its ratio to the temperature are also of importance; where there is a subnormal temperature throughout the issue is almost always fatal.

**Treatment.**—The principles that must underlie treatment are: (1) removal or limitation of the infective process to which the peritonitis is secondary. This almost always entails laparotomy; an occasional exception is in some instances of perforated peptic ulcer when further soiling may be prevented by suction of the stomach contents through an indwelling tube; (2) restoration of fluid loss by intravenous saline and glucose solutions; (3) adjustment of electrolyte balances; (4) measures to keep intestinal distension within limits, since severe distension may lead to permanent bowel paralysis and to death. This can usually be achieved by suction through indwelling tubes in stomach or bowel; such a tube naturally also prevents the discomfort and exhaustion of vomiting; its introduction before operation may prevent broncho-pneumonia from inhalation of post-operative vomit; (5) the administration of any appropriate antibiotics. Samples of the exudate or pus found at laparotomy should be sent to the laboratory for sensitivity tests.

Until a definite diagnosis has been made and operation advised and agreed to, the administration of opium in any form is contra-indicated. It masks the symptoms and by bringing to the patient and his advisers a false sense of security may lead to a fatal delay in undertaking the operation. When, however, a diagnosis has been made, and operation is agreed to, morphine is beneficial in reducing both the mental and physical symptoms while the necessary preparations are being made. Morphine as a method of treatment has been adopted more and more of recent years, the morphine being given deliberately and in doses sufficient to affect the respiration rate with the object of diminishing the activity of peristalsis, as well as of combating the shock, pain and restlessness, which help so largely to exhaust the patient's powers of resistance.

In pneumococcal cases there is not the same urgency for operation, and if the diagnosis can be made with certainty, adequate treatment with penicillin will produce a satisfactory result. In gonococcal peritonitis, if a diagnosis can be made, penicillin should also be resorted to; but if there is doubt, as there often must be, of the nature

of the infection, or if the patient shows any increase of symptoms, laparotomy is the only safe course to follow.

CHARLES DONALD.

## CHRONIC PERITONITIS

Chronic peritonitis is a condition in which widespread and progressive chronic inflammation of the peritoneum occurs independently of tuberculous or malignant disease.

**Ætiology.**—Chronic non-tuberculous peritonitis may rarely occur post-operatively, as a result of irritation from particles of talc left from the powder on the surgeon's gloves. In a few cases it is without known cause, as in benign paroxysmal peritonitis (Siegall), which is thought to be allergic in origin.

In the majority of cases, however, chronic peritonitis is either due to a small tuberculous focus which has not been discovered or is part of a general disorder affecting other serous membranes. This, though not uncommon, is of unknown ætiology. It has been given a number of names and when affecting mainly the liver is called General Chronic Perihepatitis or Sugar-iced Liver; when affecting multiple serous membranes, Concato's Disease or Polyserositis; and when mainly the pericardium, Chronic Constrictive Pericarditis, Pick's Disease or Pericarditic Pseudo-cirrhosis of the Liver. The last condition, however, is usually tuberculous in origin (see p. 881).

**Pathology.**—The liver may be covered with a thick, hard and white coating of fibrous tissue, which can be peeled off to expose the smooth peritoneal surface. Perihepatitis is almost always associated with a similar thickening of the capsule of the spleen and with thickening of other parts of the peritoneum. Extensive general peritoneal adhesions are often present.

**Symptoms.**—The condition usually occurs in the young or middle-aged and is compatible with good health for a very long period. The most important and outstanding symptom is ascites. The onset is generally gradual, but it may be acute. Frequent tapping is required and the intervals between the performance of paracentesis tend to diminish and may finally be as short as a fortnight, when as much as a pint of fluid may be poured into the peritoneal cavity in a day.

Oedema, especially of the feet, is frequent in the later stages; it is generally cardiac or renal in origin, but may also be caused by pressure on the inferior vena cava, or an actual thrombosis.

The diagnosis from cirrhosis of the liver is suggested by the absence of jaundice, long history and frequent finding of constrictive pericarditis.

**Course.**—The course of the disease is very slow, death generally occurring from some intercurrent disease. The general health may remain good for a long time.

For the diagnosis and treatment, see Ascites (p. 721).

## BILE PERITONITIS

The escape of bile into the peritoneum produces intense peritoneal irritation with symptoms of severe shock and rapid distension of the abdomen with fluid.

It is one of the most important complications that may follow needle biopsy of the liver; it also occurs after rupture of the gall-bladder and post-operatively when a stone has been overlooked in the common bile duct. In a few cases it appears to arise without any evidence of perforation or leakage from the gall bladder or bile ducts being found. It may remain an aseptic peritonitis or become rapidly infected and form turbid purulent fluid. Minor cases following liver biopsy may subside spontaneously, but in most other cases treatment is surgical.

## TUBERCULOUS PERITONITIS

**Ætiology.**—The peritoneum is involved in 15 per cent. of fatal cases of tuberculosis. Tuberculous peritonitis is rare in infants and uncommon after 30; the majority of cases occur between the ages of 3 and 20. Boys and girls are equally liable to the disease; it is found much more frequently in women than men at operations, but more frequently in men than women after death.

Primary tuberculous peritonitis is uncommon in children and rare in adults. It is probably due to infection conveyed by the intestines, which do not themselves become infected. More often, especially in children, the mesenteric glands become tuberculous, generally without any lesion developing in the intestines, and the peritoneum is infected from the glands. In males the primary focus may be the prostate, vesiculæ seminales or testes, and in females the disease frequently begins in the Fallopian tubes; but the latter may also be infected from the peritoneum. Although tuberculous ulcers are found in the gut in over 50 per cent. of fatal cases of pulmonary tuberculosis, the peritoneum is affected in only 4 per cent. of cases. The peritoneum, the pleura and occasionally the pericardium may be involved together in the absence of any other tuberculous focus.

**Pathology.**—Tuberculous peritonitis may occur in three forms—the ascitic, loculated and obliterative.

1. In the ascitic form, which may be acute, subacute or chronic, miliary tubercles are scattered over the whole peritoneum, which is free or nearly free from adhesions. In chronic cases the tubercles are larger and more fibrotic than in the acute; the peritoneum is thickened and the mesentery is shortened so that the intestines are tethered to the posterior abdominal wall. This form may closely resemble malignant peritonitis, and large effusions may collect very rapidly.

2. In loculated tuberculous peritonitis the fluid may be clear, the condition being then intermediate between the ascitic and obliterative forms, or it may be turbid or purulent. In the latter case masses of tuberculous material separated from each other by adherent coils of intestine have broken down to form suppurating foci, which may erode the intestine or open at the umbilicus or even into the vagina.

3. Chronic obliterative, adhesive or fibrous tuberculous peritonitis may occur after absorption of fluid in the ascitic form or may develop primarily. No effusion is present, but universal adhesions obliterate the lumen of the peritoneum, all the viscera being inextricably bound together and to the parietal peritoneum.

In each form of tuberculous peritonitis the mesenteric glands are generally caseous ("tabes mesenterica") and may break down in the centre; the mediastinal glands may also become tuberculous. The omentum is often rolled into a solid mass, which sometimes contains caseous nodules.

**Symptoms.**—Tuberculous peritonitis is sometimes completely latent, and may be discovered accidentally during an operation for some independent disease or for a hernia, when the sac may be the only part involved.

The onset of abdominal symptoms is generally preceded by a period of ill health. The patient loses weight and strength, his appetite is poor and his temperature may rise slightly at night. After a time he complains of general abdominal discomfort. Constipation is common, especially in the obliterative form. In other cases diarrhœa may occur owing to tuberculous ulceration of the intestines, fistulous communications between adjacent coils of intestines or simple entero-colitis. The stools are occasionally bulky owing to deficient absorption of fat caused by obstruction of the lacteals by caseous mesenteric glands (see p. 610). The spleen and less often the liver may be enlarged. The skin, especially over the abdomen, is dry, inelastic and sometimes so pigmented that Addison's disease is simulated. In chronic cases there is sometimes no pyrexia; more often the temperature is intermittently raised. In

acute and suppurative cases the temperature is generally high and irregular, and the pulse is rapid. Traces of albumin may be present in the urine owing to pressure on the renal veins caused by the large accumulation of fluid in the abdomen or to the effect of the toxæmia on the renal cells. A moderate degree of anæmia is often present, and leucocytosis develops if suppuration occurs.

In the ascitic form the abdomen gradually becomes distended. At first it is tympanitic, but after a time evidence of the presence of free fluid is obtained, but the quantity is often not very great. Less frequently a large amount of fluid collects with great rapidity and the sudden stretching of the abdominal muscles may cause a considerable amount of pain. Moderate tenderness of the whole abdomen is generally present. A large accumulation of fluid may compress the inferior vena cava and give rise to œdema of the legs. The diaphragm is pushed upwards and respiration becomes shallow and thoracic. The skin over the abdomen is shiny and the veins are enlarged. The ascitic fluid is generally clear and it often coagulates on standing. Less frequently it is turbid or blood-stained. It always contains cells, a large proportion of which are lymphocytes. Tubercle bacilli are rarely found, although they must be present, as the fluid may produce tuberculosis when injected into guinea-pigs.

In the loculated form with suppuration the abdominal pain is generally greater. Attacks of colic are common, especially after exercise. The abdomen is distended and doughy. On percussion irregular tympanitic and dull areas are found. Large caseous glands and collections of pus between adherent coils of intestines may form palpable masses, which are immobile, tender and dull on percussion. The omentum can sometimes be recognised as a thick cord stretching across the upper part of the abdomen; the transverse colon generally forms a resonant band immediately above it, which helps to distinguish it from the lower edge of an irregularly enlarged liver. The ease with which the masses are felt varies from time to time with the amount of flatulent distension of the intestines. When an abscess is about to point at the umbilicus, the latter becomes indurated, red and tender. A similar condition is occasionally observed in pneumococcal peritonitis and in pelvic peritonitis in women. On rectal and vaginal examination thickened Fallopian tubes, enlarged glands or collections of pus may be felt.

The signs of obliterative tuberculous peritonitis are ill-defined. The abdomen gives a characteristic rubbery resistance on palpation and is generally somewhat distended. Irregular masses may be felt in it, and the peristaltic waves of the small intestines are often visible, especially in children. This does not necessarily indicate that partial obstruction is present, as it may be simply a result of the abnormal thinness of the abdominal wall.

Symptoms of tuberculous disease of other organs, especially of the lungs, pleura and intestines are often present. Generalised tuberculosis may develop at any time, especially in children. Vomiting and constipation, which suggest intestinal obstruction, may be the first symptoms of tuberculous meningitis.

In rare cases acute peritonitis may develop as a result of rupture of a softened caseous gland or perforation of a tuberculous ulcer.

When a patient recovers from tuberculous peritonitis, the tubercles and adhesions may completely disappear. More frequently localised adhesions remain, and calcified tuberculous mesenteric glands are often found with the radiograph, at operations and after death. They may give rise to confusion when the abdomen is radiographed on account of suspected renal calculi. They do not, however, move with the shadow of the kidney with changes in posture, and the diagnosis can always be settled by pyelography. The bands, which may form from localised adhesions, occasionally cause acute intestinal obstruction, sometimes not until many years after the active disease has disappeared.

**Diagnosis.**—In the presence of tuberculous disease of the lungs or other organs,

abdominal distension, especially if associated with ascites or irregular abdominal masses, generally indicates that tuberculous peritonitis is present. The discovery of tubercle bacilli in the sputum, and their much less common discovery in the faeces or vaginal discharge, is very strong confirmatory evidence. Ascites in children and in females with symptoms pointing to tuberculous salpingitis is generally due to tuberculous peritonitis.

Acute cases may at first closely simulate pneumococcal peritonitis or even appendicitis; but in non-tuberculous inflammatory exudates of the peritoneum most of the cells are polymorphonuclear leucocytes instead of lymphocytes. Ascites due to cirrhosis of the liver in children is almost always mistaken for tuberculous peritonitis; on the other hand, the ascitic form of tuberculous peritonitis in middle-aged alcoholic individuals is likely to be mistaken for ascites due to cirrhosis. When cirrhosis is undoubtedly present, ascites may still be due in part to tuberculous peritonitis; a large proportion of lymphocytes in the fluid is very strong evidence in favour of this, as the ascitic fluid in uncomplicated cirrhosis contains few except endothelial cells. In simple chronic peritonitis there is no fever and little or no pain, and the ascitic fluid contains few if any lymphocytes. The presence of irregular masses together with fluid in the abdomen generally indicates tuberculous peritonitis in children; but it is more frequently due to malignant disease in adults, especially in males. The history of the case and any evidence of tuberculous or of malignant disease in other parts of the body help to settle the diagnosis.

Fever, inflammation of the umbilicus, and the presence of lymphocytes in the ascitic fluid point to tuberculosis, whilst nodular infiltration without inflammation of the umbilicus, hard and enlarged glands in the groin or neck, and the presence of large, multinuclear cells or groups of cells in the effusion point to cancer.

**Prognosis.**—Before the advent of chemotherapy recovery took place in a large proportion of cases of the ascitic form of tuberculous peritonitis. When localised abscesses developed complete recovery was rare, and when a faecal fistula formed death almost always followed. Prolonged fever, rapid emaciation and intractable diarrhoea were the most serious symptoms. Apparent recovery was sometimes followed by a relapse, generally owing to reinfection from an unhealed primary focus, such as a tuberculous gland, appendix or Fallopian tube.

**Treatment.**—The principles of treatment are the same as for tuberculosis in general (see p. 1031). Complete bed rest and a nutritious diet are essential and chemotherapeutic drugs should be given for at least 3 months. Streptomycin 1.0 g. intramuscularly daily can be combined with oral isoniazid 100 mg. twice or three times daily. Diarrhoea should be treated by a non-irritating diet, and in intractable cases by opium preparations. If fatty diarrhoea is present, fat must be excluded from the diet. With this exception, the food should be as abundant and nourishing as possible.

When the abdominal distension in ascitic cases gives rise to discomfort paracentesis should be performed. The occurrence of intestinal obstruction is an indication for operation, though it may not be possible to do anything useful owing to the extensive adhesions present and the danger of tearing the intestines. Laparotomy is not indicated for ascites alone, though it is sometimes followed by surprising improvement in the condition.

## CANCER OF THE PERITONEUM; MALIGNANT PERITONITIS

**Ætiology.**—Cancer of the peritoneum is almost always secondary. The primary disease is generally in the abdomen, especially the stomach and the ovary, the peri-

toneum becoming involved by spread along lymphatics or blood vessels, by direct contact, or most commonly by malignant cells being set free and scattered widely over the peritoneum. The disease may also spread from cancer of the breast by the deep lymphatics of the chest and abdominal wall, and by lymphatics from malignant disease of the testis.

**Pathology.**—Malignant deposits may form minute tubercles, larger white non-cascating nodules or even very large masses. The parts most generally involved are the omentum, mesentery and pelvis. Chronic fibrotic changes frequently occur, and result in the omentum being rolled up and the mesentery shortened as in tuberculous peritonitis. The diaphragm is often invaded with growth, which spreads to one or both pleuræ. Acute or subacute peritonitis may occur.

**Symptoms.**—The symptoms are caused in part by the primary disease and in part by the secondary malignant peritonitis. As the former is generally situated in the abdomen, it is impossible to distinguish between the symptoms due to the two causes. Malignant peritonitis generally results in ascites; the fluid is often blood-stained, but may be clear or turbid, or less frequently chylous owing to obstruction and subsequent rupture of lacteals. The umbilicus is often infiltrated with growth, and nodules may be felt along the falciform ligament. Tumours are often felt in the abdomen or on rectal examination; they are sometimes too small to be palpable, and in other cases they can only be felt after the fluid has been removed. The rolled-up omentum may be recognised as a thick transverse cord above the umbilicus. The malignant masses or peritoneal adhesions may give rise to obstructive symptoms.

**Diagnosis.**—The development of new abdominal tumours or ascites in a patient who is known to have cancer of the stomach or other organ is almost conclusive evidence that the peritoneum is involved. When there is no clear evidence pointing to the presence of a primary malignant or tuberculous focus, it may be difficult to distinguish between tuberculous and malignant peritonitis (see pp. 718, 720). When ascites is present and no tumour is palpable, cirrhosis, heart failure, simple chronic peritonitis or portal thrombosis may be simulated; the abdomen should be tapped, when a tumour often becomes palpable if malignant disease is present.

**Prognosis and Treatment.**—It is rare for the patient to survive for more than 6 months after the peritoneum becomes involved. Treatment is purely palliative. Considerable relief may follow paracentesis.

## ASCITES

**Definition.**—Ascites is the accumulation of free fluid in the peritoneal cavity.

**Ætiology.**—Ascites is a constant symptom of simple, tuberculous and malignant chronic peritonitis. It occurs when there is a rise of pressure in the portal circulation; it is always present in portal thrombosis and when the portal vein is obstructed by a growth or an aneurysm, and portal obstruction is in part responsible for its presence in cirrhosis of the liver. Ascites is very common in heart failure, in which it is almost always associated with œdema of the feet. It is in part due to the same causes as the œdema, but it is also in part caused by portal congestion, and by obstruction to the lymph flow from the thoracic duct owing to the rise of venous pressure. Lastly, ascites accompanies the dropsy of Bright's disease and severe anæmias, largely as a result of the hypoproteinæmia which is present.

**Symptoms.**—The abdomen becomes gradually enlarged, at first in an antero-posterior direction, the costal margin being pushed forward, but at a later stage the bulging occurs in the flanks also. The stretching of the abdominal wall gives rise to a tight sensation, which may amount to actual pain if the fluid collects rapidly. It causes the muscles to atrophy and lineæ atrophicæ develop in the skin. The umbilicus becomes everted and may form a thin-walled bladder.

The rise in intra-abdominal pressure caused by the accumulation of ascitic fluid presses on the inferior vena cava; œdema of the legs may occur, and the obstruction to the renal circulation may cause albumin to appear in the urine, the quantity of which is reduced owing to the loss of water in the ascitic fluid. Compensatory dilatation of other venous channels results: the dilatation of the veins passing between the abdominal wall and those in the falciform ligament is manifested by the development of large and prominent subcutaneous veins around and above the umbilicus; others pass from the superficial and deep epigastric veins in the middle of the groin towards the costal arch, where they join the superficial epigastric and long thoracic veins. When paracentesis is performed, the dilated veins disappear if they have developed as a result of pressure on the inferior vena cava, but not if obstruction of portal veins is the primary condition.

The diaphragm is pushed up; its excursions on respiration are reduced and dyspnoea may result. The impulse of the heart may be felt in the third intercostal space; the twisting of the heart may temporarily produce a pulmonary systolic murmur. Cardiac irregularity, palpitation and attacks of faintness may follow. The upper border of hepatic dullness may reach the fourth, third or even second intercostal space in front; the right base is dull behind owing to the liver being pushed up and the lung compressed. A pleural effusion may be suspected, but the upper limit of dullness is altered on taking a deep breath if it is due to the liver being pushed up, and the increased dullness diminishes or disappears when the patient lies on his face; in pleural effusion the dullness is higher in the axilla than behind, but this is not the case if it is due to an abnormally high position of the liver.

The pelvis and renal regions hold a considerable amount of fluid, so that no accumulation occurs in the flanks until at least a litre is present in the abdomen. As more fluid collects, the resonant note in the flanks is replaced by dullness, but the change may be delayed if there is much gas in the colon. The level of dullness now gradually rises and spreads over the pubes towards the umbilicus. On turning from one side to the other the most dependent part remains dull. Such shifting dullness may not be easy to elicit but when present is almost pathognomonic of ascites; very similar movable dullness may, however, rarely occur in chronic obstruction of the small intestines when they are distended with fluid faeces and gas.

In chronic peritonitis the mesentery may be so shortened that the intestines are unable to float on the fluid; the fluid then accumulates in front of the intestines, and the highest part of the abdomen is dull.

A characteristic fluid thrill is felt when one side of the abdomen is sharply flicked by the fingers of one hand, whilst the other hand is placed flat upon the opposite side of the abdomen. When the patient is very fat or the abdominal wall is œdematous, a similar but less marked sensation may be produced. In doubtful cases the hand of an assistant should therefore be pressed perpendicularly over the middle line of the abdomen, as this prevents the transmission of the impulse through the abdominal wall, but not through the fluid contents of the abdomen.

When the liver or spleen is enlarged and hard, or when an abdominal tumour is present, the sensation produced by dipping the tips of the fingers suddenly through the fluid on to the solid organ, which jumps away from them, is most characteristic.

**Diagnosis.**—The presence of ascites must first be distinguished from other causes of abdominal enlargement such as meteorism, pregnancy and obesity. A distended bladder, a very large hydronephrosis, or a big pancreatic or mesenteric cyst may sometimes cause confusion, as may more particularly, a large ovarian tumour. The history of the development of the abdominal swelling may help the diagnosis. In the case of an ovarian tumour, the outline of the tumour can frequently be definitely felt, and its pelvic attachments can be recognised by vaginal examination. The antero-posterior enlargement is greater than the lateral bulging, whereas the reverse is the case in ascites; the maximal girth is below the umbilicus instead of at the



umbilicus or above; the umbilicus, which is normally and in ascites an inch nearer the pubes than the ensiform cartilage, is proportionately farther from the pubes; and the distension on one side is often greater than the other instead of being uniform.

**Diagnosis of Cause of Ascites.**—In cirrhosis of the liver the fluid collects rapidly and the patient often appears ill and wasted. In chronic peritonitis the accumulation on the first occasion is generally gradual and the patient may be otherwise well. *An enlarged spleen or the occurrence of hæmatemesis points to cirrhosis.* A patient with ascites due to cirrhosis alone rarely survives the performance of paracentesis more than a few times, as his general health has often greatly deteriorated by the time that ascites develops, but this is much less true in chronic peritonitis. Tuberculous peritonitis is uncommon over the age of 30, except as a complication of cirrhosis of the liver and when secondary to tuberculous Fallopian tubes. Evidence of tuberculous disease in other parts of the body, solid masses palpable in the abdomen or on rectal examination, pain and tenderness in the abdomen except over the liver, and induration and redness of the umbilicus point to tuberculous peritonitis; the fluid is generally turbid, the specific gravity is above instead of below 1.015, and lymphocytes are present.

In malignant peritonitis there is generally evidence of the primary disease in some other organ, and nodules may be felt in the abdomen, in the neighbourhood of the umbilicus, or in the middle line above it, and enlarged glands may be present. The spleen is not enlarged, emaciation is generally greater than in cirrhosis, and, except when the primary disease is in the stomach, there is no hæmatemesis. Rectal and vaginal examinations are particularly important, as ascites, which may recur very frequently, sometimes results from ovarian tumours. In a doubtful case the diagnosis may become clear after paracentesis, when the large hard liver and spleen may be felt in cirrhosis, and an irregular enlargement of the liver, but no splenomegaly, in cancer of the liver. In malignant disease the fluid may contain cancer cells; it is more often hæmorrhagic than in tuberculous peritonitis or cirrhosis.

Rapid development of ascites with enlargement of the spleen and sometimes hæmatemesis suggests portal thrombosis. If symptoms pointing to cirrhosis are already present, it is probably secondary to this, and even in their absence it may be secondary to latent cirrhosis.

An examination of the circulatory system and the urine should prevent confusion between ascites due to cirrhosis and that due to heart failure or kidney disease, but these conditions may be associated.

An additional method of diagnosis in ascites is the direct inspection of the abdominal viscera, a procedure known as laparoscopy or peritoneoscopy. After the abdomen has been tapped for the removal of fluid 2 or 3 litres of air are introduced. The abdominal wall is punctured by a large trocar and cannula, and through the latter the instrument, which is similar to the cystoscope, is passed into the pneumoperitoneum. By this means it is possible in the majority of patients to inspect the anterior aspects of the liver and stomach, the anterior parietal peritoneum, the omentum, parts of the small intestine and the superior aspects of the pelvic organs in female patients. It is sometimes possible to see the gall-bladder, parts of the large intestine, the appendix, hernial orifices and the spleen when enlarged. Laparoscopy may sometimes enable the physician to make a reasonably certain diagnosis of cirrhosis of the liver, carcinoma of the stomach, malignant metastases in the liver, peritoneum and omentum, and various other conditions, but its value in diagnosis has proved disappointing.

**Treatment.**—Paracentesis should be performed if the accumulation of fluid causes serious discomfort or greatly interferes with the digestion, circulation or respiration. Hæmatemesis is a further indication, as paracentesis reduces venous engorgement. The trocar should be inserted in the middle line between the umbilicus and pubes, or in the flank. Care must be taken to avoid the bladder, or the liver or

spleen if they are very much enlarged. A trocar and tube of moderate bore should be used, as the very fine Southey's tubes tend to become blocked and the discomfort caused by the paracentesis is needlessly prolonged.

A salt-free diet should be given, as ascitic fluid never contains less than 8 g. of sodium chloride in each litre and if the quantity of salt taken in the day is reduced to 0.8 g., less than 100 ml. of ascitic fluid can collect during the same period.

Alternatively mercurial diuretics can be prescribed, *e.g.* injection of mersalyl B.P. 2.0 ml. intramuscularly, once or twice weekly. Diuretics are more valuable as preventatives when the fluid first appears or after it has been removed than as curatives when a large quantity is present, as the pressure on the renal veins makes the kidneys less active, and an enormous quantity of fluid has to be excreted by them before the accumulation can disappear, whereas comparatively little urine need be passed to prevent re-accumulation of ascitic fluid after tapping.

The bowels should be kept well open, but severe purging weakens the patient and is likely to aggravate the catarrh of the alimentary canal which is often already present. Epsom salts, which also promotes biliary drainage, is the most suitable aperient. High protein diet is indicated if the serum protein is low and especially if ascitic fluid has to be removed, since one paracentesis alone may mean the loss to the body of over 200 g. of protein if fresh fluid reforms.

For the surgical treatment of cirrhosis, see p. 679.

THOMAS HUNT.

## SECTION IX

### DISEASES OF THE BLOOD

THE blood is sometimes regarded as the mixed secretion or product of the blood-forming organs. For the purposes of description and for the better understanding of the changes in disease, it is more convenient to think of the blood and blood-forming organs as composed of three distinct systems or tissues: (1) the red cells and their precursors, sometimes known as the erythron; (2) the white cells and the immature cells from which they arise; (3) the platelets and the megakaryocytes. These three systems of cells exist side by side in the plasma and bone-marrow, and are often affected simultaneously by disease, but they are to a large extent independent of each other. Before discussing separately the three systems of cells and their diseases, it will be convenient to say a few words about the total volume of the blood.

#### THE BLOOD VOLUME

The total volume of the blood is about 90 ml. per kg. of body weight, i.e. some 6,000 ml. in an average individual, or about one-eleventh of the body weight. Rather lower values are given by recent techniques. Of this volume the cells constitute about 42 per cent., the remainder being plasma. The blood volume is moderately diminished in anæmia; it is moderately increased in the splenomegalies, in leukaemia and in erythrocytosis, and greatly increased, even to twice the normal, in erythræmia. There is a slight increase in œdema, due to an associated œdema of the blood, but no change in arterial hypertension. The blood volume is moderately increased in pregnancy, in order to allow for the foetal circulation. Of great importance in practice are the conditions in which the volume of circulating blood is suddenly and considerably diminished. Hæmorrhage, external or internal, is the commonest cause of a fall in the blood volume, but the blood volume may be reduced by loss of plasma alone in crushing injuries, burns, anaphylaxis and the dehydration associated with alkalosis, diabetic coma, cholera and severe infections. Symptoms of shock quickly appear. In acute anæmia from hæmorrhage or blood destruction there is extreme exhaustion, faintness or syncope, air-hunger, sweating and thirst. The degree of shock depends largely on the rate of bleeding. A sudden hæmorrhage of 1500 to 2000 ml. may be fatal, while as much as 60 per cent. of the total amount of blood may be lost without death if the hæmorrhage is prolonged over 24 hours or more. The other important factor which determines the degree of shock is the extent of any associated injuries. The blood count is of limited value in determining the patient's condition, for hæmodilution may take 2 to 3 days and hæmoglobin values around 13 g. (90 per cent.) are the rule within the first hour of sustaining injuries, no matter how severe the patient's hæmorrhage has been. In alimentary hæmorrhage the blood urea may be raised, owing to absorption of the effused blood, and the height of the rise is a fair measure of the severity of the bleeding.

In acute reduction of blood volume from any cause a systolic pressure below 80 mm. of mercury, a progressive increase in pulse-rate and the development of crepitations in the lungs are all serious signs. The patient becomes collapsed, complains of thirst, the skin is pale, cold and moist, the breathing quick and shallow, the pulse rapid and almost imperceptible, and the blood pressure low. The kidneys are inadequately supplied with blood and the output of urine may almost cease. The symptoms are often mistaken for heart failure, but there is no orthopnoea, venous

engorgement or œdema, and they are really due to loss of fluid from the circulation and stasis of blood in the capillaries.

The logical treatment in all forms of shock is to increase the blood volume and the venous return to the heart in any way possible. The foot of the patient's bed may be elevated, the legs bandaged from the ankles to the mid-thigh and the intake of fluid by the mouth increased, unless these measures are otherwise contra-indicated. A careful watch should be kept on the output of urine, suppression of urine being particularly likely to occur in crush injuries. The patient should be kept warm, but not too warm, and inhalation of oxygen or oxygen plus carbon dioxide may be helpful. Apart from sedatives for pain, drugs are of little value. Various types of infusion have been used with the object of restoring the blood volume to normal and it has thus been discovered that whole blood, plasma and serum are the most satisfactory fluids. Solutions of saline or dextrose produce only transient improvement. Blood is the fluid of choice when there has been much bleeding, though in urgent cases it may be desirable to begin treatment with plasma or serum to save time in typing and cross-matching. Plasma or serum is the fluid of choice where there is hæmo-concentration, as in burns. Plasma and serum must be obtained from human blood donors, and they may give rise to homologous serum jaundice. Efforts have therefore been made to replace them by synthetic colloidal solutions, of which dextran and polyvinylpyrrolidone are recent examples, but solutions of this kind must be regarded as still on trial. Transfusion must be begun at the earliest possible moment to prevent the patient relapsing into an irreversible state, and it must be continued until the blood pressure is raised to what can be regarded as a normal level. Up to this point it should be given as rapidly as possible, but thereafter it should be slowed to a drip and maintained at this level until the conclusion of operative or other treatment. If a patient is bad enough to require transfusion, he will usually require at least 1500 ml. of blood or plasma.

## THE RED BLOOD CELLS

The red blood cells are biconcave discs with a mean diameter of 7.20 microns (6.7 to 7.7 $\mu$ ), a mean volume of 85 cubic microns (75 to 95 $\mu\mu$ ), and a mean corpuscular hæmoglobin content of 29 micromicrograms<sup>1</sup> (26.5 to 31.5 $\gamma\gamma$ ). Their size and shape are adapted to the carriage of hæmoglobin and the supply of oxygen to the tissues. The blood of a healthy young male contains about 5.5 millions of red cells per c.mm. and 16 g. of hæmoglobin per 100 ml.; of a healthy female about 4.75 millions of red cells per c.mm. and 14 g. of hæmoglobin per 100 ml. The normal range of variation of the erythrocyte count is from a million above to a million below the average male value, i.e. any figure between 4.5 and 6.3 million red cells per c.mm. may be considered normal, and there is naturally a corresponding fluctuation in the hæmoglobin percentage. A hæmoglobin percentage below 12.5 g. (85 per cent) is always abnormal, though symptoms of anæmia rarely appear until the hæmoglobin falls below 11 g. (75 per cent.). Erythrocytes and hæmoglobin are subject to much less diurnal variation than the white cells, but significant changes may occur after exertion. For purposes of calculation the normal red cell count is taken as 5 million cells per c.mm., and the corresponding amount of hæmoglobin (14.8 g. per 100 ml. of blood) is taken as 100 per cent. hæmoglobin. The *colour index* measures the average amount of hæmoglobin contained in the red corpuscles of a sample of blood, and is calculated from the formula

$$\text{Colour index} = \frac{\text{Hæmoglobin per cent.}}{\text{Number of red cells per cent. of the normal.}}$$

<sup>1</sup> A micromicrogram is the millionth of a millionth part of a gram (1 g. $\times 10^{15}$ ), and is abbreviated by the Greek letters gamma ( $\gamma\gamma$ ).

The red cells in any sample of blood are never absolutely equal, but show a certain amount of variability in size, or *anisocytosis*. The degree of variability, or *anisocytosis*, is often increased in anæmia and may be of diagnostic significance. The mean diameter of the red cells and their variability is determined by measuring the diameter of 500 successive red cells under the microscope on a stained thin smear. The results are then plotted on squared paper, with the number of cells counted as ordinates and the diameter of the cells as abscissæ, to obtain what is known as a red cell diameter distribution curve, or Price-Jones curve (Fig. 1). Abnormal variability in the size of the cells will be shown by a widening of the base of the curve. Cells which are larger than normal and fall to the right of the limits determined on healthy individuals are called *macrocytes*. Small cells which fall to the left of the limits of health are called *microcytes*. A cell of normal diameter is a *normocyte*. The cell volume is obtained by centrifuging a sample of blood under standard conditions; the mean cell volume is calculated from the height of the column of red cells and the total red cell count. As the red cells age, they become malformed and finally broken into fragments which are engulfed by the phagocytic cells of the liver, the spleen and other tissues. These malformed red cells are called *poikilocytes*. In all forms of anæmia the cells put into circulation are less perfect than in health, and *poikilocytosis* more rapidly develops.

If a sample of citrated blood is allowed to stand, the red cells will aggregate and fall out of suspension. This is a complex phenomenon but the chief factors are the concentration of the red cells and the constitution of the plasma; anæmia and increases in globulin and fibrinogen tend to accelerate the fall. The *erythrocyte sedimentation rate* is increased in pregnancy, infections and malignant disease.

**Blood groups.**—In the year 1900 Landsteiner and his pupils made the surprising discovery that the red cells of mankind are not immunologically identical, and that the sera of many people contain antibodies which agglutinate and destroy the red cells of others. There are, in fact, four main blood groups, which are determined by the presence or absence of two agglutinogens, A and B, of which either may be present separately (groups A and B), neither may be present (group O), or both may be present together (group AB). Corresponding to these two agglutinogens are their homologous antibodies or agglutinins—anti-A (or  $\alpha$ ) and anti-B (or  $\beta$ )—which are present in the serum in reciprocal relationship to the agglutinogens of the cells. The following table illustrates the Landsteiner classification of blood groups and the distribution among the population in England.

It can be seen that the serum of group AB will not agglutinate the red cells of any other group, and for this reason group AB has been called "universal recipient". For similar reasons members of group O are called "universal donors", because their red cells contain no agglutinin; but blood from group O should only be transfused into members of other groups in extreme emergency; whenever possible patients should be transfused with their own group. It has been shown by a number of observers that the ABO blood groups have sub-groups, and interaction may occur between members of the same group. The existence of agglutinogens  $A_1$  and  $A_2$  is now generally accepted. For this reason the compatibility of donor and recipient must always be confirmed by direct cross-matching of the cells of the donor and the serum of the recipient.

The four groups A, B, AB and O constitute the ABO blood-group system. It is now known that there are a number of other blood-group systems and these are of great importance in genetics, anthropology and criminology. They are important clinically only in so far as the relevant antibodies may cause trouble during transfusion, when hæmolytic may occur, or during pregnancy, when antibodies may cross the placenta of the mother and damage the fœtus. The only blood-group systems which commonly give rise to trouble in this way are the ABO and the Rh systems. In selecting donors it is necessary to pay attention only to the ABO and Rh systems, but

of the other systems compatibility tests must be carried out with special care in patients who have had previous transfusions and may thereby have been stimulated to produce abnormal antibodies. The Rh system contains a number of separate

Blood Group.	Agglutinin.	Agglutininogen.	Per Cent.
AB	None	A and B	3
A	<i>b</i>	A	42
B	<i>a</i>	B	9
O	<i>a</i> and <i>b</i>	None (0)	46

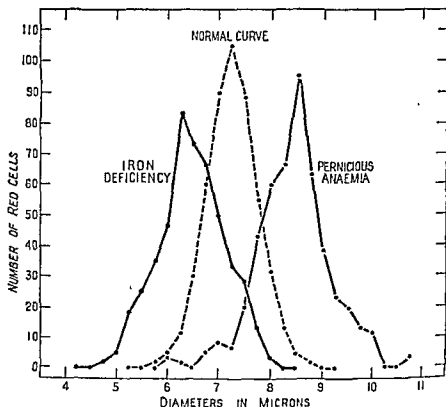


FIG. 1—Frequency distribution curves of red cell diameters in health and disease (Price-Jones curves).

blood groups, in the same way as the ABO system, but their nomenclature and determination are a matter for the expert. In routine clinical work it is sufficient to classify people as "Rh positive" (83 per cent.) and "Rh negative" (17 per cent.) according to their reaction to a serum which was originally prepared by injecting the red cells of Rhesus monkeys into rabbits. People whose erythrocytes are Rh-negative are capable under certain circumstances of forming an antibody which reacts with the

Rh antigen. This may occur after transfusion of Rh-positive blood, but it more commonly happens when a woman who is Rh-negative becomes pregnant with a child whose erythrocytes are Rh-positive.

Experience has shown that grouping is not necessary when serum or plasma is transfused. This is partly because the serum or plasma which is administered is usually a pooled product from a number of patients, but more important is the fact that the group antigens are not confined to the red cells but are present also in the body fluids and other tissues, and absorption of antibody by these agencies serves to protect the recipient's red cells from agglutination when a potentially dangerous plasma is administered. This latter fact also explains the infrequency of symptoms when group O blood is transfused into patients of other groups, inasmuch as the  $\alpha$  and  $\beta$  agglutinins in the plasma are not merely diluted, but to a large extent neutralised in the circulation of the recipient. Nevertheless, it should be the rule nowadays, when blood is transfused, to use only blood of the same ABO and Rh group as the recipient, owing to the risks in a subsequent transfusion or pregnancy when this rule is broken. The same rule applies to the intramuscular injection of blood.

*Nomenclature.*—The red cells are formed in the bone-marrow, which can be examined during life by the techniques of sternal puncture and marrow biopsy. The nucleated precursors of the red cells in the marrow are known by the generic name of *erythroblasts*. In normal marrow the erythroblasts are *normoblasts*, which subsequently develop into normocytes, but in certain diseases larger forms with more primitive nuclei are found, the *megaloblasts*, which give rise to megalocytes. The nucleated red cells lose their nuclei by extrusion or solution, but for a time they still contain remnants of the original basophil cytoplasm, which gives the red cell a bluish tinge in ordinary stained smears (*diffuse basophilia* or *polychromasia*). Certain dyes, such as brilliant cresyl blue, when brought in contact with the fresh-drawn blood, precipitate this basophil cytoplasm in a network or reticulum, and on this account these immature red cells are called *reticulocytes*. Polychromasia and reticulocytosis are identical conditions revealed by different stains. The normal reticulocyte count is  $\frac{1}{2}$  to 2 per cent. A similar precipitation may occur *in vivo* when poisons, such as lead, circulate in the blood-stream and the reticulum becomes visible in ordinary preparations (*punctate basophilia*).

Blood diseases may be due to causes originating outside the blood-stream and the bone-marrow and on this account we refer to many of them by names which merely describe the type of reaction or blood picture. Thus, anæmias may be described as hæmorrhagic, hæmolytic or aplastic in type. According as the colour index is high, normal or low, they are described as *hyperchromic*, *orthochromic* or *hypochromic*. They can also be classified by the size of the red cells into *macrocytic*, *normocytic* and *microcytic* anæmias. These two sets of terms correspond roughly with each other, but they are not absolutely interchangeable, and each should be used strictly according to definition. The description *megalocytic* is best confined to cases of anæmia in which the marrow is megaloblastic.

## THE SYMPTOMATIC ANÆMIAS

*Synonym.*—Secondary Hypochromic Anæmia.

*Definition.*—A symptomatic anæmia is one which arises in the course of some other well-defined disease. The colour index is usually low and hardly ever above unity. In the rare cases in which the colour index rises above unity, the disturbance of the erythropoietic tissues is usually so profound that for practical purposes all the megalocytic anæmias can be regarded as actual diseases of the erythropoietic tissues.

*Ætiology.*—The most obvious cause of anæmia is hæmorrhage: acute hæmorrhage occurs most commonly from trauma, bleeding from the alimentary tract and

the accidents of childbirth; chronic hæmorrhage is often due to hæmorrhoids, menorrhagia and, in tropical countries, hookworm disease. Hæmolysis is a rare event, but it may be induced by chemical poisons, such as sulphanilamide and arseniuretted hydrogen, or by infection by hæmolytic organisms, such as the *Streptococcus pyogenes* or the *Clostridium welchii*, or by malaria. Acute infections rarely produce much anæmia, but severe anæmia may develop in protracted septic infection, acute rheumatism, rheumatoid arthritis and other subacute or chronic infections, such as typhoid fever. Focal sepsis is seldom responsible for an anæmia. Tuberculosis causes little anæmia until the later stages, when hæmorrhage, suppuration or intestinal ulceration have occurred. Syphilis also is rarely the cause of anæmia, except in the more florid stages, from involvement of the liver, or from paroxysmal hæmoglobinuria. Malaria has already been mentioned. Of the toxæmias responsible for anæmia, nephritis and lead poisoning are the most important. Malignant disease is one of the commonest causes of anæmia; it may act in various ways—hæmorrhage from a malignant ulcer, cancerous cachexia, and invasion of the bone-marrow. Anæmia which is due to mechanical limitation of the bone-marrow by tumours or tumour-like conditions, such as leukæmia, Hodgkin's disease, infective granulomata and kala-azar, is sometimes described as myelophthisic anæmia, but this is an incorrect and unnecessary use of a word which is one of the synonyms for aplastic anæmia.

**Pathology.**—Two factors can be distinguished in these symptomatic anæmias. The first is loss of blood by hæmorrhage or hæmolysis. This leads to hyperplasia of the bone-marrow, and an outpouring of new red cells to repair the deficiency. The colour index is low, because hæmoglobin regeneration lags behind the restoration of a normal cell count, and the reticulocyte count is increased to 5 or 10 per cent., or higher. Chronic and repeated hæmorrhage may so exhaust the hæmatinic reserves that the body cannot repair the hæmoglobin deficiency, the anæmia remains torpid and the reticulocyte count is low; rapid recovery occurs on the exhibition of large doses of iron. The second factor in the symptomatic anæmias is depression of the erythropoietic tissues by toxæmia. Hæmopoiesis may be inhibited without much structural alteration in the marrow, but in other cases the marrow becomes hypoplastic and may even degenerate completely. The output of new red cells is diminished, the reticulocyte count is low and the colour index a little below unity. Usually increased blood destruction and diminished blood formation are present in varying degree, and the blood picture is modified accordingly. The white cells and platelets are normal or increased in number, unless the marrow is greatly depressed. The other tissues generally show anæmia, œdema and fatty change.

**Symptoms.**—The symptoms, other than those of the primary malady, depend on the speed with which the anæmia develops, and in acute anæmia from hæmorrhage or blood destruction there may be actual shock. In chronic anæmia, on the other hand, it is surprising how well the patient may feel and no complaint may be made with a hæmoglobin of 40 per cent. Inquiry elicits such symptoms as dyspnoea, palpitations, angular pain, fainting attacks and œdema of the extremities. The pallor is best seen in the conjunctivæ or the palate; the skin is a bad guide, for it is often pale when there is no anæmia, and sunburnt and deceptively healthy when anæmia is severe. The pulse is rapid and the heart dilated, and systolic murmurs may be audible over the præcordium.

**Diagnosis.**—The cause of a symptomatic anæmia may be obvious, but on the other hand, it may demand the most searching overhaul of the patient with all the resources of a modern hospital. Attention should be particularly focused on the alimentary tract, as conditions such as diaphragmatic hernia, peptic ulcer, carcinoma of the stomach or bowel, polypi and hæmorrhoids may exist with no other symptom than anæmia.

**Prognosis and Treatment.**—The prognosis and treatment are those of the primary disease. In acute anæmia the patient should be transfused if his condition



is critical. In chronic hæmorrhagic anæmia iron is of great value. In the majority of the symptomatic anæmias it is possible to produce a normal blood picture for a time by transfusion, and so bring the patient into condition for operation or similar treatment, but iron and liver have little effect if the cause of the anæmia is not removed.

## THE DEFICIENCY DYSHÆMOPOIETIC ANÆMIAS

An important group of anæmias is due to a defective supply of raw materials for blood formation. As these anæmias are the result of a disturbance in the growth of the red cells, they are called *dys hæmopoietic*. Absence of cyanocobalamin or folic acid gives rise to a megaloblastic reaction in the marrow; the megalocytes which result are treated by the body as abnormal cells, and anæmia develops which is in part due to disturbance of blood formation, in part to increased destruction. Iron and traces of copper are needed for the manufacture of hæmoglobin. The balance between the absorption of iron and the needs of the organism is a delicate one and it easily breaks down under conditions of malnutrition or the demands of growth and reproduction. In these circumstances hæmoglobin production becomes defective and a hypochromic anæmia develops. There is no hæmolytic component in the anæmia of iron deficiency. Vitamin C and thyroxine are also essential for blood formation. In their absence there is a general decline of hæmatopoiesis, rather than a specific variation from the normal. Both the latter conditions are frequently complicated by hæmorrhage and iron deficiency, but if this does not happen, hypothyroidism may produce a macrocytic anæmia which closely mimics pernicious anæmia. Lack of protein is an important factor in the anæmia of malnutrition, though it is usually complicated by other defects in the diet. The dys hæmopoietic anæmias are frequently associated with glossitis, gastro-intestinal disorders and degeneration of the nervous system. The reticulocyte count is low, and the white cells and platelets are normal or diminished. Remission of the disease is attended by an outpouring of reticulocytes in numbers directly proportional to the extent of the hyperplasia of the bone-marrow. This is called the *reticulocyte crisis*.

### 1. ANÆMIA OF IRON DEFICIENCY OF INFANTS

**Synonyms.**—Nutritional Anæmia of Infants; Anæmia of Prematurity.

Anæmia of moderate degree is present in practically all infants, whether fed by the breast or artificially. It may become very severe, especially in twins and premature babies, who come into the world with a small store of iron, or after intercurrent infection, or when suckling is protracted beyond the normal period. It disappears spontaneously on the adoption of a mixed diet, and it appears to be a pure mineral deficiency, resultant from the low iron and mineral content of the milk, and reparable by inorganic salts of iron. In severe cases the hæmoglobin is reduced to 5 g. (30 per cent.) or less. The colour index is low. Death may occur, especially when the anæmia is exacerbated by intercurrent infection. Repair of the anæmia is followed by increased resistance to infection. Treatment is by iron and ammonium citrate, in a dosage of gr.  $4\frac{1}{2}$  to 9 daily. Ferrous sulphate, gr. 3 t.d.s., or reduced iron, gr. 1 t.d.s., may also be used. It is essential to accustom the infant to the iron slowly, as the sudden administration of the full dose may cause colic and diarrhæa. For this reason administration is started very gradually, particularly in young infants. In bottle-fed babies the solution of iron and ammonium citrate is added to the milk, or proprietary foods containing iron are used. The mother should be warned that the stools will be dark. There are few babies, whether breast-fed or bottle-fed, who are not improved by the prescription of iron.

## 2. ANÆMIA OF IRON DEFICIENCY OF ADULTS

**Synonyms.**—Idiopathic Hypochromic Anæmia; Chlorosis and Late Chlorosis.

**Definition.**—A chronic anæmia of low colour index occurring almost exclusively in women and associated frequently with glossitis and achlorhydia.

**Ætiology.**—This is the commonest of all the idiopathic anæmias, occurring typically in women between the ages of 20 and 50. The reason for its appearance in them is the loss of iron in menstruation and pregnancy, and it therefore becomes more frequent in the later years of the reproductive epoch. Moreover, women tend to eat less iron-containing food than men, though they require more iron. There is a small but well-defined group of cases in adolescent males, often first recognised on examination for military service; these are presumably boys who have outgrown their intake of iron. The rôle of achlorhydia in producing deficiency of iron is still disputed but it is undoubtedly less important than was at one time assumed. It is now generally believed that when achlorhydia occurs in the anæmia of iron deficiency, it is the result rather than the cause of the disease, though no doubt a vicious circle develops in which anæmia predisposes to achlorhydia and achlorhydia to anæmia. The various epithelial lesions such as koilonychia, glossitis and atrophic gastritis can thus all be regarded as the effects of deficiency of iron, though achlorhydia differs from the others in being more frequently irreversible. An important group of cases is the sequel of partial gastrectomy and similar operations on the stomach. Here, again, the important factors are not the neutralisation of the gastric secretion, but the impaired appetite, the by-passing of the duodenum and the hurry of the meal through the jejunum; iron is best absorbed in the duodenum and upper jejunum.

**Pathology.**—The bone-marrow is moderately hyperplastic, and microscopic examination shows an increased number of normoblasts and a decreased number of cells reacting to stains for iron. The spleen is moderately enlarged by a simple hyperplasia. The epithelium of the tongue and pharynx may show a leucoplakial degeneration. In patients with achlorhydia there is a diffuse chronic gastritis which eventually leads to atrophy of the mucous membrane of the stomach. The other organs exhibit the effects of a simple anæmia.

**Symptoms.**—Symptoms may first be complained of after a pregnancy, or an influenzal attack, but careful enquiry often elicits the information that the patients were always pale, or that they have previously come under medical care for anæmia. Symptoms fall into two categories. First there are those due to anæmia: general weakness, headaches, palpitation and dyspnoea; præcordial pain on exertion is common and may be of anginal severity; slight œdema of the ankles occurs, but anasarca or ascites is unusual. The second category of symptoms is composed of those due to dyspepsia, probably the result of gastritis: lack of appetite, epigastric pain and distress, retching and vomiting after meals, flatulence and bilious attacks; constipation is frequent, but diarrhoea is unusual.

The facies is often pathognomonic, the sallow, wrinkled face and prematurely grey hair contrasting with the smooth, white and transparent body skin. The nails are frequently brittle and painful, and occasionally they are hollow and depressed like a spoon (koilonychia); on cure of the anæmia the new nail exhibits the normal contour and consistence. Glossitis is present in about half the cases. It is often painless and unknown to the patient, but, on the other hand, it may be the chief complaint. In the active stages the tongue is reddened and excoriated, and vesicles may appear and break down to form shallow ulcers. In the chronic and quiescent stages the filiform papillæ are destroyed, leaving a smooth bald tongue. The inflammation may spread to the buccal mucosa and to the corners of the mouth, the condition known as angular stomatitis. Passing backwards to the pharynx, it produces huskiness and a most troublesome dysphagia, which may be the presenting symptom (the Plummer-Vinson syndrome, see p. 542). The spleen is palpable in less than

10 per cent. of cases of idiopathic hypochromic anæmia and is rarely greatly enlarged. The other signs are those of anæmia. There are no changes in the spinal cord, but functional nervous disorders, nervous breakdowns, aphonia and pruritus frequently occur. The menses are often scanty by the time the anæmia has developed but they may be heavy after treatment with iron or in women nearing the menopause.

In about 50 per cent. of cases there is achlorhydria after stimulation with histamine but in contrast to pernicious anæmia Castle's intrinsic factor is preserved. Achlorhydria is more common in the later age groups and it can be attributed to an acceleration by iron deficiency of the normal increase of achlorhydria with age. It usually persists when the anæmia is cured but free hydrochloric acid may return. The colour index is low, and the red cells are usually smaller than normal. It is essentially a hæmoglobin deficiency, and often the red cell count is little below normal. The white cells and platelets are normal; an occasional normoblast may be present. Reticulocytes are within normal limits, and van den Bergh's reaction is negative. The serum iron is low. A typical count is: red cells, 3,500,000 per c.mm.; hæmoglobin, 5 g. (35 per cent.); colour index, 0.5; white cells, 7000; differential count, normal. On treatment with iron there is a reticulocyte crisis, most marked in the most anæmic cases, but seldom exceeding 15 per cent., the red cells are rapidly restored to the normal number, and the hæmoglobin is more slowly regenerated. There may be a transient erythrocytosis during the recovery phase.

**Complications and Sequelæ.**—The Plummer-Vinson syndrome is the most important complication, occurring in about 15 per cent. of cases. The changes in the epithelium of the tongue and pharynx predispose to malignant disease, and epithelioma of the tongue and carcinoma of the hypopharynx develop in a few instances. There is a risk of transition into pernicious anæmia, most marked in women with a family history of that disease, but in my experience the risk is not great. Indeed, if an iron-deficiency anæmia gives place to a megaloblastic anæmia, the first thing to suspect is steatorrhœa.

**Diagnosis.**—Care should be taken to exclude other causes of anæmia, more especially malignant disease, and it is wise to remember that idiopathic hypochromic anæmia is uncommon in males and in females past the menopause. The pallor is sometimes mistaken for that of myxœdema, and indeed it is a common mistake to diagnose myxœdema when it is not present and miss it when it is.

The symptoms may suggest pernicious anæmia but the blood picture and marrow findings are quite distinctive. If the spleen is enlarged the differentiation from splenic anæmia may present some difficulty. In splenic anæmia the enlargement of the spleen is greater, there is often a history of jaundice or hæmatemesis and there may be signs of liver damage or portal hypertension. In the absence of such symptoms the patient should first be treated with large doses of iron, when both the anæmia and the splenic enlargement will disappear if the correct diagnosis is idiopathic hypochromic anæmia.

**Course and Prognosis.**—The disease is chronic, and the average duration of symptoms before treatment is 5 years. It is rarely fatal, but in the absence of proper treatment many patients remain invalids for years. There is a strong tendency to relapse, which can only be avoided by re-examination at intervals or by persisting with a small dose of iron.

**Treatment.**—The patient should be encouraged to take a well-balanced diet, with adequate protein and vitamins. Medical treatment is by large doses of iron by mouth, either ferrous sulphate in tablets of gr. 3, t.d.s., p.c., or a mixture containing iron and ammonium citrate, gr. 20, t.d.s., p.c. In cases which are resistant to treatment these doses can safely be doubled. If there is intolerance, other preparations, such as ferrous gluconate or colloidal ferric hydroxide may be tried. Tablets are convenient but fluid preparations are sometimes more efficacious. Liver, stomach, folic acid and cyanocobalamin are of no value in iron deficiency and blunderbuss preparations containing iron plus these substances are to be condemned. Iron can be

given intravenously, the usual preparation for this purpose being the saccharated oxide of iron. With this it is possible to rise by graded steps from an initial dose of 25 to 50 mg. Fe a day to a maximum dose of 100 to 200 mg. Fe a day intravenously and so to satisfy within a week or 10 days the calculated deficit in circulating hæmoglobin and stores of iron. As is true of all forms of intravenous therapy, intravenous iron is not entirely free from danger and the following comments may be made. If iron is not effective by mouth, it is unlikely to be effective parenterally; the only important exception to this rule is steatorrhœa. Most iron salts are highly toxic on parenteral administration, and only preparations which have been specifically manufactured and tested for intravenous injection should be used. Apart from failure of absorption in steatorrhœa, the chief use of intravenous iron is in patients who cannot tolerate iron by mouth; such intolerance is most commonly observed in anæmia after gastrointestinal operations. Transfusion should seldom be necessary in the anæmia of iron deficiency. In younger subjects menorrhagia may be relieved by rest at the periods, but after 40 it is usually more intractable, and if it persists then, it is advisable to induce an artificial menopause by means of operation or irradiation. If dysphagia is troublesome, it is probably best treated by dilatation of the stenosed area in the hypopharynx or upper œsophagus under direct vision through an œsophagoscope.

### 3. PERNICIOUS ANÆMIA

**Synonym.**—Addison's Anæmia.

**Definition.**—A disease characterised by atrophy of the mucosa of the body of the stomach, megaloblastic anæmia and a tendency to degeneration of the spinal cord, which pursues a remittent course, and which is invariably fatal unless appropriate treatment is instituted.

**Ætiology.**—The disease is most common between the ages of 40 and 60, though analysis shows that it becomes relatively more frequent in each decade. It is very rare before the third decade, and the diagnosis should not be accepted in a child or young adult until other causes of megaloblastic anæmia have been excluded. It is a disease of the white races and is rarely seen in people of pure Asian or African stock. There is a hereditary proclivity, which probably depends on an inherited predisposition to atrophy of the gastric mucosa. Not only pernicious anæmia but also achlorhydria is believed to occur more commonly than normal in the relatives of those affected by the disease. Recent statistics suggest that pernicious anæmia is more common in women than men.

Megaloblastic degeneration of the bone-marrow was the first feature emphasised by students of pernicious anæmia. Later it was learned that this was common to a group of related anæmias, of which pernicious anæmia is only one member. The distinctive lesion of pernicious anæmia, which no treatment removes, is atrophy of the secreting epithelium of the body of the stomach, and achylia is a cardinal symptom. This atrophy is apparently not secondary to inflammation and it is therefore different from the chronic atrophic gastritis which is found in other forms of achlorhydria and in the anæmia of iron deficiency. It is usually an age change in those with the hereditary predisposition but it appears sometimes to result from endocrine disturbances such as hyperthyroidism, myxœdema and pituitary insufficiency. It is accompanied by a failure on the part of the stomach to secrete a ferment-like substance described by Castle as the *intrinsic factor*. Intrinsic factor is necessary for the absorption of cyanocobalamin, which is the *extrinsic factor*. In the absence of cyanocobalamin the bone-marrow undergoes megaloblastic degeneration and degenerative changes occur in the spinal cord and peripheral nerves. A deficiency disease of this kind is known as a *conditioned deficiency*. In pernicious anæmia it can be demonstrated by suitable techniques that there is no intrinsic factor in the gastric juice, that cyanocobalamin is not absorbed from the intestine, and that the level of cyanocobalamin in

the plasma is much below normal. An apparent objection to explaining pernicious anæmia in terms of loss of intrinsic factor is the fact that patients do not always develop pernicious anæmia after total gastrectomy. The reason for this is probably that the body normally has large stores of cyanocobalamin and after total gastrectomy the patient may not live long enough for these stores to be exhausted.

When folic acid was isolated, it was discovered that all the megaloblastic anæmias respond to it. Although pernicious anæmia responds to folic acid, the repair of the anæmia is not so satisfactory as with cyanocobalamin; the spinal lesions are not improved and may indeed be aggravated. It would appear that cyanocobalamin takes part in the chain of processes concerned in the manufacture of blood cells, and here it can to a large extent be replaced by folic acid. On the other hand, megaloblastic anæmias which are due to deficiency of folic acid cannot be cured with cyanocobalamin. This suggests that folic acid tests at a later stage of the manufacturing process than cyanocobalamin. Cyanocobalamin is also necessary for the nutrition of the long neurones of the postero-lateral columns of the spinal cord and here it cannot be replaced by folic acid. The megaloblastic anæmias can be arranged in a spectrum according to their response to cyanocobalamin and folic acid.

- (a) *Addisonian pernicious anæmia*.—A pure deficiency of cyanocobalamin due to absence of intrinsic factor.
- (b) *Fish tapeworm anæmia*.—A pernicious type of anæmia may be associated with infestation by *Diphyllobothrium latum*. Apparently the worm diverts cyanocobalamin from the host. Subacute combined degeneration may occur.
- (c) *Intestinal stenosis and intestinal anastomosis*.—Megaloblastic anæmia may occur when there is stenosis or stagnant loops of small intestine. In these conditions the absorption of both cyanocobalamin and folic acid may be affected.
- (d) *Steatorrhœa*.—Megaloblastic anæmia is almost the rule in sprue (p. 623) and a similar anæmia may occur in other conditions in which the absorption of fat is impaired, such as coeliac disease, idiopathic steatorrhœa, pancreatic disease and gastro-colic fistula. The defect is usually in the absorption of folic acid.
- (e) *Nutritional macrocytic anæmia*.—This condition is rare outside the tropics and is therefore considered on p. 475. Not all these anæmias are megaloblastic. When they are, they are usually due to deficiency of folic acid, though a primary deficiency of cyanocobalamin has been seen in vegetarians who have eschewed eggs and dairy products.
- (f) *Megaloblastic anæmia of infancy*.—A rare condition seen only in artificially-fed babies and due to lack of folic acid.
- (g) *Pernicious anæmia of pregnancy*.—See p. 749.

Megaloblastic anæmia has been ascribed to cirrhosis of the liver, but this is probably the coincidence of cirrhosis with pernicious anæmia or nutritional anæmia. A few cases of unexplained megaloblastic anæmia have been described under the headings of achrestic, idiopathic or refractory megaloblastic anæmia; such cases are extremely rare, and the majority of patients diagnosed as having pernicious anæmia with normal gastric secretion are really suffering from unrecognised steatorrhœa.

**Pathology.**—The remainder of this section deals with Addisonian pernicious anæmia. Few patients now die of untreated pernicious anæmia. In such cases the main changes seen at necropsy are anæmia, deposition of iron in the tissues, and megaloblastic hyperplasia of the bone-marrow. To demonstrate the changes in the stomach, the tissues must be fixed immediately after death.

**Symptoms.**—Patients with pernicious anæmia are not infrequently well built, with broad facies, short deep chests and wide sub-costal angles; the hair is often prematurely grey, and the skin may be pigmented. Symptoms fall into three main

categories, according as they are due to changes in the blood, the alimentary tract or the nervous system. The *anæmia* may be profound by the time the patient presents himself for treatment and the red cell count may even fall below 1 million. Dyspnea, weakness, palpitations and signs of heart failure appear. A lemon-yellow colour of the skin was common in the days before liver therapy was introduced, but now that patients come under effective treatment early, it is not often seen. The same is true of splenomegaly, which requires considerable time for its development and is now found in only about 5 per cent. of untreated patients. The temperature may be slightly raised. Angina may occur from impoverishment of the blood supplied to the heart, and intermittent claudication from similar effects in the limbs. The liver may be enlarged. The urine contains much urobilin and often a trace of albumin. Alimentary symptoms constitute an important chapter of the disease. Glossitis of the type described in idiopathic hypochromic *anæmia* occurs in over 50 per cent. of cases, but curiously enough there is no tendency to involvement of the pharynx, or to dysphagia. It may precede the *anæmia* by some years. Achlorhydria is an invariable symptom, and pepsin is greatly reduced or absent. Achlorhydria has many times been demonstrated before the onset of the *anæmia*, and it persists when the blood has been repaired. Dyspepsia is frequently present, with flatulence, ill-defined generalised abdominal pain, soft bowel movements and recurrent attacks of diarrhoea. The dyspepsia is partly due to the achlorhydria, but it is greatly aggravated by the *anæmia*; if it persists after repair of the *anæmia*, carcinoma of the stomach or disease of the gall-bladder should be suspected. Nervous symptoms, due to subacute combined degeneration of the spinal cord, are an integral part of the disease, but for convenience they are described elsewhere (p. 1550). Mental symptoms appear in a small percentage of cases; they are usually delusions of persecution, and the patient swears that he is being poisoned by his relatives or his physician. Exceptionally such patients become stuporose and die in coma, even though their *anæmia* is not profound.

The cardinal feature of the blood picture is megalocytosis. By the time the patient seeks medical advice the red cells are often less than 2 millions per c.mm., and counts of the order of half a million have occasionally been obtained. Hæmoglobin is not reduced to the same extent as the red corpuscles and the colour index is above unity. The mean diameter of the red cells averages about 8·3 microns; there is much anisocytosis and poikilocytosis. Reticulocytes are within normal limits except during a remission, spontaneous or induced. Normoblasts and megaloblasts are often present, more especially in the agonal stages of the disease and also on the inception of very active treatment; they are rarely present in the peripheral blood in mild cases. The serum is brownish-yellow, and the indirect van den Bergh reaction is positive. The white cells are reduced in number, an average count being about 4,000; the decrease is chiefly due to diminution in the granulocytes and the monocytes. The neutrophil cells are of an old type, many having 5 or more lobes to their nucleus, and occasional giant neutrophils and myelocytes are present. Platelets are scanty. The marrow smear shows megaloblastic hyperplasia.

*Remissions and relapses* were one of the most constant features of the untreated disease, which was nevertheless usually fatal in 1 to 3 years. The cause of the remissions is uncertain, but they are possibly related to phasic changes in the bacterial flora of the intestine, which affect the absorption of cyanocobalamin and folic acid.

**Complications and Sequelæ.**—Since effective treatment was introduced, complications have become infrequent. The incidence of subacute combined degeneration has fallen to about 10 per cent. Retinal hæmorrhages may be seen in patients who are severely *anæmic*; apart from this, purpura and hæmorrhage are unusual, though they undoubtedly occur on occasion. Gout and venous thrombosis occasionally occur during initial treatment. Patients with pernicious *anæmia* have about three times the normal liability to carcinoma of the stomach. This risk should never-

theless be kept in its proper perspective, for as Jennings has shown, it means that whereas the annual chance of a man in his fifties developing cancer of the stomach is 1 in 1000, in pernicious anæmia it is 1 in 300. It is a curious fact that the cancer does not usually develop in the fundus and body of the stomach, where the pathological changes of pernicious anæmia are localised, but more commonly in the pyloric region.

**Diagnosis.**—The disease is often suggested by the triad of symptoms glossitis, anæmia and acroparæsthesia in a patient in the appropriate age group, and it is confirmed by the blood picture. It is, nevertheless, not uncommonly missed in the elderly, the parchment skin and the general enfeeblement being regarded as the inevitable concomitants of age. Such mistakes can be avoided by thinking of the possibility of anæmia and testing the hæmoglobin. In cases of doubt two questions should be answered. The first is whether the anæmia is megaloblastic; this can be decided by marrow puncture. The second is whether it is Addisonian pernicious anæmia. In true pernicious anæmia the test meal reveals achlorhydria, and other causes of megaloblastic anæmia such as steatorrhœa are absent. In making the initial diagnosis it is wise to have a barium meal to exclude gross alimentary disease in general, and cancer of the stomach in particular. Aplastic anæmia may be mistaken for pernicious anæmia, but treatment with cyanocobalamin is unsuccessful and the marrow is found to be aplastic. Aleukæmic leukæmia and chronic hæmolytic anæmia can likewise be differentiated by careful analysis of the symptoms, the blood picture, and the marrow smear. In the absence of severe complications, anæmia which does not respond to cyanocobalamin in effective dosage is almost certainly not pernicious anæmia.

**Prognosis.**—The gastric lesion appears to be incurable, but with adequate and regular treatment the anæmia is cured, spinal symptoms completely arrested and the patients live out the normal span in full health.

**Treatment.**—As the treatment of pernicious anæmia is a form of substitution therapy which must be continued for the rest of the patient's life, it should never be embarked on without confirmation of the diagnosis. In cases of doubt this means marrow puncture and test meal. If doubt still remains, the patient should be referred to an expert hæmatologist. Preparations containing a farrago of iron, liver, stomach, vitamins, etc., should never be employed, for in the very rare cases in which more than one hæmatinic principle is required, they should be added seriatim and in adequate dosage so that the effects of each can be assessed. On instituting successful treatment in a patient with pernicious anæmia there is a reticulocyte crisis, which reaches its maximum between the tenth and fourteenth days with oral therapy, and between the third and the seventh days with parenteral therapy. The peak is directly proportional to the severity of the anæmia, and values of 30 to 40 per cent. are by no means uncommon. The blood and the general condition of the patient are gradually restored to normal, glossitis becomes quiescent and the surface of the tongue may be reclothed with filiform papillæ. The nervous symptoms improve more slowly, and gross spastic paralysis is unlikely to be repaired.

The modern treatment of pernicious anæmia can almost be summed up in the word cyanocobalamin. A dose of 100 microgrammes is injected intramuscularly weekly until the red cell count is normal and the maximum clinical remission has been obtained. Double this dosage should be given if there are neurological complications. For maintenance treatment a dose of 50 microgrammes is injected once a fortnight; in neurological cases the maintenance dose should be 100 microgrammes once a week for as long as improvement seems able to occur, i.e. from 6 months to 2 years. Better effects are obtained with small doses frequently than with large doses at longer intervals, but many patients remain well with doses of the order of 50 microgrammes every 3 weeks or 100 microgrammes every month. Two innovations have recently been suggested in the use of cyanocobalamin. Mollin and Ross state that a much higher initial dosage should be used to replenish the body stores. They advise 5

of 1000 microgrammes in the first week or two of treatment, followed by a maintenance dose of 50 microgrammes fortnightly, or 100 microgrammes monthly. Although intrinsic factor has not yet been isolated in a pure form, a number of commercial firms have prepared tablets containing cyanocobalamin, plus a concentrate of intrinsic factor for administration by mouth. This, of course, is merely a refinement of the original treatment with desiccated stomach. Oral treatment is more expensive than cyanocobalamin by injection, and it places a greater strain on the patient's co-operation. It should therefore only be employed when treatment by injection cannot conveniently be arranged.

Cyanocobalamin appears likely to replace all forms of liver in the treatment of pernicious anæmia. The use of folic acid is contraindicated. Hydrochloric acid is rarely necessary, for if dyspepsia persists after repair of the anæmia some cause other than achlorhydria should be suspected. Sometimes while the red cell count is rising or during maintenance treatment the patient may develop a hypochromic anæmia requiring iron therapy. Apart from patients in the initial phase of treatment and women who are still menstruating, iron deficiency is rare in pernicious anæmia and it should always suggest steatorrhæa or a complication such as carcinoma.

The action of cyanocobalamin is prompt and regeneration of the bone-marrow is apparent within a couple of hours of injection. Transfusion is therefore hardly ever required and it should be withheld if at all possible, in view of the danger of precipitating acute heart failure in patients who are profoundly anæmic. In a patient with an initial red cell count of 1 million, the count will rise to 3 million in 2 to 3 weeks. The degree of activity should be determined by the patient's feelings. Pernicious anæmia occurs in elderly people who do not tolerate strict confinement to bed well and if there are no signs of heart failure, there is no point in keeping them there. A full mixed diet is allowed. There is often a tendency to put on weight excessively in remission and this should be avoided. Regular blood examinations should be carried out at least once every 3 months. If the patient fails to get back to a normal count or if a patient who is doing well relapses while on the same maintenance dose, a complication such as hypothyroidism or carcinoma should be suspected. In the absence of indications of this kind repeated radiographic examinations of the stomach are not necessary. In general, few things in medicine are as satisfactory as the treatment of pernicious anæmia, and patients should be expected to live a life of full activity.

## APLASTIC ANÆMIA

**Synonyms.**—Aregenerative Anæmia; Refractory Anæmia; Panmyelopathy.

**Definition.**—Aplastic anæmia is produced by aplasia of the bone-marrow, which results in reduction or total failure of blood regeneration. Usually all three elements in the bone-marrow—erythropoietic tissue, leucopoietic tissue and megakaryocytes—are simultaneously involved. Rare cases occur in which there is a pure lesion of one of these tissues, and not infrequently one of them is predominantly affected. The term *aplastic anæmia* is applied more particularly to cases in which the erythropoietic tissue is especially damaged.

**Ætiology.**—The disease occurs at all ages and in both sexes. In a number of cases the aplasia of the bone-marrow is due to destruction by a well-recognised poison. The list includes benzol and many of its derivatives, such as arseno-benzol, dinitrophenol, trinitrotoluene, chloramphenicol and the sulphonamides, mepacrine hydrochloride and gold. Roentgen rays and radioactive substances are important causes, the latter being most dangerous when they are taken into the body and produce persistent radiation. In a large proportion of cases no noxious agency can be traced, and it is possible that many are due to an idiosyncrasy to substances not normally regarded as harmful, a phenomenon we have already learnt to recognise in amido-



pyrine agranulocytosis and Sedormid purpura. On rare occasions more than one member of a family has been affected. In familial cases in childhood, hypogonadism and developmental abnormalities, particularly of the hands and kidneys, may also be present (Fanconi's syndrome).

**Pathology.**—In the classical aplastic anæmia the marrow may be hypocellular or acellular or there may be replacement by fibrous tissue. An actual excess of erythropoietic tissue may be found in radium poisoning, presumably from an arrest in the maturation of the cells. A similar maturation arrest has been described in other cases which behaved like aplastic anæmia during life, though in my experience this is unusual. Necrotic ulcers may be found in the mouth and bowel. The liver, spleen and lymph glands show no gross change, but microscopically there is usually some hæmosiderosis of the liver and spleen, attributable both to the absorption of extravasated blood and to the breakdown of transfused red cells.

**Symptoms.**—Aplastic anæmia is not common, having probably only one quarter the frequency of pernicious anæmia. The onset is commonly insidious, and there may be several months of increasing fatiguability before the patient is finally pulled up by the severity of the anæmia, or by an acute crisis such as hæmorrhage or infection. Purpura, bleeding from the nose and gums, or infection of an agranulocytic type may be the first complaint. Spontaneous remissions of the symptoms occur occasionally, but they are rarely complete or of long duration. There are no specific alimentary or nervous symptoms. Physical examination is commonly negative except for the anæmia and such complications as purpura and agranulocytosis. The spleen is only rarely palpable and the lymph glands and the liver are not enlarged. The blood picture is characterised by a decrease of all the cells, erythrocytes, leucocytes and platelets; the absence of immature white cells and nucleated red cells; and the lack of signs of reaction, such as hypochromia, anisocytosis and reticulocytosis. By the time a blood count is done the red cells have often fallen to 1·5 million per c.mm. and the colour index is above unity. Van den Bergh's reaction is negative. The white cells are about 3000 or 4000 per c.mm., usually fall below 2000 before death; the diminution is chiefly due to the small number of polymorphonuclear cells. In chronic cases a very considerable degree of macrocytosis may develop, and so long as the colour index remains high and the leucocyte count low, the disease cannot be regarded as cured.

**Diagnosis.**—At the onset the illness is often confused with one of the megaloblastic anæmias, but it can be differentiated by sternal puncture and the failure to respond to cyanocobalamin or folic acid. Essential thrombocytopenia may be suggested by the low platelet count and the hæmorrhagic tendency, but is excluded by the leucopenia and the non-regenerative character of the anæmia. Aleukæmic leukaemia offers the most difficulty. The absence of enlargement of the lymph glands, liver or spleen, however, should differentiate aplastic anæmia from this disease. In doubtful cases a sternal marrow puncture or biopsy should be performed.

**Prognosis.**—In a series of cases observed during the last decade, 30 per cent. died within 1 year and 60 per cent. within 2 years of coming under treatment; a few survived for 5 to 10 years but none longer than this. Complete recovery may occur, but probably in not more than 5 per cent. of cases. Patients with thrombocytopenia and a hæmorrhagic tendency do badly. However well the patient appears clinically, the prognosis should always be guarded as long as the blood picture is abnormal, for such patients are always liable to sudden deterioration from infection or an acute hæmolytic reaction.

**Treatment.**—In all cases enquiry should be made of exposure to toxic substances and further contact prevented. Anæmia is combatted by transfusion, and infection by penicillin; unfortunately there is no remedy for the thrombocytopenia. Iron, liver and similar remedies are of little value, but it is reasonable to try the effects of cyanocobalamin and folic acid if there is any doubt about the diagnosis. The

blood should be brought approximately to normal by a rapid series of transfusions, or by a continuous transfusion of 2 or 3 litres of blood. If it is then possible to maintain a normal count by transfusions at intervals of 2 or 3 weeks, there is some hope that the bone-marrow may gradually regain its hæmopoietic function. It is undesirable to allow the hæmoglobin to remain below 50 per cent. for long periods, as there is a risk of heart failure, and it is better and more convenient to give small transfusions at frequent intervals, i.e. 1 or 2 pints of blood a fortnight.

## HÆMOLYTIC ANÆMIA

In discussing the symptomatic anæmias, I have mentioned the occasional development of anæmia from hæmolysis of the corpuscles by micro-organisms, bacterial toxins and other poisons. There is also evidence that excessive hæmolysis plays a part in the pathology of the megalocytic anæmias due to deficiency of hæmopoietic principles. There now remains for discussion a group of hæmolytic anæmias which are relatively uncommon and of which the most important examples are due to congenital anomalies in the red blood cells. Before treating these diseases individually, it will be convenient to describe the characteristics which are common to all the hæmolytic anæmias. If a great many red cells are broken down in a short time, there is hæmoglobinuria and jaundice, but in chronic hæmolytic anæmia it is sometimes surprising how slight is the jaundice. The colour index varies according to the mode of reaction of the bone-marrow, but it is usually round about unity and there may be frank macrocytosis. Owing to the vigorous attempts of the bone-marrow to repair the anæmia, the reticulocyte count is high, and nucleated red cells may appear in the peripheral blood. In chronic hæmolytic anæmia the white cells are unaffected or a little diminished. When hæmolysis is acute and rapid, there is a leucocytosis, during which immature white cells may appear in the peripheral blood; the platelets first fall and later rise above their normal level. Apart from the hæmolysis, which gives rise to anæmia, enlargement of the liver, spleen and occasionally the lymph glands, hyperplasia of the bone-marrow and hæmosiderosis, there are no signs of systemic disease and the alimentary and nervous systems are normal.

## THE HEREDITARY HÆMOLYTIC ANÆMIAS

Hæmolytic anæmias can be classified as hereditary and acquired; the hereditary are due to an intracorpuseular defect, and the acquired to an extracorpuseular defect. When there is an intracorpuseular defect the Coombs test (p. 744) is usually negative, and normal blood transfused into the patient is not hæmolysed and survives the normal time. Four inherited anomalies in the shape of the red cell are known. In *elliptocytosis* (syn. *ovalocytosis*) the red cells are biconvex; this is a relatively harmless abnormality and will not be further discussed. In *spherocytosis* they are thicker than normal. In *drepanocytosis* many of the red cells become sickle-shaped when they are deprived of oxygen. In *leptocytosis*, which is seen in Mediterranean anæmia, they are abnormally thin. The abnormalities in shape are probably secondary to abnormalities in the hæmoglobin. At the time of writing, in addition to normal adult hæmoglobin (hæmoglobin A) and fetal hæmoglobin (hæmoglobin F) there have been described sickle-cell hæmoglobin (hæmoglobin S), hæmoglobin C and hæmoglobin D. In acholuric jaundice the spherocytes are more liable to destruction by the spleen than normal red cells, and the anæmia is relieved by splenectomy. Splenectomy is not effective in the other hereditary hæmolytic anæmias, and cortisone is of no value.

These four anomalies of the red cell are apparently inherited as Mendelian dominants. In sickle-cell disease and in Mediterranean anæmia there are mild and severe forms of the disease. These are distinguished respectively as sickle-cell trait and

sickle-cell disease, and thalassæmia minor and major. The hypothesis has been advanced that the mild disease occurs in people who are heterozygous for the affected gene, and the severe in the homozygous. This theory was supported by the discovery that in sickle-cell anæmia nearly all the hæmoglobin in the red cells is abnormal (hæmoglobin S), whereas in the sickle-cell trait 40 per cent. is abnormal and 60 per cent. normal. However, it did not explain the widely different relative incidence of anæmia and trait in different parts of the world. Subsequently another abnormal hæmoglobin (C) was discovered, and it was shown that sickle-cell anæmia might be caused not only by two genes for hæmoglobin S, but one gene for hæmoglobin S and one for hæmoglobin C, or one for hæmoglobin S and one for thalassæmia. The further unravelling of these problems is now primarily of ethnological and genetic interest. It is believed that most cases of acholuric jaundice are heterozygous for the affected gene, and the reason for the variations in intensity of the disease are not known. Cases of hereditary hæmolytic anæmia which are normocytic have been described; they are rare. For convenience, hæmolytic anæmia with nocturnal hæmoglobinuria is included in this section, as it is due to an intracorpuseular defect.

### 1. ACHOLURIC JAUNDICE

**Synonyms.**—Hereditary Spherocytosis; Hæmolytic Anæmia (type Chauffard-Minkowski).

**Definition.**—A hereditary disease, which is characterised by increased fragility of the red blood cells, a variable degree of jaundice and anæmia, splenomegaly and a strong tendency to the formation of gall-stones.

**Ætiology.**—The red blood cells are more spherical than normal and therefore less resistant to swelling when exposed to hypotonic saline. In the body they are presumably less viable than normal and more rapidly destroyed by the spleen. The abnormality of the corpuscles is transmitted as a Mendelian dominant and affects chiefly people of European stock. It exists from birth, but though the symptoms of the disease may be present from early infancy, they may not manifest themselves until a much later date, and may even remain in abeyance throughout life. There are no abnormal hæmolysins in the blood, nor is there any evidence that the hæmolysis is dependent on a primary fault in the spleen.

**Pathology.**—The bone-marrow shows an extreme degree of hyperplasia of the normoblastic type. The spleen usually weighs from 1 to 3 lb. and the pulp is congested with red blood cells.

**Symptoms.**—The severity of the disease is extremely variable. There may be no symptoms at any time, the condition being recognised only on a routine examination of the blood. Most patients have a mild degree of jaundice, and give a history either that they have always been jaundiced, or that they have always been liable to attacks of jaundice. There is no pruritus. The anæmia is usually mild but it is more severe in cases presenting in early life. It is characteristically marked by periodic exacerbations. These are usually due to increased hæmolysis, and are accompanied by an exaggeration of the reticulocytosis and jaundice. Occasionally, however, more severe crises occur in which jaundice and reticulocytosis disappear, the patient becomes profoundly anæmic, and the marrow is found to be temporarily aplastic. Crises of this second type may affect several members of a family at the same time and they are probably provoked by intercurrent infection.

Calcium bilirubinate gall-stones may develop as a result of the chronic bilirubinæmia. These may give rise to attacks of biliary colic, which may be accompanied by an increase in the jaundice, which is quite independent of the hæmolytic crises. An unexplained complication is chronic ulceration of the legs, which may be the chief and sometimes the only symptom of the disease.

Splenomegaly is usually present; though occasionally extreme, it is commonly of moderate degree. The spleen may increase in size during a crisis, and may be painful and tender.

The *faeces* are normal in colour, and the urine, though dark as the result of the presence of urobilin, contains no bile.

In normal fully oxygenated blood, the red corpuscles show no hæmolysis in a 0.50 per cent. solution and only slight hæmolysis in a 0.45 per cent. solution of sodium chloride. In acholuric jaundice the fully oxygenated corpuscles show gross hæmolysis in a 0.45 per cent. solution and lesser degrees of hæmolysis in stronger solutions, sometimes even as high as a 0.80 or 0.85 per cent. solution. The corpuscular diameter is usually diminished and often very markedly so, but occasionally it is normal. The corpuscles are disproportionately thick, so that the corpuscular volume and colour index instead of being diminished are normal or above normal. This discrepancy between corpuscular volume and colour index on the one hand, and corpuscular diameter on the other, occurs in no other disease, and immediately distinguishes acholuric jaundice from pernicious anæmia. In stained films there is gross irregularity in the size of the corpuscles; the small ones tend to be deeply stained, while the large ones are feebly stained and often polychromatic. In shape they are of a remarkably uniform roundness, and stippled corpuscles are unusually scarce. The anæmia is usually only moderate in degree, red cell counts between 3 and 4 million per c.mm. being most common, and the white cells are normal. Reticulocytes frequently constitute over 10 per cent. of the red corpuscles and are sometimes much more numerous. In hæmolytic crises large numbers of normoblasts may appear in the peripheral blood and there is often a polymorphonuclear leucocytosis. There is no evidence that hæmoglobinuria ever occurs in acholuric jaundice of the familial type. As the jaundice is hæmolytic the van den Bergh test gives only an indirect reaction. Occasionally, however, obstructive jaundice is present as well owing to the presence of a pigment stone in the common bile duct; a direct reaction is then present as well.

**Diagnosis.**—The diagnosis is suggested by the association of splenomegaly with long-standing jaundice or recurrent attacks of jaundice. It is strengthened by a history of jaundice in other members of the family. Its confirmation depends on finding increased fragility of the red corpuscles and the characteristic blood picture, particularly the discrepancy between the corpuscular volume and diameter. The blood picture distinguishes the condition from other hæmolytic anæmias, from pernicious anæmia, chronic myelogenous leukaemia, and splenic anæmia. Chronic ulceration of the legs should always call to mind the possibility that the underlying cause may be acholuric jaundice, even in the absence of jaundice and splenomegaly. Finally, it must be remembered that attacks of biliary colic may occasionally be a complication of acholuric jaundice.

**Prognosis.**—The earlier in life the onset, the more serious the disease, and in infancy and childhood death may occur from anæmia, or growth may be retarded. In adults the anæmia is usually mild but the biliary complications may be dangerous. Splenectomy is almost uniformly curative and the mortality of the operation is low.

**Treatment.**—In latent cases no treatment may be required but in view of the risk of gall-stones and anæmic crises and the safety of operation, splenectomy should be advised if there are any symptoms. At the same time cholecystectomy may be performed if gall-stones are present. In very severe crises transfusion may be necessary to prepare the patient for operation. The effects of splenectomy are dramatic: the jaundice and the anæmia quickly disappear and the leg ulceration heals. The increased fragility persists, though it may be slightly lessened. The disproportionate thickness of the corpuscles and the resulting discrepancy between the corpuscular volume and the diameter remain, but the reticulocytosis and leucocytosis, which are secondary to the anæmia, usually disappear.

## 2. SICKLE-CELLED ANÆMIA

**Synonym.**—Hereditary Drepanocytosis.

**Definition.**—A severe anæmia, characterised by the appearance in the blood of a number of red blood corpuscles of a peculiar sickle shape.

**Ætiology and Pathology.**—In the sickle-cell anomaly, the blood may be relatively or completely normal when freshly drawn, but when a drop of blood is sealed under a coverslip on a slide and allowed to stand, a number of the corpuscles become elongated and sickle-shaped. The phenomenon depends on reduction of the oxygen tension and can easily be accelerated by simple physical or chemical procedures. The sickle cells do not aggregate and sediment as readily as normal cells and there is a considerable difference in the sedimentation rate of reduced and aerated blood. The sickle-cell anomaly is practically confined to the negro race, being found in about 20 per cent. of some West African tribes and in over 7 per cent. of American negroes. In the U.S.A. about 1 in 50 with the trait have anæmia, but in Africa the ratio may be less than 1 in 1000. People with the trait normally have about 1 per cent. of sickle-cells in the red cells of their venous blood, whereas in sickle-cell anæmia 30 to 60 per cent. of the red cells show sickling in the venous blood, without oxygen deprivation. The trait alone does not appear to produce any symptoms.

**Symptoms.**—The disease usually dates from infancy. The patients are obviously anæmic, and the sclerotics exhibit a greenish-yellow tinge. The liver is bulky, but the spleen is not enlarged. The disease is characterised by intermittent paroxysms of fever, up to 103° or 104° F., with severe stabbing pains in the muscles and joints, which last for 2 or 3 weeks. In the intervals the patients suffer but little, though they are listless and depressed. Chronic ulceration of the legs occurs in a high proportion of cases. The red blood corpuscles in the intervals reach a number of about 3,000,000 per c.mm., but during the paroxysms they rapidly fall to less than half that number. The white cells are usually about 15,000 c.mm., but may rise to as much as 40,000. The sickle-shaped corpuscles vary in numbers. They appear to increase in number on a warm slide. The coagulation-time, the bleeding-time, the fragility of the corpuscles and the numbers of platelets are all within normal limits.

**Course and Prognosis.**—The course of the disease is slow but progressive, and death usually occurs before the age of 30.

**Treatment.**—Up to the present time, no treatment has appeared materially to influence the progress of the disease, and splenectomy is of no value.

## 3. MEDITERRANEAN ANÆMIA

**Synonyms.**—Hereditary Leptocytosis; Thalassæmia; Familial Erythroblastic Anæmia of Cooley; Familial Microcytic or Hypochromic or Target-Cell Anæmia.

This is a hereditary dystrophy of the erythron in which the red cells are thinner than normal. Under the microscope some of them have an oval or target shape and others are large, pale, leaf-like structures. Although they are more resistant to hypotonic saline, they are more rapidly broken up in the body than normal. This abnormality is practically confined to persons of Mediterranean stock. In typical cases anæmia manifests itself soon after birth, and life is rarely prolonged past childhood. The anæmia is of the hæmolytic type and characterised by numerous erythroblasts in the peripheral blood, but the colour index is below unity owing to the abnormal shape of the red cells. Other characteristic symptoms are mongoloid facies, splenomegaly, and generalised bony changes due to hypertrophy of the marrow. The bone dystrophy is similar to osteitis fibrosa, but pathological fractures are not common, and symptoms come principally from the anæmia, which is severe and ultimately fatal. Radiographic examination shows widening of the medullary portion of the bones, erosion and thinning of the cortex, and a peculiar outline of the skull often compared

to hair standing on end. Until recently it was believed that Cooley's anæmia was a disease of children which was always fatal, but it has since been learned that other members of affected families may show the abnormal type of red cell without anæmia or with only very mild symptoms. Treatment is by repeated transfusions. Splenectomy and iron are ineffective; in fact, an anæmia of low colour index in a child which does not respond to iron should suggest the possibility of Mediterranean anæmia.

#### 4. HÆMOLYTIC ANÆMIA WITH RECURRENT HÆMOGLOBINURIA

**Synonyms.**—Nocturnal Hæmoglobinæmia; Chronic Hæmolytic Anæmia (type Marchiafava-Micheli).

A rare disease characterised by paroxysms of hæmoglobinuria, which commonly occur at night, and persistent hæmolytic anæmia. It is a disease of adult life and affects both sexes. It is apparently due to an inherent abnormality in the red cells which are unduly sensitive to hæmolysis in acidified serum. The spleen is usually enlarged though not to the same degree as in acholuric jaundice. The disease is differentiated from acholuric jaundice by the normal size, shape and osmotic fragility of the red cells, and the occurrence of hæmoglobinuria; and from the paroxysmal hæmoglobinuria of syphilis by the negative Wassermann reaction, absence of relation to exposure to cold, and persistence of anæmia between the paroxysms. Splenectomy has little effect and the disease usually leads to death after a few years. Treatment is by transfusion, which is better tolerated if washed red cells are used.

### THE ACQUIRED HÆMOLYTIC ANÆMIAS

The acquired hæmolytic anæmias are all due to extrinsic factors causing a decreased red-cell life-span. They are sometimes divided into symptomatic and idiopathic. A more useful classification is:

- (a) Due to the direct effect of chemicals, physical agents, micro-organisms, animal and vegetable poisons.
- (b) Due to the development of antibodies active against the patient's own red cells.
- (c) Due to increased activity of the spleen or other parts of the reticulo-endothelial system.

The rare Carrion's disease of the Andes is an example of the direct attack of a micro-organism on the red blood cells. More often the relation of hæmolysis to infection is obscure, as in the blackwater fever of malaria or the hæmolytic anæmia that occasionally follows typhoid fever. In certain people suffering from acquired hæmolytic anæmia antibodies can be demonstrated in the serum which react *in vitro* with the patient's own red cells. Antibodies which agglutinate the red cells in the cold may appear in the serum after infections such as virus pneumonia and in other conditions. In rare cases *cold agglutinins* are present in high titre; a moderate hæmolytic anæmia usually develops but more dramatic and troublesome is the blockage of the circulation on exposure to cold, which may lead to gangrene of the extremities, the tip of the nose and the lobes of the ear. A *cold hæmolyisin* may develop in tertiary syphilis and lead to paroxysmal hæmoglobinuria (p. 1104); this hæmolyisin may be demonstrated by the Donath-Landsteiner reaction.

In hæmolytic disease of the newborn and idiopathic acquired hæmolytic anæmia antibodies affecting the red cells can usually be demonstrated by special techniques. One method is to use specially sensitised red cells as laboratory reagents for their recognition. More convenient is the Coombs test or antihuman globulin reaction, which reveals the antibody attached to the patient's red cells. Although this test is not absolutely specific for hæmolytic anæmia due to abnormal antibodies, it is of

great assistance in practice. In hæmolytic disease of the newborn the antibodies are usually anti-Rh, due to incompatibility between mother and fœtus. In acquired hæmolytic anæmia of adults the nature of the antibodies is more obscure, but some of them are probably antibodies to one of the normal blood-group antigens, due to some perversion of the mechanism of immunity.

In all conditions in which the spleen is enlarged, the life of the red cell may be shortened, presumably by overactivity of the normal scavenging mechanism of the spleen. This may reveal itself by a non-specific anæmia and by unduly short benefit from transfusions, but in some cases, particularly in lymphatic leukæmia, a frank hæmolytic picture may be present. Anæmia of this type may also appear when other parts of the reticulo-endothelial system are diseased. Examples are seen in all forms of leukæmia, Hodgkin's disease, cirrhosis of the liver and malignant affections of the hæmopoietic system. Abnormal antibodies may appear in the serum in some of these symptomatic hæmolytic anæmias.

The treatment of the various symptomatic anæmias consists in the first place in removing the cause when possible. Iron and liver are of no value and transfusion is only temporarily effective. When there is splenomegaly, splenectomy may be desirable, even though it may be only a symptomatic remedy. Cortisone and corticotrophin are often effective.

## 1. HÆMOLYTIC DISEASE OF THE NEWBORN

**Synonyms.**—Erythroblastosis Fœtalis; Familial Icterus Gravis Neonatorum.

**Definition.**—A hæmolytic anæmia which occurs in the fœtus or newborn child and which is due to incompatibility between the serum of the mother and the erythrocytes of her offspring.

**Ætiology.**—Hæmolytic disease of the newborn results from the iso-immunisation of the mother by a red cell antigen which she lacks, but which the child has inherited from the father, and the subsequent passage through the placenta of the resulting antibody to act on the susceptible blood of the fœtus. The distribution of the blood groups is such that in 1 pregnancy in 5 the mother's serum contains an agglutinin for an antigen of the A-B-O groups contained in her fœtus and in 1 pregnancy in 10 the mother is Rh-negative and the fœtus Rh-positive. Nevertheless, iso-immunisation and hæmolysis occur in only 1 in 400 pregnancies, because ill effects are usually prevented by the impermeability of the placenta and by the presence of protective substances in the infant's plasma. Incompatibility in the ordinary blood group factors A-B-O very rarely gives rise to symptoms and the majority of cases of hæmolytic disease of the newborn are due to incompatibility in the Rh factor, the mother being Rh-negative and the child Rh-positive. Iso-immunisation to the Rh factor does not occur unless the Rh-negative individual has a transfusion of Rh-positive blood or conceives a Rh-positive child, and firstborn children usually escape hæmolytic disease, because the antigenic stimulus of more than one pregnancy may be needed to produce a dangerous level of antibody.

**Pathology.**—The heart is hypertrophied. The liver and spleen are increased in weight and show extra-medullary hæmopoiesis, bile-staining and iron-pigmentation. The placenta is usually enlarged and may contain hæmatomata.

**Symptoms.**—Various types of the disease have been described according as œdema, jaundice or anæmia predominates. In *congenital hydrops* the child is usually born prematurely at about 36 weeks, it is swollen with dropsy and is either dead or dies a few hours after birth. More commonly the child is born about the normal time but it shows signs of distress, the amniotic fluid is yellow and the vernix caseosa a golden colour. Jaundice and anæmia are usually present at birth and they rapidly deepen, the child passing into a drowsy condition and dying within a few days or weeks. In a small proportion of cases the anæmia is less acute and no jaundice

develops. A hæmorrhagic tendency due to an associated hypo-prothrombinæmia is not uncommon. Examination of the blood shows an anæmia of high colour index with reticulocytosis and many nucleated red cells. Death may occur within 24 hours of birth from heart failure, or between the second and the fifth day from damage to the central nervous system. Deaths formerly occurred at a later period from anæmia, but this should not happen when transfusion is available. *Kernicterus* is the most frequent and distressing complication (see p. 1485); cirrhosis of the liver and dysplasia of the bones are less common sequelæ.

**Diagnosis.**—Hæmolytic disease of the newborn should be suspected whenever anæmia or jaundice occurs in the first few days of life. It is differentiated from septic infection by the absence of fever, and from syphilis and congenital obliteration of the bile ducts by the presence of a hæmolytic anæmia. The distinction from physiological jaundice may be more difficult, but if the child is anæmic or the blood film shows many erythroblasts 48 hours after birth, the jaundice is unlikely to be physiological. If the mother is Rh-negative and the child is Rh-positive, the diagnosis is practically certain and it can be confirmed by the demonstration of anti-Rh agglutinin in the mother's serum and by a positive Coombs test with the child's red cells.

**Prognosis.**—The mortality in cases born alive is about 50 per cent. without treatment. The prognosis is closely dependent on the degree of anæmia at birth. Infants whose cord blood contains less than 8 grammes per cent. hæmoglobin are likely to die within 24 hours of birth, and those with hæmoglobin values over 14.5 grammes per cent. are likely to recover without treatment. In spontaneous births the nearer to term the child is born, the better the prognosis.

**Prophylaxis.**—The Rh factor is inherited as a Mendelian dominant, and the majority of fathers of erythroblastotic children are homozygous, *i.e.* they can produce only Rh-positive children. Once hæmolytic disease of the newborn has resulted from a marriage, the odds are high that subsequent children will be involved and conception should be avoided. There are no means to prevent the disease during pregnancy—cortisone is ineffective—but the mother's serum should be tested for anti-Rh agglutinin, and if this is present, arrangements should be made to begin treatment immediately after birth.

**Treatment.**—When anti-Rh agglutinin has been detected during a pregnancy, arrangements should be made to collect a sample of the infant's cord blood at birth. This will allow an immediate Coombs test, to confirm or disprove the diagnosis, and an estimation of the hæmoglobin, to decide the treatment. If the hæmoglobin concentration in the cord blood is less than 15.5 grammes per cent., the best treatment is replacement transfusion via the umbilical vein. If the hæmoglobin is above 15.5 grammes, it is legitimate to wait 12 hours and see if jaundice develops or the blood deteriorates. Points to be noted, apart from anæmia, are the degree of reticulocytosis, erythroblastosis, and bilirubinæmia. Loss of a previous child and prematurity would sway the balance towards more active treatment. If the infant is seen for the first time after 24 hours, and the hæmoglobin in a venous sample is below 15.5 grammes, a simple transfusion should be given. If the infant is about a week old before the diagnosis is made, transfusion is only necessary if the hæmoglobin is less than 12 grammes. Transfusion is always carried out with Rh-negative blood of the same A-B-O group as the child, and the blood of neither of the parents is suitable. The father's blood, being Rh-positive, will be rapidly destroyed and the mother's blood is harmful, as it contains the hæmolysin. Induction of labour is not usually advised unless previous children have died from hæmolytic disease; it may then allow a child to be brought into the world before the anæmia has become too intense for survival. Some authorities deprecate breast feeding on the ground that the hæmolysin may be transmitted in the milk, but it probably does more good than harm in these sick children. Owing to the frequency of hypoprothrombinæmia, vitamin K should be administered as for the hæmorrhagic disease of the newborn.



## 2. IDIOPATHIC ACQUIRED HÆMOLYTIC ANÆMIA

**Synonym.**—Hæmolytic Anæmia (type Hayem-Widal).

Idiopathic acquired hæmolytic anæmias may follow an acute, subacute, chronic or relapsing course. Acute cases were formerly distinguished under the names acute febrile anæmia or Lederer's anæmia, but there is no reason for this separation. Nevertheless, the group as a whole is probably not homogeneous. The disease has an affinity to, and in some cases is combined with, thrombocytopenic purpura or agranulocytosis, in both of which conditions morbid antibodies may be present. In rare cases it may be the first manifestation of disseminated lupus erythematosus. Cases are fairly evenly distributed over the decades; females are about twice as often affected as males. In acute cases there may be fever, slight rigor at the onset, headache, lassitude, vomiting and shock. Jaundice may occur and in hyperacute cases there is hæmoglobinuria. Examination of the blood shows a profound anæmia of rapid development. More commonly the progress of symptoms is less urgent and it may be insidious and spread over months. The liver and the spleen may be palpable though the latter is not, as a rule, enlarged to the same degree as in acholuric jaundice. The anæmia may be either normocytic or macrocytic, with an increased reticulocyte count, which in some cases may run at levels over 50 per cent. Spherocytes can usually be seen in the blood film and the osmotic fragility of the red cells is usually increased. Leucocytes and platelets vary in number but are often depressed. The marrow shows great erythropoietic activity of the normoblastic type. The Coombs test is usually positive. In subacute and chronic cases the serum bilirubin is rarely much raised, and clinical jaundice is usually absent.

**Diagnosis.**—The diagnosis of a hæmolytic anæmia depends on the finding of persistent reticulocytosis and increased erythropoietic activity of the marrow, in the absence of blood loss or leuco-erythroblastic anæmia. The differentiation from other forms of hæmolytic anæmia such as hypersplenism, sporadic cases of acholuric jaundice and symptomatic hæmolytic anæmias is sometimes difficult and may have to depend on the results of therapy or splenectomy. In children two conditions have caused confusion. The first is an acute hæmolytic anæmia due to sucking moth-balls which are made of naphthalene. The second is *idiopathic pulmonary hæmosiderosis*, a rare condition in which there are recurrent attacks of effusion of blood into the lungs with associated acute anæmia.

**Treatment.**—Transfusion may be required in emergency or in refractory cases, but the most effective treatment is with cortisone or corticotrophin, which may need to be given initially in relatively high dosage, e.g., cortisone 300 mg. daily. About three-quarters of the cases may be expected to respond to cortisone, and of those who respond, about half will require a permanent maintenance dosage. No correlation has yet been established between response to cortisone, on the one hand, and the Coombs test, presence of splenomegaly or duration of disease on the other. If cortisone fails, splenectomy should usually be advised, though it should be realised that the more the case departs from the characteristic picture of acholuric jaundice, the less likely is splenectomy to be successful.

## LEUCO-ERYTHROBLASTIC ANÆMIA

**Synonyms.**—Osteosclerotic Anæmia; Myelophthisic Anæmia; Leukanæmia.

Leuco-erythroblastic anæmia is uncommon. It is found typically in association with certain diseases of the bones or bone-marrow, and is characterised by the presence in the peripheral blood of immature red cells and a few immature white cells. The anæmia is characterised clinically not by its severity but by the number of cells in the peripheral blood that normally are confined to the marrow as precursors of the red and white cells of the blood. The colour index is commonly a little below unity

and the mean diameter of the red cells usually within normal limits. Reticulocytes are constantly above normal and nucleated red cells are present, often in large numbers. The leucocyte count is commonly normal or only a little raised, but occasionally very high values may be observed, even above 100,000 per c.mm. There is always an excess of myelocytes and on occasion myeloblasts are also present. The platelet count is usually low. The van den Bergh reaction is usually negative, unless complications are present. The spleen may be palpable, either as a result of myeloid metaplasia or more rarely from neoplastic infiltration. The anaemia has been ascribed to irritation or disturbance in the maturation of the hæmopoietic tissues by the bony disease, but it is essentially hæmolytic in type. It does not respond to iron or liver, and transfusion is the only effective treatment. Leuco-erythroblastic anaemia has been observed in the following conditions, but in some of them it is the exception rather than the rule. In the adult, at any rate, malignant disease is the most important cause of leuco-erythroblastic anaemia.

(a) **MARBLE-BONE DISEASE OF ALBERS-SCHÖNBERG.**—This is a congenital disease characterised by increased density of the bones, spontaneous fractures, splenomegaly and anaemia which is often of the leuco-erythroblastic type. Symptoms usually begin in childhood with fractures following trivial injury and general backwardness. The anaemia is mainly due to narrowing of the marrow cavity from progressive broadening of the cortex and the radiographic appearances are pathognomonic.

(b) **ANÆMIA PSEUDO-LEUKÆMICA INFANTUM.**—Under this term von Jaksch described a group of cases of anaemia in children under the age of 3, characterised by anaemia, splenomegaly and leucocytosis, with many immature red and white cells in the peripheral blood. It now appears probable that this syndrome was not a disease entity but included examples of different blood diseases, such as Mediterranean anaemia, which have since been more clearly delineated. The term has therefore fallen into abeyance.

(c) **CARCINOMATOSIS OF BONE.**—As already emphasised, this is the most important cause of this type of anaemia. Symptoms of the primary growth may be elicited, and radiographic examination will usually reveal the metastases in the skeleton. It is often stated that growths of the thyroid and the prostate are especially liable to metastasise in the bones, but growths of the breast, stomach and lungs are more common causes of leuco-erythroblastic anaemia, owing presumably to their greater frequency.

(d) **MULTIPLE MYELOMA.**—Only a small percentage of cases of multiple myeloma are accompanied by leuco-erythroblastic anaemia (p. 1184).

(e) **CHRONIC NON-LEUKÆMIC MYELOID SPLENOMEGALY.**—These are cases in which enlargement of the spleen, often of an extreme degree, occurs as a result of an unexplained myeloid metaplasia. The marrow may be hyperplastic, normal or sclerotic, and neither the marrow nor the viscera show the characteristic changes of leukaemia. The blood picture is commonly of the leuco-erythroblastic type, but cases described as "polycythæmia with osteosclerosis" and "polycythæmia with leukaemia" are probably examples of the same syndrome. In other cases the platelet count is very high, and the names idiopathic thrombocythæmia and megakaryocytic myelosis have been used. The general appearance and behaviour is that of an unusually benign myeloid leukaemia. Although the condition eventually leads to the death of the patient, this rarely happens in less than 5 years, and life may be prolonged for 15 or 20 years after the onset of symptoms. Correct diagnosis is important as cases are often unfavourably affected by irradiation or splenectomy; help may be obtained from radiographs of the skeleton, bone-marrow biopsy or splenic puncture. Treatment is by transfusion; cortisone is usually ineffective. Although fibrosis of the bone-marrow, known as *myelofibrosis* or *myelosclerosis*, is usually present, it is not pathognomonic of chronic non-leukæmic myeloid splenomegaly, occurring also in aplastic anaemia and much more rarely in leukaemia.

(f) **LEUKÆMIA AND OTHER CONDITIONS.**—In rare instances of true leukaemia

large numbers of reticulocytes and nucleated red cells may appear in the circulating blood. This phenomenon has been described as "mixed leukæmia" when myelocytes and erythroblasts appear in a case of lymphatic leukæmia, or as "leukanæmia" when the disturbance of erythropoiesis is prominent. Some of these are examples of symptomatic hæmolytic anæmia, which will respond to cortisone, but others are leuco-erythroblastic anæmia due to irritation of the bone-marrow by leukæmic deposits. Numerous immature red and white blood cells may very rarely appear in the blood in the course of miliary tuberculosis, syphilis and Hodgkin's disease. The evidence suggests that in all such cases the bone-marrow is involved and the blood disorder is of the leuco-erythroblastic type, but, owing to their great rarity, their pathology has not yet been satisfactorily worked out.

### ANÆMIA IN PREGNANCY

The *physiological anæmia of pregnancy* is due to dilution of the blood in pregnancy owing to altered circulatory conditions and increased blood volume. The hæmoglobin rarely falls much below 75 per cent. in healthy women, the colour index is unity and there is no hypochromia or poikilocytosis. It often gives rise to unnecessary anxiety. It is distinguished from *pernicious anæmia* by its mildness and from *iron-deficiency anæmia* by the normal colour index. It requires no treatment. The same circulatory phenomena are likely to aggravate the anæmia of iron deficiency in pregnancy, and in women who have suffered from anæmia in a previous pregnancy or who are unable to take an optimal diet, it is wise to prescribe iron as a prophylactic throughout the period of gestation and lactation. Megaloblastic anæmia is rare in pregnant women in Western Europe and North America, though it is common in tropical or sub-tropical zones. The following causes of megaloblastic anæmia in pregnancy have been differentiated:

1. *Nutritional macrocytic anæmia* is much aggravated by pregnancy, and then assumes a frankly megalocytic type.

2. Pregnancy may occur in a patient with *pernicious anæmia*, or pernicious anæmia may first begin in pregnancy, persisting after gestation; achylia gastrica is present, and subacute combined degeneration may develop.

3. Pernicious anæmia may occur as a temporary phenomenon during pregnancy, disappearing after gestation. This is the true *pernicious anæmia of pregnancy*. It probably occurs in about 1 in 1000 pregnancies in Great Britain. The anæmia does not develop until the last trimester and may not be apparent until the puerperium. The blood picture may not be macrocytic and the diagnosis may depend on examination of the marrow. Pernicious anæmia of pregnancy may be rapidly fatal if it is not effectively treated, and it should therefore be the rule to examine the marrow in severe anæmias in late pregnancy and the puerperium, particularly if there has been failure to respond to iron. The gastric secretion may be normal and the anæmia appears to be due to a disturbance in the metabolism of folic acid. Subacute combined degeneration does not occur. Treatment is by folic acid by mouth in a dosage of 20 mg. a day, which may be gradually tailed off when the anæmia is repaired and the puerperium is over. The disease may or may not recur in subsequent pregnancies.

### POLYCYTHÆMIA

Polycythæmia is a condition in which there is an increased number of erythrocytes per unit of circulating blood. The upper limits of normality are 6.5 million red cells per c.mm. and 17.5 g. hæmoglobin per 100 ml. (120 per cent.). It may be due to known causes, when it is called secondary polycythæmia, or *erythrocytosis*; or it may be an independent disease of the blood-forming organs, when it is called *polycythæmia vera*, or *erythræmia*. The following causes of erythrocytosis are known:

1. Concentration of the circulating blood, such as occurs in the dehydration of choleraic diarrhœa.

2. Diminution of the oxygen tension in the circulating blood or tissues. Examples of this are—(a) residence at high altitudes; (b) cardiac diseases with cyanosis, especially congenital pulmonary stenosis and acquired sclerosis of the pulmonary arteries (Ayerza's disease, or *cardiacos negros*); (c) conditions interfering with normal pulmonary ventilation, such as emphysema, asthma, fibrosis and neoplasms of the lungs.

3. Chronic poisoning by a number of chemical agents, such as arsenic, phosphorus, carbon monoxide and aniline derivatives.

4. Cirrhosis of the liver, tuberculosis of the spleen and similar conditions associated with splenomegaly or portal stasis, in rare instances.

5. A transient erythrocytosis may occur in the stage of recovery from anæmia.

These causes should always be excluded before diagnosing polycythæmia vera; in doubtful cases estimation of the blood volume is helpful, for polycythæmia vera should not be diagnosed unless the blood volume is considerably increased.

### 1. POLYCYTHÆMIA VERA

**Synonyms.**—Erythræmia; Osler-Vaquez Disease.

**Definition.**—A disease characterised by well-marked and persistent increase in the number of red corpuscles, due to an excessive erythroblastic activity of the bone-marrow.

**Ætiology.**—Erythræmia is a disease of the second half of life. It is a little more common in males, but the difference in the two sexes is not striking. Familial cases of polycythæmia occur; they tend to be mild. Present opinion is that erythræmia is a proliferative condition or benign neoplasia of the bone-marrow, with strong affinities to leukæmia and non-leukæmic myeloid splenomegaly.

**Pathology.**—The marrow of most of the shafts of the long bones is converted into active red marrow. The spleen is enlarged and engorged, and often contains thrombotic infarcts. The liver is congested, but no anatomical change is present in it.

**Symptoms.**—The most frequent symptoms are due to disturbance of the cerebral circulation by the increased volume and viscosity of blood. They take the form of nervousness, headache, lack of concentration and vertigo. Sometimes temporary disturbances of vision, aphasia or paralysis occur, which recover completely in a few hours. Itching of the skin, particularly after a hot bath, is a common complaint. Other symptoms are loss of weight and strength, shortness of breath on exertion, angina of effort and abdominal pain or dyspepsia caused by the splenic tumour. The three cardinal signs are rubor, splenomegaly, and polycythæmia. There is cyanosis of the exposed surfaces, especially the cheeks, the tip of the nose and the ears. The colour varies with the temperature, being scarlet in a warm atmosphere and dark blue in the cold. The eyeballs are often bloodshot, the conjunctivæ deep red, and the retinal vessels engorged and tortuous. Papilloedema does not occur in polycythæmia vera and its presence would suggest either that the polycythæmia was complicated by venous thrombosis or that it was secondary to intracranial or pulmonary disease. The spleen is palpable in three-quarters of the cases; it rarely extends beyond the umbilicus and varies in size, shrinking after a hæmorrhage or successful treatment. The liver is palpable in about one-half the cases. The urine may contain a little albumin. The blood contains from 7 to 14 million red corpuscles per c.mm. and 17 to 25 g. hæmoglobin per 100 ml. (120 to 170 per cent.). The red cells are usually smaller than normal, and the colour index is less than unity. The white cells are over 10,000 per c.mm. in three-quarters of the cases but they rarely reach 50,000. The reticulocytes are normal but the platelets may be much increased in number.

**Complications.**—The most important complications are vascular, and result

from the increased volume and viscosity of the blood and its sluggish flow. It is noteworthy, however, that hypertension is no more common than in normal individuals in the same age-groups. Not uncommonly there are massive hæmorrhages, especially from the stomach, but also from the nose, lungs, bowel, uterus and bladder or internally. Thrombosis is not infrequent, and in the cerebral vessels or the portal vein its consequences may be grave. Symptoms of peripheral vascular disease are frequent, though they may improve strikingly on restoration of the blood to normal. Peptic ulcer is probably a little commoner than in normal people. When the illness runs a long course leukaemia, myelosclerosis, purpura hæmorrhagica and anæmia may intervene, but it is not clear whether these conditions are the effect of the primary malady or of prolonged depression therapy.

**Course and Prognosis.**—So long as the blood count is abnormally high, there is always the immediate danger of death from one of the vascular accidents. In cases controlled by effective treatment, the expectation of life is probably not greatly reduced and is comparable to that of diabetics treated with insulin. Spontaneous remissions are described, and in any large series, spent cases are found in which the disease process appears to have burnt itself out, though the spleen remains enlarged. In properly treated cases the most serious risk is leukaemia.

**Treatment.**—Whatever treatment is eventually used, it is best to begin by removing the excess of blood by bleeding. A pint of blood should be removed twice weekly until the hæmoglobin falls below 14·5 g. (100 per cent.) and the hæmatocrit below 45 per cent. Frequently 10 or 12 successive venesections are needed before this happens. The blood may then be maintained at this level by venesection at longer intervals, but this has the disadvantage of depleting the patient of iron and protein. Radioactive phosphorus is the treatment of choice. A first course of 3·5 to 4 millicuries is given and then no more for 3 months. At the end of that time, if the count is above 6 million red cells per c.mm., a second course of 1 to 3 millicuries is given, and some patients need a third course 3 months later. Roentgen rays may be used in a similar manner, though they are less convenient than radioactive phosphorus, and less certain in effect than in leukaemia. The rays should be applied over the long bones and the chest. Treatment by any form of ionising radiation probably increases the incidence of leukaemia and malignant disease, but it appears to be justified by the results. Chemotherapy with arsenic, phenyl-hydrazine, or nitrogen mustard is now rarely employed if radioactive phosphorus, or Roentgen rays are available.

## 2. METHÆMOGLOBINÆMIA AND SULPHÆMOGLOBINÆMIA

**Synonym.**—Enterogenous Cyanosis.

**Definition.**—A condition characterised by cyanosis without cardiac or pulmonary lesions, associated with the presence of methæmoglobin or sulphæmoglobin in the circulating red cells.

**Ætiology.**—In the vast majority of cases the condition is due to the use of drugs, especially aniline derivatives, and it has become much more common since the introduction of the sulphonamide group. Other drugs which have been incriminated are acetanilide, phenacetin, antipyrine, Trional, sulphonal, potassium chlorate and nitrites. Methæmoglobinæmia is produced by the direct action of the chemical or a breakdown product of it on the red cells. In sulphæmoglobinæmia the chemical sensitises the red cells, so that the hæmoglobin combines with hydrogen sulphide absorbed from the intestine. Sulphæmoglobinæmia is therefore much more likely to develop in constipated patients. A common sequence of events is: constipation; headaches; the use of headache powders which contain phenacetin or acetanilide; and sulphæmoglobinæmia. In very rare cases methæmoglobinæmia occurs spontaneously, apparently as a result of excess production and undue absorption of nitrites

from the gastro-intestinal tract; this condition is known as *enterogenous cyanosis*. Equally rare is a familial form of methæmoglobinæmia attributed to an inborn error of metabolism—*hereditary methæmoglobinæmia*. Chronic methæmoglobinæmia and sulphæmoglobinæmia are more common in women than men, and should always arouse suspicion of drug addiction, hysteria or malingering.

**Symptoms.**—The degree of cyanosis is sometimes out of proportion to the amount of methæmoglobin or sulphæmoglobin present, and it is probably aggravated through absorption by the red cells of coloured derivatives of the drugs themselves. The colour varies from a slight muddiness of the complexion to a deep blue. In marked cases the appearance of the patient is indeed ghastly, and yet it is belied by the comfortable general condition, the absence of any respiratory distress, and the extreme rarity of a fatal issue. In acute cases there may be no symptoms. In chronic cases the patient complains of weakness, nervousness, vertigo or fainting attacks, palpitation, headache and constipation. The blood may show a slight polycythæmia.

**Diagnosis.**—The diagnosis depends on the spectroscopic examination of the blood for methæmoglobin or sulphæmoglobin. The brown colour of the blood can often be recognised with the naked eye. Methæmoglobinæmia, in which the altered hæmoglobin is within the corpuscles, must be distinguished from methæmalbuminæmia, in which altered hæmoglobin is present in the plasma; in the latter, there is no cyanosis, and the patient may be jaundiced. The use of drugs should always be suspected, especially in chronic and apparently inexplicable cases in women. It is surprising how skilfully they deceive their attendants and escape detection. I have known more than one woman who has lived many months in hospital and has been shown at medical meetings as a rare and mysterious case when all the time the symptoms were being produced by a bottle of phenacetin tablets concealed in the locker.

**Prognosis.**—In patients who are anæmic or who have to work at a high altitude, the condition may encroach dangerously on the reserve of functioning hæmoglobin. In other respects it is harmless.

**Treatment.**—Recovery occurs spontaneously in 24 to 72 hours after the drug is discontinued. The cyanosis can be promptly relieved by the intravenous injection of methylene blue, 1 or 2 mg. per kg., but it will return again if the offending drug is continued. It can be prevented, however, by the continuous administration of methylene blue by mouth, gr. 1 or 2 four-hourly. Large doses of ascorbic acid are also effective.

## LEUCOCYTOSIS

It is important to be familiar with the normal fluctuations of the white cells. In healthy individuals the total number of white cells may vary from 4000 to 11,000 per c.mm., the average being 7500. A typical differential count is: neutrophils 66 per cent., eosinophils 2.5 per cent., basophils 0.5 per cent., lymphocytes 24 per cent., monocytes 7 per cent.; but there are great physiological variations which are best illustrated by the absolute values of the different cells. The total number of neutrophils may vary from about 1500 to 7500; eosinophils from 0 to 400; basophils from 0 to 200; lymphocytes from 1000 to 4500; and monocytes from 0 to 800. The total white count is at a minimum or basal level when the subject is at rest in the morning; activity, mental or physical, increases it by 60 or 100 per cent.; in addition there are rhythmical fluctuations in the number of polymorphonuclears, lymphocytes and monocytes, which are probably associated with the replacement of dead or emigrated cells. It is unwise to draw far-reaching conclusions from a single count of the white cells, and the test should always be repeated when an anomalous result is obtained, or when it is uncertain whether the figures fall within normal limits. The most obvious task of the white cells is to protect the body from attack

and invasion by bacteria or similar agencies. They may be compared with a standing army which performs no useful service in times of peace, but which possesses great reserves which may be mobilised in time of war. We might press the analogy further and compare the three main groups of blood cells, the granulocytes, the lymphocytes and the monocytes, with the different fighting branches, for just as different types of warfare require different arms, so the three main groups of blood cells show independent variations in the various phases of an infection, and respond differently to different kinds of disease. An increase in the neutrophil leucocytes should strictly be called neutrophil leucocytosis or neutrophilia, but when the term leucocytosis is used without qualification it is taken to mean a neutrophil leucocytosis. Leucocytosis occurs physiologically during the later stages of pregnancy and for about a week after delivery; in the newly born infant; and after exercise, as many as 35,000 cells per c.mm. having been found after violent exertion. The causes of pathological leucocytosis are:

1. Haemorrhage, or trauma in which tissues are injured and blood is extravasated.
2. Acute infections, especially by the pyogenic cocci.
3. Acute intoxications, such as diabetic coma, uræmia, gout, lead colic, coal-gas poisoning and poisoning by a number of organic and inorganic substances.
4. Malignant disease, especially when the tumour grows rapidly, or involves the alimentary tract or the bone-marrow, and some cases of Hodgkin's disease.

The number of white cells in these conditions commonly varies from 12,000 to 40,000 per c.mm., according to the acuteness of the infection or intoxication, and the patient's ability to respond; in exceptional cases the count may even exceed 100,000. The neutrophils are less mature than normal, or are altered by the toxæmia, so that many of the cells have only one or two lobes to their nuclei—a phenomenon described as the "shift to the left". In profound infections in which the patient's resistance is overcome there may be no increase in the total number of white cells but a considerable shift to the left is present; this is a sign of very ill omen. When there is a considerable leucocytosis, as in pneumonia and scarlet fever, small numbers of myelocytes may appear in the peripheral blood.

## EOSINOPHILIA

The function of the eosinophil cells is not known, though it is suggested that they protect the body against the absorption of foreign proteins or of abnormal products of protein metabolism. Their number is increased by certain drugs, such as emetine, and also by feeding with whole liver. They are decreased in surgical shock, and by the hormones corticotrophin and cortisone. There is a rare condition of *hereditary eosinophilia* which sometimes manifests itself in different members of a family, and in which the normal proportion of eosinophils and neutrophils is reversed; in such cases infection is attended by a neutrophil leucocytosis and a temporary diminution of the eosinophilia. A constitutional tendency of the same kind is probably present in a number of individuals, and explains the high eosinophilia that may sometimes appear from trivial or unusual causes. In the symptomatic eosinophilias tabulated below it is rare for the total white count to be much increased, or for the eosinophils to exceed 20 per cent., but occasionally they may constitute over 50 per cent. of a total white count of 50,000 to 100,000. The eosinophils are usually increased in:

1. Infestation by parasites, especially hydatid cysts, ancylostomiasis and trichiniasis. *Læffler's syndrome*, a condition in children in which transient pulmonary infiltrations are associated with blood eosinophilia, has been ascribed to the migration of larvæ of *ascaris lumbricoides* through the lungs. *Tropical Eosinophilia* (Weingarten's syndrome) is a very similar syndrome which has been observed particularly

in India and Ceylon, and in which eosinophilia is associated with asthma and bronchitis. The eosinophil count is of the order of 40 to 80 per cent.—or even higher. In some cases the symptoms have been ascribed to infestation of the bronchi and bronchioles by mites. Tropical eosinophilia responds extremely well to a course of injections of neoarsphenamine and I have seen an equally favourable result in a woman with eosinophilic bronchitis who had never been in the tropics.

2. Convalescence from acute diseases; they are diminished in the acute stage, except in cases of scarlatina in which there is a slight eosinophilia at the time of the eruption, and sometimes in acute rheumatism.

3. Allergic states, such as asthma and hay fever.

4. In many skin diseases.

5. In Hodgkin's disease in about one-quarter of the cases, but rarely to a high degree, in polyarteritis nodosa, and in rare cases of malignant growths, more especially when the peritoneum is involved.

6. In myeloid leukaemia and erythræmia.

### EOSINOPHILIA WITH SPLENOMEGALY

**Synonym.**—Eosinophilic Leukæmia.

This is an uncommon syndrome in which enlargement of the spleen is associated with persistent eosinophilia; the liver and the lymph glands may also be palpable. The total white count is usually between 10,000 and 25,000, but it may exceed 50,000 cells per c.mm.; eosinophils constitute from 20 to 80 per cent., the majority being mature and only a small fraction myelocytes. Anæmia, if present, is of moderate degree. Post mortem the hyperplastic bone-marrow is seen to be filled with eosinophils in all stages of development. Eosinophil cells are present in the other organs, especially the spleen and the lymph glands, but here they are mainly adult cells. Areas of hæmorrhage and fibrosis may be found in the spleen and the lungs, and granulomatous tumours have also been observed. The benign course of the disease in many instances, the absence of anæmia and the small percentage of myelocytes in the blood and tissues are arguments against regarding the condition as a true eosinophilic leukaemia. It is probably not a disease entity, but a syndrome of varied ætiology. Some cases are examples of hereditary eosinophilia in its severer form; others are acquired on the basis of asthma and bronchitis, syphilis, malaria, hepatic cirrhosis, myeloid leukaemia, Hodgkin's disease and other known causes; and a few cases remain obscure. The prognosis is moderately good, but death may occur from intercurrent infection. Cortisone or corticotrophin should be tried. Splenectomy is contraindicated, as it aggravates the eosinophilia. Great improvement follows anti-syphilitic treatment in cases with a positive Wassermann reaction.

### LYMPHOCYTOSIS

Little is known about the function of the lymphocytes, though they are believed to play an important part in the protection of the mucosæ and the formation of antibodies. They are increased by exposure to ultra-violet light, and diminished by excessive irradiation, vitamin deficiency and the hormones corticotrophin and cortisone. Lymphocytes are more numerous in the blood of children than of adults, constituting from 40 to 60 per cent. of a total count of 7000 to 9000 white cells per c.mm., and their reactions to disease are much greater in early life. There are few infections in childhood which may not now and again be associated with an extraordinarily high lymphocyte count. The lymphocytes are especially increased in whooping-cough, chicken-pox, small-pox, typhus, malaria and most constantly in glandular fever (acute mononucleosis). In isolated instances of these various infections, the lymphocytes may rise as high as 75 per cent. or more of a total count of 100,000 white cells per



c.mm., and leukæmia may be suspected. Usually the absence of anæmia should quiet this suspicion. The lymphocytes are moderately increased in the stage of healing of acute infections, and in tuberculosis which is progressing favourably. They are diminished in miliary tuberculosis and lesions of the lymphoid tissues, such as glandular tuberculosis, Hodgkin's disease, carcinoma and lymphosarcoma.

## MONOCYTOSIS

The monocytes are increased during and after the crisis in acute infections, and also in active tuberculosis, sympathetic ophthalmia and undulant fever. Very high counts are occasionally obtained in miliary tuberculosis and infective endocarditis.

## BASOPHILIA

The basophils are moderately increased in a number of diseases of the blood-forming organs, such as leukæmia, erythræmia and acholuric jaundice. The increase of basophil cells in myeloid leukæmia is sometimes of a diagnostic importance, as it may be the only abnormality present during a remission.

## LEUCOPENIA

Leucopenia implies a condition in which the total white cell count is reduced below the normal range, *i.e.* below 4000 per c.mm. Granulocytopenia or neutropenia indicates a similar diminution in the number of granulocytes or neutrophils respectively, *i.e.* less than 1500 neutrophils per c.mm. While the majority of infections induce a leucocytosis, it is characteristic of certain diseases that the white count is normal or diminished. The most important infections in which there is leucopenia are the enteric fevers, undulant fever, influenza and measles. Leucopenia may also occur in septic infections when the resistance is overwhelmed by the severity of the infection; it is nevertheless unusual for the white blood count to sink to the low levels characteristic of agranulocytosis, and a total white count below 2500 should arouse the suspicion of an underlying abnormality in the blood-forming organs. Leucopenia resulting from septic infections differs from agranulocytosis in the presence of septic foci, positive blood cultures, and at necropsy the septic type of splenitis. As might be expected, leucopenia occurs in cachectic and debilitated states and in diseases of the blood-forming organs in which the leucopoietic tissues are depressed. There is a temporary fall in the number of leucocytes in the peripheral blood in anaphylactic shock and similar conditions, owing to the collection of the cells in the internal organs.

In the conditions already discussed, the leucopenia is usually moderate in degree and produces no obvious clinical effects, the symptoms being those of the primary disorder. Leucopenia of a much more severe degree occurs in aplastic anæmia and leucopenic leukæmia. The bacteria which are constantly present on the surfaces of the body are then able to invade the tissues, and the trivial infections to which all of us are exposed take on a malignant character. The most common invaders are Vincent's organisms, with the production of fetid ulceration in the mouth and throat or elsewhere. Lesions such as cancrum oris, noma and putrid sore throat rarely develop unless the white blood cells are depressed. Such extreme leucopenia is nearly always accompanied by signs of damage to the other hæmopoietic tissues, such as anæmia and a tendency to bleed. The leucopenia is indeed only one manifestation of a general depression of marrow function. There are, however, cases in which the lesion is strictly confined to the white cells and the leucopoietic tissues, so that the red cells and platelets remain intact. It is to cases of this last type that the

term *agranulocytosis* should strictly be confined, as they form a clinical entity with characteristic pathological changes, but the term is often loosely applied to any condition in which the white cell count is greatly depressed, and necrotic ulceration is present.

### AGRANULOCYTOSIS

**Synonyms.**—Malignant Neutropenia; Primary Granulocytopenia; Agranulocytic Angina.

**Definition.**—A disease characterised by profound leucopenia, an acute febrile illness, necrotic ulcerations and a high mortality.

**Ætiology.**—The majority of cases are due to an idiosyncratic reaction to drugs, especially amidopyrine and the related phenylbutazone, the sulphonamides and the related thiourac derivatives, and tridione (Tridione) and related anti-epileptic drugs. During the active phase of agranulocytosis following the administration of amidopyrine, an antibody can be demonstrated in the plasma which agglutinates the white cells. It is assumed that this antibody leads to greatly increased peripheral destruction of the granulocytes with consequent depletion and exhaustion of the bone-marrow. Leuco-agglutinins have also been demonstrated in other forms of agranulocytosis, including some in which there is no history of taking drugs, and the Coombs test may be positive.

Patients who have an idiosyncrasy to amidopyrine may become sensitive to the drug after taking quite a small quantity, and in the sensitised subject a dose as small as 0.2 g. may be followed by an abrupt diminution in the white cells and changes in the marrow. Agranulocytosis therefore occurs typically in patients who are taking amidopyrine in small doses or at long intervals. When a patient has taken a total of 50 g. amidopyrine with impunity (in divided doses, of course) it becomes progressively less likely that he will become sensitive, though there can be no absolute surety of safety. The position with the sulphonamides is different. Agranulocytosis from the sulphonamide group rarely occurs until at least 30 g. of the drug has been taken. It is therefore infrequent before the tenth day and is more likely to be found with second or later courses of treatment. With thiouracil agranulocytosis occurs most commonly in the second month of treatment, but it has been observed after both short and prolonged periods of administration, and at all dosage levels. Agranulocytic syndromes may also occur after most of the poisons mentioned under aplastic anæmia (p. 738), but they are rarely so clear-cut and tend to be complicated by anæmia and hæmorrhage. Chronic and recurrent types of agranulocytosis are occasionally met with, especially in females, for which no explanation can be found. There is also a very rare disease, *primary splenic neutropenia*, in which chronic agranulocytosis occurs in association with splenomegaly, without cirrhosis or drug and bacterial idiosyncrasies, and is completely relieved by splenectomy. This may be regarded as the counterpart of idiopathic hæmolytic anæmia and essential thrombocytopenic purpura.

**Pathology.**—Necrotic, ulcerative or gangrenous lesions are present, most constantly in the mouth and pharynx, but they may affect any part of the alimentary canal, the rectum and the vagina. Oedematous or brawny swellings may be present about the teeth, the neck, in the subcutaneous tissues or elsewhere. The bone-marrow contains its normal complement of megakaryocytes, and erythropoiesis is normal, but granular leucocytes and myelocytes are absent; in cases dying early, small islands of myeloblasts are seen, but in the later stages these too may disappear and the only white cells seen in the marrow are focal accumulations of lymphocytes.

**Symptoms.**—In cases due to amidopyrine, there is often a long history of mental or physical over-exertion, followed by chronic fatigue, loss of weight and vague pains in the limbs. If the blood is examined in this prodromal phase, leucopenia of moderate degree will be found. Acute symptoms are often precipitated by dental extraction

or an influenzal attack. The onset is abrupt, sometimes with rigors, and the patient complains of aching pains in the limbs and sore throat, and is rapidly prostrated. The temperature is high, ranging from 100° to 105° F. In the majority of cases ulcero-membranous lesions soon appear on the tonsils and gums, and the cervical glands may be enlarged, with surrounding brawny induration. As already indicated, other mucous surfaces may be involved, and in rare cases the sole infective lesion may be a mild redness of the throat without any other tissue or blood infection. The patient is pale but not anæmic. The liver and the spleen may be palpable, and jaundice is an occasional complication. As the disease advances, the usual symptoms of a profound toxæmia appear. Examination of the blood at this stage shows a total white count below 2000, often only a few hundred cells per c.mm.; the reduction affects especially the granulocytes, which may be diminished to about 5 per cent. or even completely absent.

**Diagnosis.**—Cases arising in the course of another illness which has been treated by amidopyrine or one of the sulphonamides may be very difficult to recognise. The diagnosis depends chiefly on the history and the blood picture. Specific inquiry should be made as to the use of amidopyrine, which is contained in many analgesic and hypnotic preparations. The author has seen several cases in which the amidopyrine hypothesis had been discarded, but further questions revealed the fact that the drug had indeed been used or was still being used. Aplastic anæmia and leukæmia can be excluded by the blood picture, as the red cells and platelets are not affected in agranulocytosis, and there are no primitive white cells such as appear in acute leukæmia.

**Prognosis.**—Spontaneous recovery from an acute attack may occur, but the mortality of untreated cases is about 75 per cent. The results of current therapy have not yet been appraised but in cases diagnosed early the mortality should not exceed 25 per cent.

**Prophylaxis.**—No one should ever be given a prescription which allows amidopyrine to be taken without close medical supervision. Patients taking phenylbutazone, anti-epileptic or anti-thyroid drugs should be warned to report at once if they suffer from fever, sore throat or other untoward symptoms. If drugs of the sulphonamide group are given for more than a week, the blood should be examined at regular intervals. The occurrence of drug fever 7 to 10 days after beginning sulphonamide treatment may herald the onset of agranulocytosis. It is not known how long the patient remains sensitive to drugs capable of producing agranulocytosis but it may be for the rest of his life. After an attack, therefore, the patient should be specifically told not to take the drug again.

**Treatment.**—The first step is the removal of the cause where this can be identified as a drug. At the same time corticotrophin or cortisone should be given in full doses to accelerate the disappearance of the morbid antibody and the recovery of leucopoiesis. Penicillin or other antibiotic should be given in large doses and in the majority of cases the infection will clear up in 3 to 10 days. For local treatment penicillin lozenges may be used or the mouth and throat may be frequently washed out with a hypochlorite solution. In severe cases the mouth may be sprayed with a saturated solution of potassium chlorate, and ulcerated areas then swabbed with a solution of copper sulphate, 10 grains to an ounce of water. Abscesses and areas of cellulitis should be drained but only essential surgery should be done until the white count is stabilised at a normal level. In chronic and recurrent cases of granulocytopenia, splenectomy is of value in the small group of cases in which the spleen is enlarged and the bone-marrow is hypercellular.

## LEUKÆMIA

**Synonym.**—Leukosis.

**Definition.**—Leukæmia is a morbid condition characterised by widespread

hyperplasia of the leucopoietic tissues, either myeloid or lymphatic, which is usually associated with qualitative and quantitative changes in the white cells of the circulating blood.

**Ætiology.**—The ætiology is unknown, and the disease appears to occupy an intermediate position between the reaction to infections and noxious agencies on the one hand and the true neoplasms on the other. Leukæmia occurs in the lower animals also, and (like the sarcomata of these animals) it is sometimes transmissible by cell-free filtrates. In its more acute forms in man it often resembles an infection, and very similar changes in the blood and the blood-forming organs may sometimes be produced by infections and similar clearly apprehended agencies; it is difficult, however, to reconcile the tumour-like growths which sometimes develop in leukæmia with a hypothesis of infection. It differs from the ordinary neoplasms in being a system-disease, and affecting the whole organ simultaneously. The neoplastic hypothesis presents fewer difficulties, the diffuse character of the lesion being explained by the labile character of the leucopoietic tissues and being paralleled by the diffuse carcinomas of the breast and the cirrhotic liver. In experimental animals leukæmia has been induced by indole, benzol and tar, and in man it has been thought to be unduly frequent in those whose work exposes them to benzol, Roentgen rays and radium. There has been a real increase in leukæmia in the last 50 years and it has been speculated that this may be due to the increased opportunities for contact with synthetic chemicals in our present civilisation. In experimental animals stocks with a high incidence of leukæmia can be produced by selective breeding, and in man it is probable that the disease only occurs in those with the appropriate genetic make-up.

**Classification.**—We might expect to find forms of leukæmia corresponding to each of the different types of white blood cell, and classify them accordingly. In practice it is found that the only forms of leukæmia which occur at all frequently are those which involve predominantly the neutrophils and their precursors, or myeloid leukæmia, and those which involve the lymphocytes, or lymphatic leukæmia. Eosinophilic leukæmia has already been discussed; in exceptional cases of myeloid leukæmia basophil cells may predominate. Monocytic leukæmia has recently attracted much interest, but many cases so described are actually myeloblastic leukæmia, and in the majority, at any rate, myeloblasts or myelocytes as well as monocytes are present in the blood and tissues. In cases in which monocytes predominate, the leukæmia is usually acute or subacute, with fever, severe anæmia and necrotic mouth lesions, and a tendency to temporary remissions and aleukæmic phases. In leukæmia the immaturity of the cells is just as important as the type of cell present, and for clinical work the leukæmias are therefore described as chronic myeloid leukæmia, chronic lymphatic leukæmia and acute leukæmia. Whichever strain of cells is affected, the disease breeds true, and the two groups of cells are never involved simultaneously. Confusion has sometimes arisen owing to the ease with which very immature cells of the myeloid series, the myeloblasts, can be mistaken for lymphocytes. The increase in leukæmia in recent years has particularly affected acute leukæmia and chronic lymphatic leukæmia. At present about 40 per cent. of cases are acute leukæmia, 33 per cent. chronic lymphatic and 25 per cent. chronic myeloid.

### 1. CHRONIC MYELOID LEUKÆMIA

**Synonyms.**—Myelocytic Leukæmia; Spleno-Medullary Leukæmia; Chronic Leukæmic Myelosis.

**Ætiology.**—The two sexes are equally involved. The disease is very rare before puberty, and about half the cases begin between 30 and 50, the greatest incidence being between 35 and 55.

**Pathology.**—The changes which are found in the body are almost confined to the hæmopoietic organs. The bone-marrow is firm and fleshy, pale pink or grey in

colour, rarely of a greenish hue. The predominant cell is the myelocyte, but there are also large numbers of myeloblasts and nucleated red cells. The spleen is usually enormously enlarged, but its outline is preserved; its surface is smooth, its consistence firm, its colour on section a greyish-red, usually mottled with infarcts. Microscopically the Malpighian corpuscles are obliterated, and the pulp is filled with myeloid cells and resembles the bone-marrow. The liver is large, firm and of a pale yellow tint, and its capillaries contain large numbers of myelocytes. The other organs may show anæmia, hæmorrhages and infiltration with myelocytes.

**Symptoms.**—Early symptoms are easy fatigue, slight loss of weight and strength, and gastro-intestinal disturbances, but the patient may first complain of the enlargement of the abdomen due to the increasing size of the spleen. The anæmia at this time is not marked, indeed the appearance is not infrequently one of good health. Pain in the left side is sometimes felt, either as a result of the dragging weight of the enlarged spleen or from perisplenitis over an infarct. The average duration of symptoms before medical advice is sought is about a year. Fever is commonly slight, and there are often long periods of normal temperature interrupted now and then by small rises of short duration to  $101^{\circ}$  or  $103^{\circ}$  F. The basal metabolic rate is increased. Tenderness is often present over the sternum, more marked during exacerbations of the disease.

On examination the striking feature is the size of the spleen. It occupies the greater part of the left side of the abdomen, often reaching to the iliac crest below and the middle line at the umbilicus. It forms a hard smooth tumour, with rounded edges, not tender to palpation and easily recognised by the characteristic notches in the anterior margin. The size tends to vary in the course of the disease, often leading to false hopes as to the efficacy of treatment. Sudden enlargement is due to hæmorrhage or infarction, and marked diminution may occur with the approach of death. The liver is larger than normal, and smooth. The lymph glands are rarely palpable, except sometimes near the end. Impairment of vision may occur from leucocytic accumulations or hæmorrhages in the retina, while involvement of the inner ear may lead to deafness and Ménière's syndrome.

In the later stages the anæmia becomes severe, and cachexia develops. Ascites and œdema make their appearance, the heart weakens and the patient becomes emaciated. Hæmorrhage is frequent, but rarely lethal. Death occurs from exhaustion or from intercurrent infection. It should be noted that infection may produce a temporary improvement in the blood picture, but such a remission is often followed by an aggravation of the disease, which then pursues an acute and rapidly fatal course. Conversion of chronic into acute leukæmia may also happen spontaneously.

**The blood.**—The principal characteristics are progressive loss of hæmoglobin and of red cells, and increase, frequently enormous, of the leucocytes. The white count ranges from 100,000 to 1,000,000 cells per c.mm., values about 400,000 being most usual. The increase is mainly composed of cells of the granulocyte series. The typical cell is the neutrophil myelocyte, which constitutes 20 to 40 per cent. of the total; but the neutrophil, eosinophil and basophil polymorphonuclears are also increased, eosinophil and basophil myelocytes are present, and occasional myeloblasts are encountered. The anæmia is of the orthochromic type, and as it becomes more severe, anisocytosis and polychromasia develop, and nucleated red cells appear in the blood. The platelets are normal or slightly increased at the beginning of the disease, but decrease in the terminal phase.

**Diagnosis.**—This is usually made with ease from the characteristic blood picture and the great splenic enlargement, though difficulty may arise when the white cells fall to normal or subnormal values as a result of treatment. In these circumstances the presence of immature white cells and of basophil leucocytes may indicate the correct diagnosis.—Myeloid leukæmia usually runs true to type and rarely presents an aleukæmic phase. The differential diagnosis of chronic myeloid leukæmia and

non-leukæmic myeloid splenomegaly may be difficult, but in the latter the blood picture is not frankly leukæmic and total white cell counts above 30,000 per c.mm. are unusual.

**Course and Prognosis.**—Chronic myeloid leukæmia is invariably fatal. The average duration of life is just over 3 years from the onset of the disease, or 2 years after coming under treatment. There is no evidence that treatment prolongs life, though it greatly increases the comfort of the patient. In any large series exceptional cases are observed in which life is prolonged for 10 to 20 years, though one may suspect that most of these are examples of chronic non-leukæmic myeloid splenomegaly. At the other extreme are subacute cases which shade indefinitely into acute leukæmia. The prognosis in an individual case will depend on the general condition of the patient and the presence or absence of cachexia, the degree of anæmia, and the height of the white count, very high and also very low values being unfavourable. Enlargement of lymph nodes and the appearance in the blood of large numbers of myeloblasts are each unfavourable signs. (See also under Treatment.)

**Treatment.**—Chronic leukæmia is treated either by the ionising radiations of Roentgen rays and radioactive substances, or by chemotherapy with mitotic poisons such as arsenic, benzol, colchicine, nitrogen mustard, urethane and Myleran. Both types of agent act by disturbing or destroying the proliferating white cells during cell division, or when cell division is about to begin. As a result a temporary remission of the disease is induced. The natural course of chronic myeloid leukæmia is steadily downhill, and during the latter half of the untreated disease the patient is confined to his bed, cachectic and miserable. After a course of treatment with Roentgen rays or chemotherapy, the patient is restored to what he feels his normal condition. The spleen usually remains enlarged and the blood abnormal, but in rare cases the blood returns almost to normal and the spleen recedes beneath the costal margin. Such a remission lasts from a few months to a year, when repetition of the treatment again produces improvement, though not so complete as before. After a varied number of cycles treatment finally becomes ineffective, and a time arrives when, despite all efforts, the patient becomes steadily worse. The period of decline is usually swift, and in the majority of cases death occurs within 4 or 5 months of entering this final phase. A patient who has become resistant to radiotherapy may respond to chemotherapy, and vice versa, but the point of attack of the two types of therapy is similar and as a result life can seldom be much further prolonged by alternating treatment in this way.

Irradiation is the treatment of choice. The rays may be applied to the bones or the spleen, or both, though there is some evidence that radiation is most effective when applied over the spleen. The best results appear to be obtained with small doses frequently repeated. Treatment is stopped when the white count has fallen to about 15,000, as the fall may continue for 2 or 3 weeks after cessation of treatment; it should be resumed whenever the white count rises above 50,000 cells per c.mm. Radioactive phosphorus may be used instead of Roentgen rays, though it appears to be inferior in value. An initial dose of 1 to 2 millicuries intravenously is followed by 4 doses of 0.5 to 1.0 millicurie at 3 or 4 days' interval, and then 0.5 to 1.0 millicurie is given weekly until the leucocyte count has fallen to 30,000 per c.mm.

Other forms of chemotherapy have been displaced by Myleran (1:4-dimethanesulphonyloxybutane) which has a specific action in depressing the production of granulocytes. Treatment, which is given by mouth, is begun with a dosage of 4 to 6 mg. a day, and if a favourable response is obtained, this may later be reduced and a maintenance dose determined. Thrombocytopenia may develop, even with therapeutic doses, and it is essential to examine the blood weekly until the dosage has been stabilised; the marrow should also be examined at intervals as there is some risk of aplasia. Hormone therapy with corticotrophin or cortisone is of no value in chronic myeloid leukæmia. With successful radiotherapy or chemotherapy, the hæmoglobin

and red cells return spontaneously to more normal levels; iron and transfusion may be useful in accelerating recovery.

## 2. CHRONIC LYMPHATIC LEUKÆMIA

**Synonym.**—Chronic Lymphocytic Leukæmia.

**Definition.**—A chronic overgrowth of the lymphatic tissue throughout the body, accompanied by an increased number of lymphocytes in the blood.

**Ætiology.**—The disease is one of middle and later life, and is hardly ever met in children. The average age of incidence is 60, over 10 years later than chronic myeloid leukæmia. Males are affected about twice as often as females.

**Pathology.**—Post mortem, the striking feature is the enlargement of the lymph glands and other lymphoid tissues. The glands are seldom larger than a walnut, discrete, homogeneous and pinkish grey on section. The lymphoid tissue of the pharynx is hypertrophied, and lymphoid nodules may be present in the intestines, the kidneys and elsewhere. The liver and spleen are uniformly enlarged, the bone-marrow is hyperplastic and grey or greyish red in colour.

**Symptoms.**—The disease may be present for months or years before the patient feels it necessary to consult a physician. Swelling of the glands is usually the first symptom to attract attention, or the patient may complain of increasing tiredness and loss of weight. Less frequently enlargement of the tonsils is first noticed, or enlarged glands and spleen are discovered by chance during a routine examination. In exceptional cases a tumour extirpated by the surgeon is found to be a lymphoma, and subsequent examination of the blood reveals chronic lymphatic leukæmia. Other early symptoms are itching eruptions of the skin, and impotence.

In typical cases all the superficial lymph glands are enlarged. The enlargement is moderate and the glands are rarely so big as in Hodgkin's disease or lymphosarcoma. They are freely movable and not adherent to one another, moderately hard and do not alter in consistence during the course of the disease. Spontaneous fluctuations in their size may occur. In atypical cases only one group of glands may be enlarged. The tonsils may be hypertrophied, the spleen is nearly always palpable, though it does not often extend more than a hand's breadth below the costal margin, and the liver is enlarged. Tenderness of the sternum or of the long bones is unusual. Hyperplasia of the lymphoid tissue in various parts of the body may lead to the formation of tumours or other unusual symptoms. Nodular lesions, infiltrations and actual tumours may develop in the skin. Enlargement of the thymus and the mediastinal lymph glands may produce the signs of an intrathoracic tumour. Lymphomata may develop in the breast or other organs. The salivary and lacrimal glands may be symmetrically enlarged, producing one of the varieties of Mikulicz's syndrome.

**The blood.**—The red cells and hæmoglobin are unaffected in the early stages, but later severe anæmia develops, with anisocytosis, polychromasia and nucleated red cells. The platelets are unaffected till the end, and hæmorrhage is rare. The total white count is increased, usually to about 200,000 cells per c.mm., but not to the high level seen in chronic myeloid leukæmia. Lymphocytes predominate and may constitute 95 to 99 per cent. of the white cells. The majority are small lymphocytes, though a few large lymphocytes are nearly always present. The nuclei may be more deeply indented than normal, and azur-granules are usually absent. The absolute number of polymorphs is unaltered, and no myelocytes are present. It is probable that the proliferation of lymphoid tissue in the glands and elsewhere may precede by some time the increase of lymphocytes in the blood-stream. In rare cases the blood is normal when the patient first comes under observation, but later the characteristic picture develops (*aleukæmic leukæmia*); or the total white count may not be increased, though there is a high percentage of lymphocytes (*leucopenic leukæmia*).

**Diagnosis.**—Only in the rare aleukæmic cases is diagnosis difficult. Points of

importance are the generalised enlargement of the lymph glands, their uniform consistence and moderate size, and the enlargement of the liver and spleen. Biopsy of a gland or sternal puncture may assist.

**Prognosis.**—The disease is invariably fatal. The average duration is  $3\frac{1}{2}$  years from the onset, or about 18 months after coming under treatment. A few cases are more chronic, and exceptionally life may be prolonged for 10, 15 or 20 years. Death occurs from cachexia, hæmorrhage or most commonly from intercurrent infection, sepsis being a very dangerous complication. It is doubtful whether treatment greatly modifies the course of the disease.

**Treatment.**—Roentgen rays should be applied to the lymph glands if the enlargement is troublesome. Radioactive phosphorus, general irradiation or irradiation of the spleen is rarely as effective as in chronic myeloid leukaemia; it may be followed by depressing reactions and is often better avoided if the patient is maintaining a reasonable level of hæmoglobin. The hormones corticotrophin and cortisone are less effective in chronic than in acute lymphatic leukaemia; they are most useful in cases complicated with skin eruptions or with a hæmolytic type of anæmia. The chemotherapeutic drugs, nitrogen mustard and its derivatives, tri-ethylene-melamine and urethane should theoretically be of value but they have likewise proved rather disappointing; they are particularly indicated in the later stages when there is widespread infiltration. Transfusion has been the most useful therapy in the author's experience and it may be followed by a sustained improvement. If the effect of transfusion is not well maintained, hypersplenism should be suspected and splenectomy may be contemplated, but operation is not justifiable in cachectic patients. In all forms of leukaemia, and especially in chronic lymphatic leukaemia, it is important to assess therapy in terms of its effect on the patient as a whole and not merely on the disordered white cells.

### 3. ACUTE LEUKÆMIA

**Ætiology.**—The two sexes are approximately equally affected. Acute lymphatic leukaemia is most common in the first 5 years of life; the incidence then falls and about age 20 reaches a uniform level comparable with that of the myeloid and monocytic forms. Acute myeloid and acute monocytic leukaemia are fairly evenly distributed over the decades.

**Symptoms.**—The onset is usually abrupt and more than half the cases begin with symptoms regarded as a cold, influenza or bronchitis; it is only when the infection fails to respond to treatment and the patient remains prostrated that a more serious disease is suspected. Other early symptoms are ulcerative stomatitis, or tonsillar enlargement with sore throat, and some cases first come under the physician's care after a prolonged hæmorrhage from tonsillectomy, dental extraction or some trifling operation, which has left the patient exsanguinated. The course of the disease varies from fulminating cases in which the patient succumbs within a week, through cases of average acuteness with a duration of less than 2 months, to subacute cases which shade indefinitely into chronic leukaemia. Usually the rapid development of anæmia, weakness and loss of weight soon compels the patient to take to his bed. He complains of sore throat, headache and pain in the bones. The temperature becomes high and purpuric manifestations set in, which aggravate the anæmia or bring the patient's sufferings to an abrupt termination by loss of blood or cerebral hæmorrhage.

On examination the extreme pallor and the enlargement of the superficial lymph glands, especially those in the neck, first attract attention. The pallor is most striking when there are in addition purpuric hæmorrhages into the skin, varying in extent from a pinpoint to large patches which may break down and ulcerate. The size of the spleen varies; usually it is easily palpable, but it may not be felt, or it may be greatly enlarged. The liver may be enlarged. The lungs may show bronchitis,



broncho-pneumonia, or pleurisy, with or without effusion. Pericarditis and endocarditis may occur. The mind usually remains clear to the end. Certain symptoms may be so prominent as to colour the whole clinical picture and give a special aspect to the disease. In the anginal type, there is necrotic ulceration of the tonsils or other areas of the buccopharyngeal mucous membrane, or bleeding from the gums, complicated by secondary infection. In the hæmorrhagic type, purpura and hæmorrhages are the predominant features, and the disease may be mistaken for purpura hæmorrhagica. There may be hæmorrhage from any of the mucosæ, and in one of my cases there was so much blood in the urine that firm clots formed in both pelves and ureters, leading to death from suppression of urine. Disturbances of vision or deafness may result from hæmorrhage into the retina or the labyrinth. The fever and slight splenomegaly may be suggestive of some systemic infection, and there may be leucopenia and an eruption resembling the rose spots of typhoid fever. Bone pains may suggest the diagnosis of acute rheumatism, and there may even be serous effusion into the joints.

In the more subacute forms of the disease, tumours may develop in various parts of the body. They are composed of undifferentiated white cells and infiltrate the surrounding tissues like a malignant growth. Plum-coloured nodules appear in the skin or in the gastro-intestinal tract, in the latter situation leading to vomiting or profuse diarrhœa, often blood-stained in character, or to intussusception of the bowel. In the abdomen or in the mediastinum large growths may develop from the lymph nodes or the thymus, compressing and infiltrating the adjacent structures. Tumours of the bones have been distinguished by the special title of *chloroma*, owing to the greenish colour sometimes seen in the freshly cut surface of the growth. They have a predilection for the subperiosteum of the orbit, and cause headache, deformity of the temporal and frontal bones, exophthalmos, proptosis, papillædema and swelling of the veins of the head, neck and face. They may, however, occur in other parts of the skeleton, and sometimes seem to arise within the bone, which is expanded over them in a brittle shell. The spinal meninges may be invaded, with consequent transverse myelitis, while infiltration of the nerve roots leads to peripheral nerve palsies. It is a curious feature of these neoplastic phenomena that they often begin with a very atypical blood picture, the total white count not being greatly increased and in rare cases the differential count being normal at the onset, though the typical blood picture of leukæmia appears later.

**Hæmatology and Pathology.**—The outstanding feature of the blood in acute leukæmia is the presence of a large number of mononuclear cells of a primitive type, except in rare cases of acute lymphatic leukæmia, in which the predominant cells may be typical lymphocytes. The classification of the cells is not easy and sometimes they are too primitive to be identified. Figures for the incidence of the different types of acute leukæmia in recent series are 40 to 55 per cent. lymphatic, 25 to 33 per cent. myelogenous, and 20 to 25 per cent. monocytic. The total white count is rarely high in the early stages of the disease, usually not exceeding 25,000 to 30,000 per c.mm., but, as a rule, there is a rapid rise to 100,000 or more before the termination. Primitive cells constitute 90 per cent. or more of the white blood cells. Sometimes the total number of white cells is diminished and the count may be below 1000, the majority of the cells being myeloblasts. Such *leucopenic* cases are very prone to necrotic ulcerations and infectious complications. Much more rarely both the total and the differential white count are normal at the onset of the disease, as if the morbid process had not yet invaded the blood-stream—*aleukæmic leukæmia*. The overgrowth of the primitive white cells in the marrow and the hæmorrhages soon lead to a profound anæmia, usually of a normocytic type. The number of platelets is diminished in almost all cases, and sooner or later this is reflected in the hæmorrhagic character of the disease. The bleeding-time is prolonged, the tourniquet test is positive, and the clot may not retract well.

The post-mortem findings vary only slightly from those of chronic leukaemia. There is diffuse hyperplasia of the leucopoietic tissues in the marrow, lymph glands and spleen, and all the tissues are infiltrated with myeloblasts, which may form nodules or tumour-like masses in various situations. Terminal hæmorrhagic and infectious lesions are rarely absent.

**Diagnosis.**—Acute leukaemia may simulate a number of diseases, among which may be mentioned the severe systemic infections, septic or diphtheritic inflammation of the mouth and throat, scurvy and the hæmorrhagic diseases, and malignant disease or tumours of bone. Usually the blood picture will be decisive, but the possibility of agranulocytosis or of septic infection should be remembered in cases in which only a few immature white cells are present in the blood. Glandular fever may cause confusion in the early stages, but the benign course and the absence of anæmia and hæmorrhages will soon differentiate it from leukaemia; in doubtful cases the heterophil antibody reaction, a serological test which is positive in glandular fever and negative in leukaemia, may be employed. The blood picture in acute leukaemia is sometimes suggestive of pernicious anæmia, but the other symptoms of that disease and its favourable response to liver are absent; examination of a bone-marrow smear obtained by sternal puncture is decisive.

**Course and Prognosis.**—Few diseases are more tragic than acute leukaemia, as it is invariably fatal and it so often affects lives which seemed full of promise. Onset at an early age, high fever and great immaturity of white cells, all point to a speedy fatal issue. Death often comes by intercurrent infection, especially in the leucopenic cases, or as a result of hæmorrhage. Rarely the disease may pass into a subacute or chronic form, and death be postponed for a year or longer. The average duration of life is about 6 months; in childhood about 50 per cent. die within 4 months and about 10 per cent. live for as long as 11 months. One of the most remarkable features of the disease is the occurrence of spontaneous remissions, often following some intercurrent infection. Remissions are described as complete, when both the clinical condition and the bone-marrow return to approximate normality, and partial, when the clinical condition is normal but the bone-marrow remains obviously abnormal. Remissions may last from a few weeks to a few months. The frequency of spontaneous remissions in the untreated disease is difficult to ascertain, but almost certainly less than 10 per cent. The aim of treatment is to provoke and maintain remissions.

**Treatment.**—The basic treatment of acute leukaemia consists of transfusion to relieve the anæmia and penicillin or other antibiotics to check infection. Exchange transfusions were used for a time, as they may initiate remissions, but it is now believed that the same effect may be produced with less disturbance of the patient by ordinary transfusions plus cortisone.

More active treatment raises difficult ethical questions and it should be made clear to the relations, before embarking on active treatment, that there is no question of cure but merely of a short prolongation of life and that the side-effects may be distressing. Active treatment may be of two kinds. The first is hormone therapy with corticotrophin or cortisone in doses sufficient to produce hypercortisonism. The second is chemotherapy with antagonists to folic acid or the purines. The chemicals most commonly used are aminopterin in a dosage of 0.5 to 1.0 mg. daily and amethopterin in a dosage of 3 to 5 mg. daily. Treatment is continued till either remission is produced or toxic symptoms appear; treatment is then suspended for the time or a maintenance dose may be determined. The folic-acid antagonists are extremely toxic and their use should be confined to the expert. Toxic effects may be partially reversed by the administration of folinic acid.

With either form of therapy partial or complete remissions are obtained in rather less than half the cases in children; in adults remissions are rarely obtained. The best results are obtained in the lymphatic type, particularly the subacute leucopenic

form; acute myeloid leukaemia reacts in only a small proportion of cases and acute monocytic rarely if at all. The average duration of remissions is about 2½ months. When relapse occurs, the attempt may be made to provoke a second remission with the same drug, or if this fails, to alternate chemotherapy and hormones. Sooner or later a cell population develops which is resistant to all forms of therapy and the patient dies. By active therapy the 12-months' survival rate has been raised from approximately 5 to 30 per cent. Radiotherapy is contraindicated in acute leukaemia; it aggravates the low neutrophil and platelet counts and does not produce a remission.

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## BLOOD COAGULATION

When normal blood is shed, it forms a firm fibrin clot in 5 to 10 minutes. The appearance of this clot is the last stage in a series of reactions—the clotting mechanism—which has been the object of intensive research since 1905. It has given rise to a number of increasingly complex theories and hypotheses, as more and more phenomena occurring in the course of coagulation have been described, and often variable interpretations attached to them. The basic outlines of the coagulation mechanism are contained in the "classical" theory of Morawitz (1905), and are now generally accepted, but the important discoveries of more recent years, including anticoagulant drugs, have necessitated modifications of this simple scheme.

Blood clot results from the conversion of the globulin fibrinogen to fibrin by thrombin, a protein which can be obtained from plasma in fairly pure form. This reaction is probably enzymatic and may be due to the polymerisation of fibrinogen molecules. Thrombin is not naturally present in normal blood, and is formed quantitatively during the clotting process from its precursor, prothrombin. It is in the reactions involved in the conversion of prothrombin to thrombin that the most important new advances have been made, and this stage in the clotting mechanism is the important one in studying the actions of anticoagulant drugs; of the coumarin type.

It has long been known that calcium is necessary for blood coagulation, and that tissue extracts greatly accelerate the clotting of citrated or oxalated plasma in its presence—from a clotting time of several minutes to 15 seconds or less. Active extracts can be prepared from most tissues, notably brain, lung and placenta, and are called tissue thromboplastin. The basis of the classical theory (Morawitz) is that such thromboplastin converts prothrombin to thrombin in the presence of calcium. This tissue thromboplastin probably acts as a catalyst, and a constant constituent of it is a lipoprotein of high molecular weight.

It has long been known that platelets play some part in the initiation of clotting, and Quick (1947) and Brinkhouse (1947), working with hæmophilic plasma, suggested that a factor from platelets acted on antihæmophilic globulin, to form blood thromboplastin. That these two factors—platelet factor and antihæmophilic globulin—are necessary for the formation of thromboplastin in blood is now clear, but additional important clotting factors in plasma and serum have been described which modify and extend the classical theory, and throw much light on the problem of how blood itself may form a potent thromboplastin. Of these new factors, the two most important are generally called factor V and factor VII. Factor V is found in normal plasma, is very labile on storage, is not adsorbed by inorganic precipitates and disappears in the course of clotting, i.e. it is not found in normal serum. In its absence, the conversion of prothrombin to thrombin in the presence of tissue thromboplastin and calcium occurs more slowly than normally, and it has generally been regarded as an accelerator of prothrombin conversion. Factor VII, of greater importance in the study of anticoagulant drugs, is found in high concentration in normal serum, and is

probably formed from a precursor in the plasma by contact with a foreign surface; it is stable on storage, and is adsorbed by  $\text{Al}(\text{OH})_3$ ,  $\text{BaSO}_4$  and  $\text{Ca}_3(\text{PO}_4)_2$ ; it increases the activity of brain thromboplastin, and, like factor V, has been regarded as an accelerator of prothrombin conversion to thrombin. Vitamin K is probably necessary for the formation of factor VII, and of prothrombin.

It is now known that under certain conditions, such as contact with a foreign surface, blood generates thromboplastin in which platelets and antihæmophilic globulin are constituents, and which converts prothrombin to thrombin in the presence of factor V, factor VII and calcium. Until 1953, the action of intrinsic blood thromboplastin was thought to be weak in view of the relatively long clotting time of normal whole blood or plasma compared with the greatly accelerated clotting time of plasma when tissue thromboplastin is added. It has now been shown by Biggs, Douglas and Macfarlane (1953) that a very potent thromboplastin is generated from a mixture of the above blood factors in optimal amounts, viz. platelet factor, antihæmophilic globulin, factor V, factor VII and calcium, together with another serum factor called Christmas factor (from the name of a family that lacked it) which in its chemical properties resembles factor VII and physiologically resembles antihæmophilic globulin. This blood thromboplastin can clot recalcified plasma in 10 to 15 seconds, i.e. it is as potent as any tissue thromboplastin, but its generation in the mixture of factors is delayed for 3 to 8 minutes; hence in all probability, the delay in the clotting time of normal blood. If any one or more of these factors is deficient, the thromboplastin generated is greatly reduced in quantity. Lack of antihæmophilic globulin delays thromboplastin generation, with consequent prolongation of the whole blood clotting time. Deficiency of the other factors, e.g. factor VII, can impair the process without affecting the clotting time, unless the deficiency is extreme.

It is now possible to draw up a more detailed scheme of the clotting mechanism, showing the generation of blood thromboplastin from its constituents, with the consequent conversion of prothrombin to thrombin. Thrombin, once formed, also accelerates the generation of blood thromboplastin. Tissue thromboplastin is equivalent in its action to a mixture of platelet factor, antihæmophilic globulin and Christmas factor. Factors V and VII, the accelerators of the action of tissue thromboplastin, are necessary constituents of blood thromboplastin. Accurate laboratory methods are available for the qualitative and quantitative determination of deficiencies in all these factors, and play a big part in the study of hæmorrhagic diseases and the action of anticoagulant drugs.

**ACTION OF ANTICOAGULANTS OF THE COUMARIN TYPE ON BLOOD COAGULATION.—**The one-stage "prothrombin" test (Quick) was based on the classical theory of Morawitz, the reaction taking 10 to 15 seconds and the end-point being the formation of a fibrin clot. It was suggested that if all the other factors were present in optimum amounts the time taken to form a clot depended on the amount of prothrombin present. This test has proved valuable in clinical work and it is usual to keep the "prothrombin" time of plasma of patients under treatment with coumarin type anticoagulants at two to three times the control clotting time.

Recent work has shown that it is factor VII which is principally affected by the action of the coumarin type anticoagulants and the mode of action is by impairing blood thromboplastin generation. The concentration of prothrombin in the blood is also reduced by the drugs, but only to 30 to 60 per cent. of normal as measured by the two-stage method of Biggs and Macfarlane. These amounts of prothrombin are perfectly adequate for normal blood coagulation, and it is therefore unlikely that anticoagulants produce their therapeutic benefit by this action. The one-stage "prothrombin" test is a sensitive measure of factor VII concentration, and as factor VII reduction is responsible for the therapeutic effects of anticoagulants, the test remains satisfactory for routine clinical use.

R. B. HUNTER.

## THE HÆMORRHAGIC DISEASES

## A. DISTURBANCES OF BLOOD COAGULATION

The hæmorrhagic diseases may be arbitrarily classified into those which are due to defective coagulation of the blood, of which hæmophilia is the typical example, and those in which the blood clots normally, of which purpura is the typical example. Blood clots are dissolved by ferments known as fibrinolysins.

It is doubtful whether the clotting process is ever affected by shortage of calcium, as this would produce other serious manifestations first. Fibrinogen has to be reduced to a fifth of the normal value before effects on coagulation are seen. Deficiency of this degree is seen in the rare congenital disorder, *congenital afibrinogenæmia*. Acquired fibrinogen deficiency has been described as an acute phenomenon in childbirth and after the operation of lobectomy; it is attributed to sudden defibrination of the blood by the absorption of thromboplastic material into the circulation. A few cases of disturbance of coagulation by naturally occurring anticoagulants have been described. The only two important conditions in which coagulation is impaired are hæmophilia and hypoprothrombinæmia. In hæmophilia the blood clots normally on the addition of thromboplastin; the word hæmophilia should be strictly confined to hereditary hæmorrhagic disorders of this type and words like pseudo-hæmophilia and para-hæmophilia should be avoided. In hypoprothrombinæmia the blood does not coagulate normally even in the presence of an excess of thromboplastin.

## 1. HÆMOPHILIA

**Definition.**—A hereditary disease of males, characterised by a tendency to uncontrollable hæmorrhage and a great prolongation of the coagulation time.

**Ætiology.**—The disease is inherited by the law of Nasse, according to which it is transmitted only by females and manifested only by males. In Mendelian terminology it is a sex-linked recessive; theoretically it might be expected to occur in females in the proportion of 1 to 200 affected males, and in a small number of cases it has been convincingly demonstrated in females. True hæmophilia occurs sporadically in children without previous family history in about 25 to 30 per cent. of the total cases recorded. There is no reason to believe that the sporadic condition differs from the inherited. It is probably due to a mutation, so that either hæmophilic males or female transmitters may arise *de novo*. The latter is the commoner explanation and the mother of a boy with the sporadic form of hæmophilia should be warned that other sons will probably be affected. Hæmophilia is the commonest of the hereditary hæmorrhagic disorders, and its occurrence in the royal households of Europe has made it generally known.

**Pathology.**—The disease is due to inadequate release of thromboplastin. In classical hæmophilia (Hæmophilia A or Hæmophilia I) this is due to deficiency of antihæmophilic globulin but a variant is now recognised (Hæmophilia B or Hæmophilia II) due to shortage of another factor in the plasma, which was called "Christmas factor" after the name of the patient in whom the condition was first diagnosed.

**Symptoms.**—The disease usually manifests itself in early life, but not at birth, so that there is no excessive hæmorrhage from the cord. Severe bleeding at circumcision is common, and in 60 to 70 per cent. of recorded cases the disease was recognised before the second year. It is doubtful whether the bleeding is ever spontaneous, and there is no purpura, but excessive hæmorrhage may occur from a mere scratch, and great bruises or ecchymoses from trivial injuries. Some patients cannot use a toothbrush on account of bleeding from the gums. Epistaxis is common, but internal bleeding is unusual, though hæmaturia, melæna and hæmatomyelia have been

described. Trauma and dental extraction are the most usual causes of severe hæmorrhage, and a rick of the muscles which would pass unnoticed in an ordinary boy may lead to an extensive intramuscular hæmorrhage which leaves the patient exsanguinated. The bleeding is not so much severe as persistent; hence it is rare for the hæmophilic to die of a sudden profuse hæmorrhage, he rather fades out of life owing to the inability to stop the slow continued loss of blood.

The most remarkable form of hæmorrhage, and one which is common, is into the cavities of the joints. The joints which suffer most often are the knees and elbows, but any joints may be affected. The swelling and effusion take place with great rapidity, and with a great deal of pain. The joint is hot, tender, reddened and the surrounding tissues swollen. The temperature is raised to 101° or 102° F. The effusion is almost pure blood, but as absorption proceeds it becomes a dirty brown colour, which stains the synovial membrane and the cartilages of the joint. It is sometimes absorbed rapidly, and the joint restored to complete mobility. When absorption is slow or effusions repeated, contraction and ankylosis may cripple the patient permanently. In a joint often affected, there is always considerable destruction of the cartilages and of the ligaments, with the result that the bones are exposed and undergo changes resembling those of osteo-arthritis. Osteophyte formation is however, rare, and so is bony ankylosis. Fibrous ankylosis is, on the other hand, common. The spleen is not palpable.

**Diagnosis.**—The diagnosis is based on the family history and on the delayed coagulation of the blood; the cytology and chemistry of the blood are normal. Special laboratory tests are available, such as the prothrombin consumption and the thromboplastin generation, with which the diagnosis can be confirmed with practical certainty in cases of doubt. The joints are sometimes mistaken for tuberculous joints. A more serious error is to incise a hæmatoma on the mistaken diagnosis of an abscess. Hæmophilia should be differentiated from other hereditary hæmorrhagic states and from acquired conditions, such as essential thrombocytopenia.

**Prognosis.**—It is said that less than 12 per cent. of hæmophiliacs survive to puberty, but the disease undoubtedly becomes less severe in later life, though still present. A peculiar feature of the disease is its variability, the blood at times clotting almost normally, at other times seeming almost incoagulable, and if the patient survives a severe hæmorrhage there is often a temporary improvement in the blood.

**Treatment.**—Treatment is unsatisfactory, and it is much better to try to stamp out the disease by discouraging the reproduction of affected families. The only members of a hæmophilic family who can safely beget children are the unaffected males. Sufferers from the disease should be protected from trauma as far as possible, and operations should be discouraged unless they are essential to life. It is wise to admit the patient to hospital for minor operations, such as dental extraction, and not more than two or three teeth should be taken out at a time. If hæmorrhage from trauma or dental extractions persists, transfusion is the best general treatment. In local treatment a purified thrombin or snake venom may be used, and it is now possible to repair wounds which would previously have been fatal. Purified thrombin can be applied either as a powder or in solution. It can also be used in conjunction with fibrinogen or fibrin; thus a bleeding tooth socket may be filled with fibrin foam which has been moistened with thrombin. The venom of Russell's viper (1 in 10,000 solution) or of the Australian tiger snake (1 in 5000 solution) has also been used. The loose clot is washed away from the bleeding point with hot water, and tampons or other appropriate dressings soaked in the venom solution are then applied. When cavities have to be packed, an absorbable material, such as oxidised cellulose, may be used. Devitalisation of tissues by local anæsthetics, cauterisation or excessive pressure should be avoided. It is better for the patient to bleed externally than into the tissue planes. Threatened asphyxia from bleeding into the tongue or the tissues of the neck is not an uncommon accident and it is better treated by intubation than by tracheotomy.

## 2. HYPOPROTHROMBINÆMIA

The term hypoprothrombinæmia is now known to include not only conditions in which prothrombin is deficient but also conditions in which certain closely associated factors (Factor V and Factor VII) are deficient. Hypoprothrombinæmia is recognised by the fact that the blood does not coagulate normally even in the presence of an excess of thromboplastin. Prothrombin is formed in the liver under the influence of the fat-soluble vitamin K. Prothrombin deficiency may therefore occur under the following circumstances:

- (i) Deficient intake of vitamin K in states of extreme malnutrition.
- (ii) Deficient absorption of vitamin K in intestinal diseases and in fatty diarrhoea, as in obstructive jaundice, coeliac disease and sprue.
- (iii) Deficient utilisation of vitamin K when the liver parenchyma is diseased.
- (iv) Depression of formation of prothrombin by the specific action of dicoumarol and similar anticoagulants.
- (v) In the newborn (*melena neonatorum*), see below.

Hypoprothrombinæmia can be prevented or treated by the administration of vitamin K, except in cases where the liver parenchyma is diseased. Failure to respond to treatment with vitamin K in a case of jaundice is a strong indication of hepatic damage. Transfusion is relatively ineffective in raising the level of prothrombin, even though large amounts of fresh blood or plasma are given. Vitamin K is commonly given in the form of one of the water-soluble compounds such as menadione, Sodium Bisulphite (U.S.P.) or one of the similar proprietary preparations. Dosage varies with the particular preparation but is of the order of 5 to 30 mg. daily. In over-dosage with dicoumarol and similar drugs the water-soluble preparations of vitamin K may have no effect and the patient should be treated with vitamin K<sub>1</sub> by mouth in a dosage of 10 to 50 mg., which may be repeated at intervals of 4 to 6 hours if the prothrombin does not show a satisfactory increase.

## 3. MELÆNA NEONATORUM

**Synonym.**—Hæmorrhagic Disease of the Newly-born.

**Ætiology and Pathology.**—The blood is cytologically normal and the condition is essentially due to hypoprothrombinæmia. Both the bleeding time and the clotting time may be greatly prolonged. The incidence has been placed as high as 1 per cent. of all births, male and female. Heredity seems to play no part. In some cases acute gastric and duodenal ulcers have been found at autopsy, but it is more probable that these represent necrosed areas from submucous hæmorrhages than that they are the cause of the bleeding.

**Symptoms.**—The bleeding is spontaneous, commencing at any time in the first week or two of life, most commonly on the third or fourth day. The bowel is the usual site of hæmorrhage, but blood may also ooze from the mouth, nose and urinary tract, or be extravasated into the viscera or the cavities of the body. If the disease is not immediately treated, death from hæmorrhage and shock soon occurs.

**Diagnosis.**—This can be confirmed if necessary by estimating the prothrombin time. Hæmorrhagic states may occur in the newborn as a result of sepsis, syphilis, thrombocytopenia and other blood dyscrasias, but all are rare.

**Prognosis and Treatment.**—The prognosis depends on the promptitude of the treatment and the amount of blood already lost. Hæmorrhagic disease can be prevented by giving the mother 25 mg. menaphthone or 50 mg. acetomenaphthone at the beginning of labour; or by giving the baby 5 mg. of menaphthone as soon as possible after birth. If the baby is not seen until the disease has developed, an immediate transfusion of fresh blood should be given, or if this is difficult, 10 to 15 ml.

of fresh blood may be injected subcutaneously. Owing to the risk of sensitisation to the Rh factor, female children should be typed and given blood of the same group except in the direst emergency. At the same time 5 mg. menaphthone in oil may be injected intramuscularly or 2 mg. menaphthone sodium bisulphite subcutaneously. During treatment the infant is kept as quiet as possible and not lifted from the cot. He can be fed by a bottle or spoon with breast milk, or if necessary, with an artificial food.

## B. PURPURA AND ALLIED DISORDERS

In the narrow sense purpura refers merely to the occurrence of bleeding in the skin in the form of petechiæ, macules or larger areas. In the wider sense it connotes a group of diseases which are characterised not only by these cutaneous lesions but also by bleeding from the mucosæ and internally. Purpura can be conveniently classified into thrombocytopenic and non-thrombocytopenic forms, but it should be noted that factors which reduce the platelet count commonly damage the capillary endothelium as well. Hæmostasis appears normally to occur in two stages, first, contraction of the damaged vessel, and second, occlusion by thrombosis. In all the purpuras, whether thrombocytopenic or non-thrombocytopenic, the first stage of hæmostasis appears to be at fault, the capillaries do not retract properly when they are injured and the bleeding time is prolonged. In hæmophilia the second stage is at fault and though hæmostasis begins normally, bleeding recurs after a short interval.

*The blood platelets.*—The platelets are the third formed element in the circulating blood. They are spherical or oval, non-nucleated disks, with an average diameter of 2 to 3 microns, and with a hyaline cytoplasm which contains numerous granules. The average number of platelets is from 250,000 to 450,000 per c.mm., but there are great variations in health and according to the method of estimation employed. The platelets are believed to be produced by the megakaryocytes in the bone-marrow, and after a life of a few days they are phagocyted by the cells of the reticulo-endothelial system. Large numbers of platelets are present in the spleen, but it is not certain whether they are held there in reserve or in process of destruction. The platelets play an important part in the arrest of hæmorrhage, sealing wounds in the endothelial lining of the vessels, promoting the coagulation of the blood and securing the firm adhesion of the clot. Purpuric symptoms commonly appear when the blood platelets fall below 40,000 per c.mm. The following signs may also be observed in thrombocytopenic purpura: 1. The platelets are very variable in size and shape, and giant platelets may be present. 2. The blood clots in the normal time, but the clot does not retract and express the serum as rapidly and completely as in health. 3. The bleeding-time is greatly increased. If the blood from a sharp prick in the finger is soaked off with a filter paper without pressure every 30 seconds, bleeding normally ceases in 1 to 2½ minutes, but if the platelets are defective it may be prolonged even to an hour or more. 4. The capillaries are more fragile than normal. The sphygmomanometer is applied to the upper arm and the pressure is maintained midway between the systolic and diastolic level for 5 minutes. When the platelets are defective, a coarse purpuric rash may appear on the lower arm.

An increased number of platelets or thrombocytosis occurs after hæmorrhage, trauma, operation or childbirth and favours the development of thrombosis. There is a rare condition known as *essential thrombocytosis* or *idiopathic thrombocythæmia* in which a hæmorrhagic tendency is associated with enlargement of the liver and spleen and high platelet counts, often over 1 million per c.mm. This is a variant of the conditions previously referred to as non-leukæmic myeloid splenomegaly (p. 748). In rare cases, but more particularly in leukæmia and allied conditions, the platelets may be normal in number but inadequate in function; the bleeding-time is prolonged, the clot retraction is poor and the prothrombin consumption is reduced. This is classified as thrombocytopathic purpura. In exceptional cases this may occur



as a hereditary abnormality, also known as *hereditary thrombasthenia* or *Glanzmann's disease*. It should be noted, however, that the majority of the hereditary purpuras are the result of a capillary defect and the platelets are normal.

*The endothelium.*—A hæmorrhagic tendency due to a pure endothelial lesion is characteristic of scurvy, in which the plasma and the platelets are normal but the fragility of the capillaries is much increased. The same is true of the purpura of old age and nervous purpuras, such as stigmatisation. When hæmorrhagic states are due to lesions of the capillaries, plasma may also pass through the endothelial lining, producing wheals, local œdema of the tissues and urticaria, and the purpuric areas may be elevated above the surrounding skin.

*Symptomatic hæmorrhagic states.*—In hospital practice purpura and allied states are about six times as common as coagulation defects. The majority of these purpuras are secondary to other diseases. Symptomatic thrombocytopenic purpura is commonly caused by infiltration, fibrosis or aplasia of the marrow. It therefore occurs in leucæmia and allied disorders, aplastic anæmia and secondary carcinoma of the bone-marrow. The platelets are likely to be depressed in any condition in which the spleen is enlarged, though the mechanism by which this "hypersplenism" works is not clear. Thrombocytopenic purpura may also occur in association with glandular fever and rubella. Symptomatic non-thrombocytopenic purpura is seen most commonly in the infectious diseases. Purpura and a hæmorrhagic tendency have been observed in infections with the pyogenic cocci, scarlatina, chicken-pox, diphtheria, the enteric fevers, typhus, malaria and gonococcal and meningococcal septicæmia. They are also seen in malignant endocarditis and in tuberculosis, especially the miliary form. In all such conditions we have reason to believe that the endothelial lining of the vessels is damaged. The platelet count is usually normal or slightly depressed. In rare cases it may be diminished, and the combination of thrombocytopenia and vascular damage produces a severe hæmorrhagic disorder which is known as *purpura fulminans*; this has been most commonly described after scarlet fever. Chronic nutritional disturbances and cachexias, such as uræmia and ulcerative colitis, may give rise to purpura and a hæmorrhagic tendency from vascular damage. Purpura of endothelial origin may also occur in conditions in which the plasma is unduly viscid and there is stasis in the peripheral vessels, as in hyperglobulinæmia from multiple myeloma and similar causes. Drug rashes not uncommonly take the form of non-thrombocytopenic purpura. After a number of organic and inorganic poisons, such as the sulphonamides, arsenicals and gold preparations, there may be both endothelial damage and thrombocytopenia.

The treatment of the symptomatic hæmorrhagic states is primarily the treatment of the underlying disease. The only reliable general remedy is the transfusion of fresh human blood. Liver, folic acid and cyanocobalamin are of value in the megaloblastic anæmias only, vitamin C in scurvy and vitamin K in prothrombin deficiency—they are not general hæmostatics. Vitamin P has little or no definable clinical action. For local treatment the measures advised for hæmophilia may be used.

### 1. IDIOPATHIC THROMBOCYTOPENIC PURPURA

*Synonyms.*—Essential Thrombocytopenia; Morbus Maculosus Hæmorrhagicus of Werlhof.

*Definition.*—A disease characterised by multiple hæmorrhages in the skin or from the mucous membranes, a reduced platelet count, a prolonged bleeding-time, but a normal coagulation time.

*Ætiology.*—Some 40 per cent. of the cases occur before puberty and at this age the sex incidence is equal. After puberty females preponderate in the proportion of approximately 3 to 1. Endocrine factors are also suggested by the exacerbation at menstruation and pregnancy and by the occasional association with thyrotoxicosis.

A few cases have been traced to idiosyncrasy for certain foods, such as milk, and for certain drugs, such as quinine or Sedormid. Ingestion of the offending food or drug is followed within a few hours by the onset of thrombocytopenia and purpura. Investigation of some of these cases has shown that the purpura is due to destruction of the platelets by an antibody reaction, in which the drug, complement and a fraction of the patient's plasma take part. Further investigation along these lines has revealed the presence of abnormal antibodies in the active stage of many cases of idiopathic thrombocytopenic purpura unconnected with drugs. These can be demonstrated by special tests for platelet agglutinins and in addition the Coombs test may be positive. Moreover, the plasma of a patient with idiopathic thrombocytopenic purpura may induce thrombocytopenia and purpura when injected into a normal individual. Finally, it may be noted that the child of a mother with idiopathic thrombocytopenic purpura may be born with thrombocytopenia and purpura which pass off in a few weeks. In thrombocytopenic purpura there appears to be a dual defect, firstly an abnormal vascular fragility and secondly an increased destruction of platelets. This dual defect may be explained by the antigenic similarity of the platelets and the capillary endothelium. As previously indicated, there is a link between idiopathic thrombocytopenic purpura and acquired hæmolytic anæmia (p. 747), and in rare cases thrombocytopenic purpura may be a manifestation of disseminated lupus erythematosus. It is appropriate here to mention the very rare syndrome of *thrombotic thrombocytopenic purpura*, in which thrombocytopenic purpura is associated with fever, hæmolytic anæmia and fluctuating neurological disturbances, and widely disseminated thrombi are found in the small vessels at necropsy; this syndrome, which has been fatal in all cases recorded, is likewise thought to be related to the collagen diseases.

A few cases of hereditary thrombocytopenic purpura affecting several children or several generations in one family have been described.

**Pathology.**—The bone-marrow usually contains rather more than its normal complement of megakaryoblasts and megakaryocytes and the younger forms predominate. The spleen shows no pathognomonic changes.

**Symptoms.**—It is customary to describe acute and chronic forms of the disease with the dividing line at 4 months, though this should not be regarded as a hard-and-fast division. The acute form begins suddenly and without warning, though sometimes there is a history of an acute infection a couple of weeks before. There is no pyrexia and the spleen is not palpable. Purpuric patches appear in the skin, of variable size and of irregular distribution. There is no erythema or whealing. Hæmorrhages occur from any of the mucosæ, the nose and mouth, the alimentary canal and the urogenital tract. The slightest injury gives rise to excessive bleeding or the formation of large hæmatomata. The bleeding time is greatly prolonged, and the tourniquet test is positive. Examination of the blood reveals a thrombocytopenia, platelets being perhaps completely absent; there is usually a slight leucocytosis, and immature red cells and even normoblasts may be poured out to combat the anæmia. In favourable cases recovery occurs in a few days or at most a few weeks, and the platelet count returns to normal. This may be the only attack, but in other patients a recurrence months or years later reveals that the disease is present in a relapsing form. In a second group the acute attack merely marks the onset of a chronic form of the disease and treatment by splenectomy ultimately becomes necessary.

The chronic form of the disease, which accounts for 2 out of every 3 cases in adults, may be of a continuous or a relapsing type. In the continuous type, which is the more common, there is persistent thrombocytopenia, with exacerbations of symptoms due to fluctuations of the platelets above and below the critical level of about 40,000 per c.mm., or to the effects of trauma or intercurrent infection. In the relapsing type there are long intervals of freedom during which the platelet count is quite normal. There may be persistent purpura, especially on the legs or the parts

exposed to trauma, or purpura may be completely absent. The spleen may be slightly enlarged. There is a tendency for hæmorrhages to recur from the same site, as if it were an area of predilection, so that one patient may suffer from hæmatemesis, another from hæmaturia, another from menorrhagia.

**Diagnosis.**—The diagnosis depends on the thrombocytopenia and the associated symptoms of platelet shortage, but it should be remembered that the platelets may be normal in the free intervals. The presence of any considerable degree of splenomegaly is a point against the diagnosis of essential thrombocytopenia. Many forms of symptomatic thrombocytopenic purpura are excluded by the examination of the peripheral blood. The marrow should be examined to confirm the diagnosis, and marrow puncture should be regarded as essential before beginning treatment with cortisone or splenectomy. Specific enquiry should be made for the taking of drugs likely to induce thrombocytopenia. Acute leukæmia is an important cause of purpura hæmorrhagica, which should be excluded by the differential white blood count and, if necessary, the marrow smear. Henoch's purpura can commonly be distinguished at the bedside by the presence of toxæmia and joint pains and the characteristic appearance and distribution of the rash; further investigation shows that the platelet count is normal. In the chronic form of idiopathic thrombocytopenic purpura it is rather easy to overlook the possibility of a hæmorrhagic disease altogether, especially when there is no purpura and bleeding is always from one organ. On this account this diagnosis should always be considered in cases of symptomless hæmaturia or hæmatemesis or the like, or ill-advised operations may be performed.

**Prognosis.**—Death may occur in the acute attacks, or irretrievable damage be done, as by hæmorrhage into the vitreous humour of the eye or into the central nervous system. In childhood the disease is usually self-limited and the mortality should not exceed 5 per cent. More than half of the children are better within a month and only in about 1 in 7 cases does the disease run on over 6 months. After puberty the outlook is less hopeful and spontaneous recovery is less frequent, but with modern methods of treatment the mortality should not exceed 15 per cent.

**Treatment.**—In childhood and in mild cases in adults no treatment may be necessary. If the symptoms persist or are severe, an attempt should be made to provoke a remission with corticotrophin or cortisone. Large doses are desirable, e.g. 300 mg. of cortisone a day for 3 weeks in the adult. The hormones may act on the disease in two ways. They may diminish the abnormal fragility of the capillaries and they may increase the platelet count. Unfortunately in many cases they produce only the former of these effects, the platelets remain low and the remission is therefore only partial. No other drugs are known to have any effect on the disease and radiotherapy is of dubious value. The anæmia may require treatment by transfusion.

If the disease is chronic and a satisfactory remission cannot be provoked by cortisone, splenectomy should be considered. Operation is rarely desirable in childhood, as sooner or later nearly all cases remit and experience has shown that expectant treatment is justified. Operation is also rarely desirable in acute cases, where the symptoms should be controlled by cortisone and transfusions. Finally, splenectomy appears to be ineffective in the hereditary form of thrombocytopenic purpura. In chronic cases in adults operation should only be advised if the symptoms are really troublesome, as an appreciable proportion of cases are not benefited by operation. A common indication for splenectomy is menorrhagia and operation should not be unduly postponed if the patient is being exsanguinated by the periods. The result of splenectomy cannot be predicted from the response to cortisone or the Coombs test, but it appears likely to be successful in patients in whom platelet agglutinins are demonstrated.

Apart from cases with splenomegaly and hypersplenism, which do not properly come into the category of idiopathic thrombocytopenic purpura, the mode of action

of splenectomy is obscure. It removes an organ which may be producing abnormal antibodies and it protects the damaged platelets from the destructive action of the spleen. In addition it improves the capillary resistance, though this is probably the non-specific effect of any operation. The operation is usually followed by a great rise in the platelet count; this may be sustained, or it may subsequently fall to a sub-normal level without return of the purpura, or a frank relapse may occur. With proper selection of cases and preparation by transfusions and hormone therapy, the operative mortality should be negligible. There is little risk of interference with wound healing with ordinary therapeutic doses of cortisone. The immediate result is remission in about 85 per cent. of cases but permanent remissions are obtained in only about 66 per cent. Relapses after operation have been attributed to growth of a splenunculus but this is certainly not the only, or indeed the usual, cause. An aortogram may be taken to look for such a splenunculus. If severe menorrhagia persists after splenectomy, hysterectomy should be advised and at the same time a splenunculus should be sought for.

## 2. HENOC'S PURPURA

**Synonyms.**—Henoch-Schoenlein Syndrome; Anaphylactoid Purpura; Hemorrhagic Capillary Toxicosis.

**Definition.**—Although the term Henoch's purpura is sometimes restricted to cases characterised by purpura, colic and gastro-intestinal lesions, it is profitable to extend it to a group of non-thrombocytopenic purpuras, which are of obscure origin, and which may be accompanied by urticaria, œdema, swollen joints and various visceral manifestations. For this reason the milder cases which are known as purpura simplex, and also the peliosis rheumatica or arthritic purpura of Schoenlein are considered under this same heading, for all appear to be manifestations of the same pathological state.

**Ætiology and Pathology.**—The disease is related to allergic conditions, such as erythema multiforme, erythema nodosum, angioneurotic œdema and serum sickness. The lesions probably result from an abnormal permeability of the capillaries, which allow plasma and blood to escape through their walls. The sensitising agent is not always the same. In some instances it is the streptococcus, the attack following a sore throat, or persisting until a septic focus is drained. In other instances sensitisation to foods has been demonstrated, and the disease has been cured by removing them from the diet. Children and adolescents are chiefly affected, the incidence reaching a peak in the teens and falling off abruptly after 30. Seventy per cent. of the cases are males.

**Symptoms.**—The attack is usually preceded by symptoms of general bodily disturbance, such as headache, malaise, loss of appetite and a rise of temperature. In the mildest cases (purpura simplex) a fine purpuric eruption appears, often affecting the limbs rather symmetrically, and with a special tendency to develop round the hair follicles. In the typical Henoch-Schoenlein syndrome the first lesions are small urticæ, which later become dusky-red macules which do not fade on pressure. The lesions have a characteristic and symmetrical distribution—on the backs of the elbows, on the buttocks and lower back, and on the extensor surfaces of the lower legs, ankles and feet. Successive crops may appear. In severe cases there may be extensive, irregularly distributed ecchymoses, and there is much œdema of the face. Wheals and pemphigoid lesions may develop, and careful examination will often show that the purpura is not a pure hæmorrhage, but that it is raised or surrounded by a zone of erythema. Bleeding is not necessarily confined to the skin, but may be subperiosteal, intramuscular or intravisceral. Joint pains are rarely absent, though the joints are seldom much swollen, and there may also be myalgia or neuralgia. The gastro-intestinal symptoms take the form of colic, bilious vomiting and diarrhœa, with blood-

mixed stools. The abdominal wall may be rigid, and it may be difficult to differentiate the lesion from an intussusception, which may indeed occur from invagination of a piece of intestine whose walls have been stiffened by the exudation of serum and blood. Similar lesions occur in the urinary tract, but extensive hæmorrhage from the mucosæ is rare. The spleen may be palpable and the urine may contain albumin, blood cells and casts. In rare instances death has occurred from cerebral convulsions, suggestive of acute uræmia; nephritis is, indeed, the most important complication.

The blood is normal, save for a slight anæmia or a mild leucocytosis. The platelets are normal or only slightly diminished, and the coagulation and bleeding times are normal. The tourniquet test may be positive, but in general there is little tendency to spontaneous or excessive external bleeding, and the mucosal hæmorrhages are small and attributable to oozing from areas of œdema and congestion.

**Diagnosis.**—The disease is not sharply divided from the symptomatic purpuras. It should, however, be clearly differentiated from essential thrombocytopenia and similar blood disorders by the absence of specific changes in the blood, and the presence of signs of toxæmia and increased capillary permeability. Cases with intestinal lesions may closely simulate intussusception, and they may occasionally be complicated by intussusception or peritoneal effusion.

**Prognosis.**—The prognosis depends almost entirely on the presence or absence of complications. Acute nephritis occurs in about 40 per cent. of cases; it is usually a diffuse glomerulo-nephritis and the prognosis is as for that condition. Gross alimentary lesions may give rise to intussusception or perforation. In patients admitted to hospital a mortality of 18 per cent. has been recorded, but the general mortality is probably a good deal lower than this. Usually the disease tends to spontaneous recovery after an illness of a few weeks, though chronic and relapsing cases occur and can be very troublesome. Exceptionally the disease may persist for 2 to 4 years.

**Treatment.**—There is no specific treatment. Corticotrophin and cortisone have proved disappointing and there is no evidence that they modify the course of the illness. Salicylates are likewise disappointing. A short course of penicillin may be given in cases following a throat infection. Nephritis should be treated on the usual lines. Abdominal exploration may sometimes be necessary, but in view of the relapsing nature of the disease it should be avoided if possible.

### 3. HEREDITARY HÆMORRHAGIC TELANGIECTASIA

**Synonyms.**—Hæmangiomas; Rendu-Osler-Weber Disease.

**Definition.**—A hereditary disease characterised by multiple telangiectases, which cause hæmorrhages from various sources, especially the nose.

**Ætiology.**—The disease is a hereditary dystrophy of the capillary system, which is transmitted directly from generation to generation, affecting both sexes equally and behaving as a Mendelian dominant. As in hæmophilia, there is a small proportion of sporadic cases without a family history of the disease.

**Symptoms.**—Epistaxis generally begins in childhood and before any cutaneous telangiectases have been recognised, but it tends to become more frequent and severe with advancing years. The telangiectases are not present at birth, and are sometimes not noticed till middle life. They vary in kind, appearing as dilated venules; spider capillary networks; punctate red or purple spots and blebs; and raised nævi up to an inch in diameter. They are most common about the face, nose and mouth, and the trunk and limbs are generally spared, except for the tips of the fingers. Epistaxis is the common complaint, but external bleeding, hæmoptysis, gastrostaxis, hæmaturia or cerebral hæmorrhage may occur. The blood is normal, except for the anæmia induced by the bleeding.

**Diagnosis.**—This depends on the family history and the presence of telangiectases, and both these may be missed if they are not sought for. Few telangiectases may be visible, and epistaxis or alimentary hæmorrhage may be the presenting symptom. Many cases are first seen by the rhinologist.

**Prognosis and Treatment.**—There is no curative treatment, and death from hæmorrhage occurs in a considerable percentage of the cases. Affected members of these families should, therefore, be strongly advised against having children, as half of their offspring will inherit the disease. Treatment of the nævi by cauterisation or radium is only moderately successful.

#### 4. HEREDITARY CAPILLARY FRAGILITY

**Synonym.**—Von Willebrand's Disease.

**Definition.**—A hereditary disease characterised clinically by an abnormal tendency to bruising and bleeding and pathologically by abnormalities in the morphology and function of the capillaries.

**Description.**—In our experience 60 per cent. of the hereditary hæmorrhagic disorders are accounted for by hæmophilia, 25 per cent. by hereditary capillary fragility and 15 per cent. by hereditary hæmorrhagic telangiectasia; all other forms are extremely rare. Hereditary capillary fragility and hereditary hæmorrhagic telangiectasia can probably be regarded as related genetic defects. In hereditary capillary fragility the tendency to bleed appears in childhood and there may be bleeding from the cord at birth. Bruising, epistaxis, bleeding from the gums and gastro-intestinal bleeding occur and there may be prolonged bleeding after injuries and operations. In women menorrhagia may be the most serious symptom. Petechiæ and ecchymosis may occur but purpura is not very common.

There is a positive family history in over 80 per cent. of reported cases. The sexes are equally affected. In most of the families inheritance is of the simple dominant type and the affected members may pass the condition to their children. The essential abnormal finding on investigation is the prolonged bleeding time. The platelets and the coagulation time are normal. The capillaries may be seen to be abnormal in shape and reaction if they are examined under the capillary microscope. There is no specific treatment though loss of blood may require treatment by transfusion. Splenectomy is useless and dangerous.

L. J. WITTS.

## SECTION X

# DISEASES OF THE SPLEEN AND THE RETICULO-ENDOTHELIAL SYSTEM

## INTRODUCTION

THE spleen is not essential to life since the tissues found in it are also present in other parts of the body. It is, however, important because it contains the largest single mass of lymphatic tissue in the body which is concerned with the filtration of blood, and also because it is the main site of the reticulo-endothelial system. There are a few diseases which are confined to the spleen, but the vast majority which affect it, involve, in addition, other organs. Many of these, *e.g.* diseases of the blood, are fully described in their clinical aspects elsewhere in this volume.

The spleen is a soft reddish-purple organ that shows considerable variation in size although it usually has a length of about 5 in. It has a well-marked hilum through which the main vessels pass. It lies in close relation to the diaphragm, kidney, stomach and left colic flexure and is opposite the ninth, tenth and eleventh ribs behind the mid-axillary line. The spleen moves downwards about 2 in. on deep inspiration but is normally not palpable below the costal margin. When it enlarges it moves downwards and forwards towards the right iliac fossa.

In order to understand some of the difficult and, in many ways, still anomalous diseases of the spleen, it is necessary to consider briefly the structure and functions of the organ. An important general point to realise is that the spleen is made up essentially of lobes, not recognisable in the complex mammalian organ but clearly defined and with a separate end-artery in some lower animals. This lobularity explains abnormalities such as spleniculi (*q.v.*) which are simply isolated lobes or groups of them.

The tissues which make up the spleen are the capsule and trabeculae, the vascular structure, reticulo-endothelial and lymphoid tissues and the hæmopoietic or blood-forming tissues.

**THE CAPSULE.**—This differs from that of a lymph node in that it contains numerous elastic fibres and a few muscle fibres. It is distensible and slightly contractile.

**THE TRABECULÆ.**—These invade the splenic pulp from the hilum and the capsule and possess both elastic and a few muscle fibres.

**THE SPLENIC LOBULE.**—This is difficult to define in man. At the core of the lobule is the central artery which reaches it from the trabeculae. This artery runs in a Malpighian body, some capillaries nourish the Malpighian body—lymphoid tissue—while arterioles extend into the surrounding tissues—red pulp. Before they branch in the pulp their walls thicken and they are then termed sheathed arterioles. These are thickenings of reticulo-endothelial tissues. Thereafter as capillaries the vessels pass into the surrounding venous sinuses. The venous sinuses are drained by the trabecular veins, and the principal trabecular vein drains the lobule.

**CIRCULATION IN THE SPLEEN.**—The exact manner in which the blood circulates in the red pulp is not known with certainty. Some think the endothelial walls of the capillaries are incomplete. Others are of the opinion that they are complete but cells easily pass through the wall. Recent animal studies give a description of the passage of blood through the red pulp and of its filtration by the venous sinuses. Between the Malpighian body and the main trabecular vein draining the lobule there are two groups of sphincters, an afferent group at the sheathed arterioles and at the beginning of the capillaries, and an efferent group in the venous sinuses. If all sphincters are

open whole blood will pass through and the trabecular veins draining the blood sinuses may pulsate like arterioles. If the efferent sphincter is closed, blood flows in and the blood sinuses fill. As the blood fluid is absorbed by the walls the sinus becomes packed with blood cells. This is called filtration filling. A third phase begins with closure of the afferent sphincters. The blood cells contained in the sinuses are then shut off from the blood-stream. Storage may last from a few minutes to several hours. Cells may pass through the walls of the sinuses into the pulp during phase two or phase three. The last phase is emptying, the sphincters suddenly open and masses of blood cells enter the general circulation via the portal vein. There is such a great species difference that this may not be the mode of circulation in man.

**THE SPLEEN AS A BLOOD RESERVOIR.**—It has been conclusively shown that in animals such as the horse, the spleen is an important blood reservoir, but there is no evidence for such a function in man. True, subcutaneous injection of 1 mg. of adrenaline causes a reduction in size of the human spleen and discharge of some of its fluid contents into the circulation; at the same time there is a rise in the red cell content of the peripheral blood. This effect is due to arteriolar constriction. Such an increase of hæmoglobin and red cells also occurs in the splenectomised person and is due simply to a redistribution of red cells and plasma which increases the proportion of cells in the peripheral blood.

**RETICULO-ENDOTHELIAL TISSUE.**—The cells of this tissue are found in the framework of the red pulp, the endothelial cells of the sinuses together with those cells which form the mesh-like stroma and the lymph sinuses of the follicles. They are found also in the liver (Kupffer cells), bone marrow and in the lymphatic glands.

**THE SPLEEN AS PART OF THE RETICULO-ENDOTHELIAL SYSTEM.**—The main functions of the spleen as part of the reticulo-endothelial system are:

(a) *Phagocytosis.*—This is most active and results in the destruction of bacteria, protozoa and red blood corpuscles. This "filtering out" activity at once brings to mind the splenic changes in infections (typhoid fever, malaria) and the enlargement of the organ in hæmolytic anæmias (pernicious anæmia, acholuric jaundice).

(b) *Storage.*—The cells of the reticulo-endothelial system play an important part in the intermediary metabolism and storage of lipids, hæmoglobin and iron. These functions are referred to in detail in connection with Gaucher's and other diseases.

(c) *Immunity reactions.*—Much work has been done suggesting that the reticulo-endothelial cells of the body are the main source of antibodies, antitoxins, precipitins and agglutinins. It is certain that in chronic infective diseases these cells proliferate. Some hitherto unexplainable examples of splenomegaly (reticulo-endotheliosis of the spleen) may come into this category.

**THE HÆMOPOIETIC OR BLOOD-FORMING TISSUES.**—Monocytes are produced and enter the blood-stream. The normal adult spleen has lost its embryonic power of producing erythroblasts and myelocytes. In certain circumstances, however, the spleen can regain its erythropoietic power, particularly in diseases where the medullary spaces of the bones are decreased in size as in osteosclerosis, in severe hæmolytic anæmia, and occasionally in infectious diseases.

**LYMPHATIC TISSUES.**—Histologically the Malpighian bodies resemble lymphatic nodes but, as explained above, their vascular and lymphatic connections are by no means the same.

## DISEASES OF THE SPLEEN

### ABNORMALITIES OF THE SPLEEN

The spleen may be completely absent, or may take the form of small spleniculi (synonyms—splenunculi, accessory spleens), scattered throughout the upper abdomen.



A few small accessory spleens, in close proximity to an otherwise normal spleen, are quite common, and are involved in all the pathological processes of the main organ. Congenital lobulation is occasionally found, and demonstrates the essential lobular structure. Normally only the characteristic notch or notches on the anterior border persist as evidence of this fact.

### FLOATING OR DISLOCATED SPLEEN

Rarely, because the splenic ligaments are lax and longer than usual, an otherwise normal spleen may be easily palpated on abdominal examination.

### RUPTURE OF THE SPLEEN

**Ætiology.**—Rupture of the spleen may occur in the healthy person following injury. The injury need not necessarily be violent but is always sudden. The diagnosis may be particularly difficult in children when the injury may not be followed immediately by signs of shock. Spontaneous rupture may take place in chronic infections such as malaria where the spleen is much enlarged, in acute infectious diseases such as typhoid and diseases of the spleen or blood-forming tissues where there is gross splenomegaly. In all these conditions the spleen capsule has lost its elasticity and any sudden distension, rapid enlargement, or rough handling on physical examination may result in rupture of the capsule. Trauma sufficient to produce rupture may be so slight as to escape notice.

**Pathology.**—The tears in the splenic capsule may be longitudinal, transverse, single or multiple. In traumatic rupture of the healthy spleen they are almost always multiple. Usually both the capsule and the splenic tissue are torn.

**Clinical Features.**—Immediately following injury physical signs may be absent or symptoms and signs of blood loss may be present associated with pain in the left hypochondrium. Pain in the left shoulder may be complained of or may be produced by pressure in the left hypochondrium or by raising the intra-abdominal pressure as a whole. Even in the absence of signs of blood loss this is an indication for abdominal exploration.

**Prognosis.**—In the healthy person with traumatic rupture of the spleen the prognosis is good if efficient blood transfusion and surgical treatment is readily available. In pathological states the outlook is serious, particularly in acute infectious diseases.

**Treatment.**—This is surgical.

### INFARCTION OF THE SPLEEN

Partial infarction or multiple infarctions, both aseptic and septic, are common in a great variety of diseases. They are usually of little clinical importance and do not require treatment unless there is pain due to perisplenitis. The commonest cause of abscess of the spleen is septic infarction. Surgical intervention is indicated when an abscess bursts giving rise to a generalised peritonitis.

### CYSTS OF THE SPLEEN

Three varieties of cysts of the spleen have been described, namely, dermoid, echinococcus (hydatid) and serous or hæmorrhagic. All are uncommon. Only serous or hæmorrhagic cysts will be discussed.

**Ætiology.**—It has been claimed that this variety of cyst is congenital, and also that it may follow injury. Whatever the origin when once formed, it continues to grow slowly.

**Pathology.**—Serous or hæmorrhagic cysts may be single or multiple. They contain a mixture of fluid and light chocolate-coloured debris, with abundant cholesterol crystals producing a distinct sheen. Perisplenitis is common, but rupture is rare. A cyst may be deep within the splenic tissues.

**Symptoms.**—The cysts may be large enough to bring about considerable enlargement of the organ. A thinned-out but apparently normal anterior margin, with the characteristic notch, may be felt through the abdominal wall and may cause confusion with other forms of splenomegaly.

The only pathognomonic sign is fluctuation, but even this can be given by a congenital cystic kidney. Repeated attacks of acute perisplenitis are a noteworthy feature.

**Treatment.**—Splenectomy should be performed as early as possible, before dense perisplenic adhesions have formed.

## PERISPLENITIS

Perisplenitis, or inflammation of the splenic capsule, is encountered in a great many acute and chronic diseases, and is of considerable clinical importance. When acute, it is usually painful. Perisplenitis may be detected by manual palpation or frequently only by auscultation over the tender area. Acute perisplenitis may be of diagnostic importance, while in the chronic stages it may present a serious problem to the surgeon and hinder or prevent successful splenectomy, especially if there are dense adhesions between the upper pole of the spleen and the vault of the diaphragm. Perisplenitis over the anterior surface of the spleen, even when of long duration, seldom gives rise to adhesions.

## SPLENIC ENLARGEMENT

The spleen is enlarged in many infectious diseases (*e.g.* typhoid, typhus, bacterial endocarditis, abortus fever) and as far as the acute specific fevers are concerned the finding may be important only as an aid to the diagnosis of the particular infection. Splenic enlargement may be of considerable diagnostic importance in bacterial endocarditis, in amyloid disease, in miliary tuberculosis, sarcoidosis, in blood diseases such as leukaemia, in the reticuloses, portal hypertension and in tropical diseases such as kala-azar and malaria.

In the recognition of slight splenic enlargement percussion is of little value and it is best to palpate the tip of the organ below the ribs with the patient lying on his right side.

An enlarged spleen may be difficult to distinguish from (1) tumours, enlargement and displacements of the left kidney, (2) a greatly enlarged left lobe of the liver, (3) carcinoma of the splenic flexure of the colon, (4) carcinoma of the body of the stomach, (5) a mass of carcinomatous or tuberculous tissue in the omentum. If these can be excluded a mass in the left upper abdomen is almost certainly an enlarged spleen. The splenic notch can usually be detected when the enlargement is generalised.

## TUMOURS OF THE SPLEEN

Simple tumours are very rare, but fibromas, hæmangiomas and lymphangiomas have been noted.

Sarcoma is the only primary malignant tumour. Primary carcinoma of the spleen,

because of the absence of epithelial tissue, cannot exist, and even secondary carcinoma is rare.

Sarcoma is of two types—one diffuse and the other arising in, and producing great enlargement of, the Malpighian bodies. There may be great difficulty in deciding whether true tumour growth exists, or merely excessive proliferation of reticulo-endothelial cells. Secondary nodules in lymphatic glands may afford the only proof. Diagnosis is impossible without laparotomy. Splenectomy should be carried out, and cases of permanent cure are on record.

## HYPERSPLENISM

This is not a disease *sui generis* but is a syndrome. It occurs in a variety of diseases involving the spleen—non-inflammatory, *e.g.* hæmolytic anæmias; inflammatory, *e.g.* chronic malaria; neoplastic, *e.g.* lymphosarcoma and Hodgkin's disease.

**Clinical Features.**—There is always some degree of hypochromic or normochromic anæmia, marked granulopenia and sometimes thrombocytopenia. Sternal marrow biopsy reveals a hyperactive marrow and delayed cellular maturation. Three possible causes of this condition have been suggested. (i) Increased destruction of cells in the enlarged spleen. (ii) Endocrine inhibition of the marrow (splenic in origin). (iii) Excessive lymphocytopoiesis in the enlarged spleen with consequent disturbance between the lymphatic and myeloid systems. It is possible that all three factors are concerned.

**Treatment.**—Treatment of an infective condition, *e.g.* malaria or syphilis may cure the syndrome. Irradiation should be considered in neoplastic diseases. In other cases splenectomy should be considered.

## THROMBOSIS OF THE SPLENIC VEIN

The sudden onset of thrombosis of the splenic vein gives rise to great congestion and enlargement of the spleen and the flow of blood in the gastric veins may be reversed with resultant engorgement and danger of severe and repeated gastric hæmorrhage. Abdominal pain and collapse may precede a fatal gastric hæmorrhage.

Partial or incomplete obstruction will be dealt with under congestive splenomegaly together with portal vein obstruction.

**Diagnosis.**—This is difficult. The signs are those of an intra-abdominal hæmorrhage.

**Treatment.**—Removal of the spleen by prompt surgical intervention is the only possible treatment.

## BANTI'S SYNDROME

**Synonyms.**—Congestive Splenomegaly; Hepato-lienal Fibrosis.

**Definition.**—The syndrome consists of congestive splenomegaly, hypochromic anæmia, leucopenia, thrombocytopenia and a history of attacks of gastro-intestinal bleeding or demonstrable evidence of the presence of œsophageal varices. The terminal stage is associated with hepatic cirrhosis, jaundice and ascites.

**Ætiology.**—Originally described as "anæmia splenica", 1866, and as splenic pseudo-leukæmia before the pathology of the leukæmias was understood, the name splenic anæmia was again brought into clinical use by Osler in 1902. In recent years the syndrome of portal hypertension has been described, and its clinical features are indistinguishable from those of Banti's syndrome. The synonym, hepato-lienal

fibrosis, indicates the gross pathological changes. The presence of œsophageal varices indicates portal hypertension which is present at some stage of the disease. Disagreement exists as to whether this is primary, *i.e.* the cause of the condition, or secondary, *i.e.* occurring late in the disease as the result of the liver changes which are indistinguishable from cirrhosis. The thesis that all cases are produced by hypertension resultant from changes in the portal venous system is not accepted by all authorities. In favour of the view that the disease is a separate entity of unknown ætiology is the absence in some cases of demonstrable portal block and of œsophageal varices. When portal block with subsequent hypertension is present the cases may be divided into two groups depending on the site of the obstruction, (1) intra-hepatic and (2) extra-hepatic where the block is in the portal vein or the splenic vein. The second group make up 30 per cent. of the cases and the block is most often in the portal vein itself.

**Pathology.**—The characteristic histological changes in the spleen may be briefly summed up as peri-arterial hæmorrhages (some of which may develop into fibro-siderotic nodules); dilatation of the blood sinuses; proliferation of histiocytic (reticulo-endothelial) cells around the sinuses and in the pulp; and generalised fibrosis of the trabeculæ and reticulum. The Malpighian bodies also share in the fibrosis. The liver changes vary greatly in degree; in early cases biopsy and liver function tests may be normal, but the later stages differ in no way from those of ordinary hepatic cirrhosis. There are no other primary pathological changes of importance. The dilatation of the venous sinuses is evidence of venous congestion. It has proved possible in animals to produce congestive splenomegaly, thickening of trabeculæ and reticulum and hæmorrhages with fibro-siderotic nodules by the maintenance of portal hypertension. These changes in animals and the dilated collateral channels and the frequent severe hæmorrhages in man are conclusive evidence of a hæmodynamic component.

**Symptoms.**—Splenomegaly is inevitable but its degree varies. The average weight in a series of cases was about 900 g., but in extreme cases it may be as much as 3000 g. The spleen feels smooth, and is of firm consistence. Moderate anæmia is the rule unless the case is complicated by recent hæmorrhage. The bone marrow is normal or hyperplastic and the blood findings may be those characteristic of hypersplenism, *i.e.* a leucopenia is present in association with a normochromic or hypochromic anæmia. Thrombocytopenia is unusual.

Hæmorrhage into the stomach, derived from large veins in the gastro-splenic omentum (*vasa brevia*) or from œsophageal varices occurs in a large number of cases and may be severe and repeated. The patient who escapes the hazard of gastric hæmorrhage dies from hepatic failure with portal obstruction, ascites and jaundice.

**Course.**—This is chronic, the duration varying from several to many years and in the majority 5 to 15 years.

**Diagnosis.**—The diagnosis is made by a process of exclusion after considering other forms of chronic splenomegaly.

**Treatment.**—This may be considered under two headings, surgical and medical. Surgical treatment is most urgently required to prevent or at least to reduce the risk of further hæmatemeses. Ligation of the splenic artery is useless, since more than 30 per cent. of cases have further severe hæmatemesis. Splenectomy should be reserved for those cases where thrombocytopenia is present or when the block is in the splenic vein. Ligation of the hepatic artery has been tried in selected cases. Operations to reduce blood flow through œsophageal varices are disappointing and the result in any particular case unpredictable.

The best way to reduce an increased portal pressure is to establish a porto-caval shunt. This operative procedure appears to protect many patients from œsophageal hæmorrhage. The operation should not be carried out where there is evidence of extensive liver damage.

**Medical treatment.**—In the early stages of the disease when the patient's general health is good the anæmia which results from alimentary bleeding responds satisfactorily to the administration of iron. Later, when cirrhosis of the liver and its sequelæ are present, the response is not so satisfactory. If profuse bleeding occurs from œsophageal varices blood transfusion is urgently needed. Many patients have survived numerous hæmorrhages with the aid of transfusion.

The diet should be bland and non-irritating to avoid trauma to the œsophageal varices and to the stomach. For treatment of cirrhosis of the liver, see p. 679.

## DISEASES OF THE RETICULO-ENDOTHELIAL SYSTEM

Two prominent sites of reticulo-endothelial cells in the body have been referred to under Diseases of the Spleen (p. 778) and Lymphatic System (p. 787). Two other important sites are the bone marrow and the liver (Kupffer cells). Diseases affecting these cells have been loosely grouped under the term "Reticuloses". Some histopathologists have confined the term to irreversible atypical and systematised proliferation of the particular cells of the system. Others use the term to include the primary neoplasms, benign and malignant, of the reticulo-endothelial system. As an ætiological classification is not yet possible, considerable confusion exists and this is intensified by the difficulty of interpreting the histological changes.

Of the diseases variously classified as reticuloses only those associated with the deposition of lipid in the cells will be considered here. Leukæmias are dealt with in the section on Blood Diseases, p. 757, and Hodgkin's disease under Diseases of the Lymphatic System, p. 789.

## LIPOID DEPOSIT DISEASES

### HAND-SCHÜLLER-CHRISTIAN'S DISEASE

**Synonyms.**—Normocholesterolæmic Xanthomatosis; Eosinophilic Granuloma.

Hand, 1893, Schüller, 1915, and Christian, 1919, have all drawn attention to a clinical syndrome, limited to children, of defects in the membranous bones, exophthalmos and diabetes insipidus. Rowland, 1928, demonstrated the identical character of the pathological changes present in the granulomatous lesions of bone, brain and lung.

**Ætiology.**—The fundamental abnormality of this disease is still quite unknown, but although the cholesterol content of the xanthomatous lesions is as high as is found in the lesions of hypercholesterolæmic and hyperlipæmic xanthomatosis, the serum of patients with this condition is normal in its cholesterol phospholipid and neutral fat content. Blood chemistry studies have differentiated this condition from hypercholesterolæmic and hyperlipæmic xanthomatosis though all these conditions may show xanthomatous skin lesions.

**Pathology.**—The lesions are granulomatous in character, consisting of reticulum cells and histiocytes, cholesterol containing foam cells and eosinophils, red cells and polynuclear elements.

There are roughly four phases of development of the lesions—(1) reticulo-histiocyte proliferation, (2) granulomatous phase with increase of blood vessels and fibrils, reticular cells, histiocytes, eosinophils, giant cells and incipient lipid accumulations, (3) xanthomatous phase containing foam cells, (4) a fibrous stage considered to be a healing phase.

Letterer-Siwe's disease is considered to be an acute early phase of the same condition which has not progressed to the stage of lipoid storage.

**Clinical Features.**—The syndrome occurs mainly in children and infants, adult cases are rare. It may be complete with bony changes, exophthalmos, diabetes insipidus, lung lesions and associated xanthoma disseminata, or any case may present one or more of these features. In these circumstances diagnosis may only be established by biopsy. The commonest non-symptomatic type is the solitary eosinophilic granuloma of bone. Diabetes insipidus and xanthoma disseminata may occur without lung or bone involvement. Xanthoma disseminata has to be distinguished from juvenile benign xanthoma, which is an innocent lesion. Even in the fully developed picture enlargement of the spleen and liver is rare.

**Prognosis.**—When the disease appears in early life it is rapidly fatal, whereas an onset in adolescence or adult life may mean many years survival.

**Treatment.**—Dietetic restrictions are valueless. Radiotherapy will often lead to disappearance of local lesions. The diabetes insipidus responds to the usual therapy for that disease (p. 490).

## HYPERCHOLESTEROLÆMIC XANTHOMATOSIS

This condition is familial, unlike the normocholesterolæmic type (Hand-Schüller-Christian's disease) which never runs in families. Xanthomatous deposits occur around tendons, in the eyelids or the blood vessels (atheroma), but other members of the family may show equally high serum cholesterol values without any evidence of local deposits.

**Pathology.**—The histology differs from the normocholesterolæmic type. Xanthoma cells (foam cells) are found at all stages of the disease. The lesions may soften and cholesterol crystals appear in the tissue spaces.

**Clinical Features.**—Tuberous xanthomata are found as nodular elevations of the skin, but not on the mucous membranes. They occur as isolated lesions or in small groups, with a brownish-yellow discoloration. The serum cholesterol levels are high.

**Prognosis.**—The cases show a remarkably high incidence of myocardial infarction in early life.

**Treatment.**—Diets low in cholesterol content are advised.

## HYPERLIPÆMIC XANTHOMATOSIS

Hepato-splenomegaly and secondary xanthomatosis result from hyperlipæmia with excessive phagocytosis by the reticulo-endothelial system and production of foam cells. The condition is rare. The reason it is mentioned is that dietary treatment with restriction of fat is said to produce considerable improvement in this condition. Such treatment is of no value in hypercholesterolæmic xanthomatosis. When hyperlipæmia is associated with diabetes mellitus treatment of the latter condition will reduce the degree of the lipæmia.

## GAUCHER'S DISEASE

**Synonym.**—Lipoid Storage Spleno-hepatomegaly.

**Definition.**—A rare familial constitutional disorder of the cellular metabolism in the reticulo-endothelial cells. Reticulum cells and histiocytes become enlarged and filled with a lipoid substance named kersin. This leads to an enlargement of the spleen and liver, and deposits in bone marrow and lymph nodes.

**Ætiology.**—The disease is a disorder of lipid metabolism but whether it is an upset of the intermediate metabolism of lipoids or a metabolic disorder involving only certain cells in the affected organs is unknown. Plasma lipoids are normal. The disease begins insidiously in early life, most cases being recognised before 10 years of age. Several members of a family may suffer from the disease. It is commoner in females, and many of the cases are of the Jewish race.

**Pathology.**—The characteristic feature of the disease is the large pale striated Gaucher cell containing glucosido-cerebrosides (kerasin) and the spleen, liver, lymph nodes and bone marrow are packed with such cells. They are the immediate cause of the enlargement of the organs. In the later stages of the disease there is marked increase in the connective tissue of the liver and spleen.

**Symptoms.**—Slowly progressive splenic enlargement is the first sign. The spleen may become enormous. This is followed later by the enlargement of the liver, and to a lesser degree of the lymph glands. Skeletal changes with spontaneous fracture may occur, caused by destructive infiltration from the bone marrow. The skin of the face, neck, forearms and hands frequently shows a brownish-yellow pigmentation, and it is less commonly seen on the legs. It has nothing to do with exposure to light. The eyes show a phenomenon which is so constant as to be almost pathognomonic. A brownish-yellow wedge-shaped thickening or pinguicula appears in the bulbar conjunctiva near the cornea, first on the nasal and later on the temporal side, of each eye. Hæmorrhages from mucous membranes are common and are associated with thrombocytopenia. There are no characteristic changes in the white cells of the blood but leucopenia is frequent. Anæmia occurs late in the disease.

**Course and Prognosis.**—There is an acute infantile form of the disease which starts in the first 6 months of life. Death usually results in the second year. The chronic form begins in the first 10 years of life and exhibits a slow progressive advance. Cases are on record of over 40 years' duration, and of 20 years after splenectomy in adult life. Death often ensues from some intercurrent disease.

**Diagnosis.**—The familial history, early onset, great and progressive splenomegaly, hepatic enlargement, changes in the eyes, and dermal pigmentation constitute an almost unmistakable picture. Sternal marrow biopsy confirms the diagnosis, the characteristic large pale striated cells being sometimes recognisable in the films and, more frequently, in sections made from the fragments. Glycogen disease (p. 452) is distinguished clinically by the great hepatic enlargement, without accompanying splenomegaly.

## NIEMANN-PICK'S DISEASE

**Synonym.**—Phosphatide Lipoidosis.

**Definition.**—A very rare familial constitutional disorder of cellular metabolism of reticular and histiocytic cells. There is an accumulation and retention of the diamino-phosphatide sphingomyelin within these cells.

**Pathology.**—The foamy Niemann-Pick cells are not part of a granulomatous or inflammatory tissue as seen in the different types of xanthomatous disease discussed above. The liver, spleen and, to a less extent, the lymph glands are enlarged. Histological examination reveals the presence of many foamy cells containing lipid in the bone marrow and elsewhere and may be demonstrated on marrow biopsy. The blood picture is normal. There is involvement of the central nervous system.

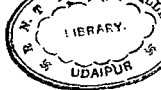
**Course and Prognosis.**—The disease begins in the first year of life with enlargement of liver, spleen, lymph nodes, anæmia, diffuse pigmentation of the skin and patchy bluish-black spots on the mucous membranes of the mouth. Mongoloid facies is sometimes present. With physical and mental deterioration there is rapid progression to extensive cachexia, and death occurs invariably within 2 years of birth.

**Diagnosis.**—Tay-Sachs disease (amaurotic family idiocy), in which there is lipoid degeneration of the central nervous system, may be confused with Niemann-Pick's disease. Cases have been described suffering from both conditions. The liver and spleen are not enlarged in Tay-Sachs disease. Gaucher's disease, see p. 784, begins later in childhood and persists into adult life. Gargoylism is a lipoid disorder of the Tay-Sachs type in which skeletal defects, cranial deformity, mental deficiency and corneal opacification are associated with hepato-splenomegaly.

**Treatment.**—This is essentially symptomatic.

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## SECTION XI

# DISEASES OF THE LYMPHATIC SYSTEM

## INTRODUCTION

THE lymphatic system consists of the lymphatic vessels (lymphatics), the thoracic duct, the lymph nodes or glands and many large and small collections of lymphoid cells scattered throughout almost every organ and tissue of the body. Examples of large collections are the tonsils, the Peyer's patches of the intestine, the Malpighian bodies of the spleen and the thymus gland.

Lymph flows from the tissues to the great vein at the base of the neck. It is *carried in lymphatic vessels which begin in the tissues as naked endothelial tubes*. How fluid gets into the lymphatic channels has been much debated. It has been suggested that they are actually pulled open when there is an increased amount of fluid in the tissues. Lymphatic vessels differ from capillaries in the possession of valves and supporting walls consisting of connective tissue cells. The flow of lymph depends on muscular contraction, respiration and gravity. The lymph enters the lymph glands by afferent lymphatic vessels and within the node the lymph spreads out under the capsule in a space called the peripheral sinus. From there it seeps into the substance of the node along sinuses lined with reticulo-endothelial cells. All the internodal streams flow together at the hilum of the lymph gland to join the efferent lymphatic vessels. Thus the fluid from the tissues is presumably filtered in its passage through the lymph gland. There are many follicles in the node and it is claimed that the large pale cells at the centre of each follicle constitute the "germinal centre" in which new lymphocytes are formed. It is possible that they also have a reticulo-endothelial function.

The thymus gland is also double in structure, the larger cortical part being chiefly composed of ordinary lymphoid tissue while the smaller medulla (Hassall's corpuscles) is epithelial in origin.

## DISEASES OF THE THORACIC DUCT

Apart from obstruction of the duct by tumours, usually malignant, either within or pressing on the duct, and less often by tuberculosis, aneurysm and lymphadenoma, lesions in this situation are rare and are very difficult of recognition during life. Obstruction results in chylous pleural effusion and (or) chylous ascites. Since chyliform ascites may occur without obstruction to the thoracic duct, as in tuberculous peritonitis, peritoneal carcinomatosis and even in cirrhosis of the liver, the presence of a milky pleural effusion is better evidence of a thoracic duct lesion than is a milky ascites. But even here the diagnosis is by no means certain on this fact alone. Chyluria, with chylous oedema of the genitals and lower extremities, if occurring with one or both of the above does, however, make diagnosis of obstruction to the thoracic duct almost certain.

## DISEASES OF THE LYMPHATIC VESSELS AND GLANDS

**LYMPHANGITIS.**—Acute or chronic inflammation of the lymphatic channels is commonly found in infections, and in acute lymphangitis there are reddish lines in the skin. They often reveal the site of the infection and there is soon an associated enlargement and tenderness of the regional lymph nodes. Always an indication for

prompt treatment lymphangitis is particularly serious in limbs where the blood supply is impaired. Chronic lymphangitis is usually tuberculous in origin.

**Treatment.**—Active treatment with antibiotics is urgently indicated.

**ACUTE LOCAL LYMPHADENITIS** is generally associated with acute lymphangitis and is due to the same causes—acute septic inflammation of the skin or mucous surfaces in the region drained by the affected lymphatics. The lymphatics associated with the fauces are those most often involved, for obvious reasons. The tender and swollen nodes may suppurate, in which case the inflammation spreads, leading to periadenitis and involvement of the skin.

**ACUTE GENERALISED LYMPHADENITIS.**—This occurs in almost all the acute infectious diseases, but is particularly frequent, and therefore of special diagnostic importance, in German measles, measles, scarlet fever and diphtheria. In glandular fever there is generalised lymphadenitis associated with mononucleosis.

**TUBERCULOUS LYMPHADENITIS.**—Lymphatic channels and glands are invariably involved in tuberculosis, and in primary tuberculous infection it is the mediastinal and mesenteric glands which are affected. Involvement of the cervical glands is common particularly in children; in some cases the tonsils are tuberculous and therefore should be carefully examined. The cervical glands may be invaded on one or both sides of the neck. Pain is not a feature. The condition may regress with medical treatment but often the glands become matted together and caseation occurs. In order to prevent the formation of a chronic sinus the caseous material should be evacuated through a small incision. Widespread dissection of the glands should not be attempted, but a period of treatment with streptomycin and other chemotherapeutic agents (p. 1033) may be necessary. They are of value in promoting healing when caseous glands have been evacuated.

For the treatment of intra-thoracic and abdominal tuberculosis, see pp. 720, 1031.

Local tuberculous enlargement of the lymph glands in the axillæ or groins, or generalised enlargement, are so rare that other diseases should always be suspected.

## LYMPHŒDEMA

Obstruction of lymphatic drainage by external pressure or low-grade inflammation may lead to œdema of the extremities. In the tropics filariasis is a common cause, see p. 327. Obstruction is commonest in the lower limbs.

Lymphœdema is also found without evidence of inflammation or pressure and may be due to an abnormality of the lymphatic channels. It can occur at puberty and disappear later. Milroy's disease is the familial type. At first the œdema pits on pressure but later the tissues compress with difficulty and elevation of the limb does not relieve the swelling. Though painless, the deformity is distressing to the patient.

**Treatment.**—It is unfortunate that the majority of cases of lymphœdema occur in the female sex because elastic stockings provide the simplest and best treatment in the early stages of the condition. Rest and frequent elevation of the limbs is also necessary. These measures should be employed early in order to postpone thickening of the tissues by fibrosis, and later, the liability to skin infections. When the condition is caused by filariasis the treatment is of that condition (p. 328). It is essential to eradicate any infection, in particular epidermophytosis.

## NEOPLASTIC DISEASE

Lymphatic node enlargement may be due to carcinoma or sarcoma. In carcinoma the involvement is secondary, and its situation and line of spread are often of critical importance in diagnosing the site of the primary growth. Primary lymphosarcoma

is dealt with separately (p. 791). Rhabdomyosarcoma occasionally produces secondary growths in lymph nodes.

Enlargement of lymphatic glands, local or general, in Hodgkin's disease and chronic lymphatic leukaemia, is discussed elsewhere.

## HODGKIN'S DISEASE

**Synonym.**—Lymphadenoma.

**Definition.**—A disease principally affecting the lymph nodes which become enlarged, remain discrete and of rubbery consistence. The enlargement is not associated with pain. Commencing in one group of lymphatic glands it spreads to others and also to the lymphoid tissues of the spleen, liver and other organs. Rarely is there softening or necrosis of the enlarged lymph glands and the capsule remains intact.

**Ætiology.**—This is unknown. Most observers favour a neoplastic cause, though many of the features in the histological picture could be explained by an infective process.

It is important to recognise that the disease may occur at any age but its incidence is highest between the ages of 10 and 50. Seventy per cent. of the cases are males. There is no proof of hereditary tendency though occasionally cases are seen in two or more members of one family. It may coexist with tuberculosis and occasionally appears to follow an infective process of a pyogenic or spirochætal nature, though there is no proof at the moment that this is anything other than coincidental.

**Pathology.**—The disease process may involve isolated groups of lymph nodes in different regions of the body and when this happens the enlarged nodes tend to remain discrete, have a rubbery consistence on palpation and on section show yellow strands passing in from the intact capsule with whitish tissue between them. Areas of necrosis are unusual. Less commonly, at the onset of the illness the process may be widespread, involving in particular abdominal and intrathoracic lymph glands. Very rarely cases have been reported which would appear to be Hodgkin's disease where the spleen alone has been involved.

From post-mortem examinations it is clear that the retroperitoneal and para-aortic lymph nodes are the most frequent primary sites of the disease. This is an important finding and it contrasts sharply with the clinical observation that the cervical nodes are the primary site in a large percentage of cases. The difficulty of recognising involvement of the deeper nodes during life should make the physician very cautious in concluding that the disease is confined to comparatively localised superficial nodes. It is important in doing biopsy studies that a lymph node of the axilla or the neck should be used. Inguinal glands are frequently the site of secondary infection.

Microscopic examination reveals a great proliferation of the reticulo-endothelial cells, hyperplasia of the lymphoid cells and a mixture of plasma cells and eosinophil leucocytes. Certain endothelial cells which have been termed Reed-Sternberg cells are 12 to 40 microns in diameter, their shape is irregular and their cytoplasmic processes frequently extend to neighbouring cells. The nucleus in its most characteristic form is lobulated or multilobed and a nucleolar mass is present. The nature of these cells is obscure but it is their presence together with eosinophil cells which constitutes the most characteristic feature of the lymphadenomatous lesion. The spleen is involved in the disease process but great enlargement is unusual. The organ is firm, it preserves its natural contours, and the surface may be slightly irregular or finely nodular. The liver is frequently involved.

Apart from the generalised lymphadenoma, almost every organ of the body with the exception of the central nervous system proper may be affected.

**Symptoms.**—In a great majority of cases the first symptom is painless enlargement of the lymph nodes in the cervical region. They may be situated in the anterior or posterior triangles or under the sterno-mastoid. Occasionally enlarged glands are

first noted after an acute upper respiratory infection. This may lead to confusion and delay in diagnosis but persistent masses of glands in the neck after minor infections must be regarded with suspicion, particularly if the posterior triangle or the supra-clavicular region is involved. Full investigation is often delayed because the patient does not feel ill and at this stage there may be no clinical evidence of disease elsewhere. Pain, usually in the abdomen or back, or enlarged axillary lymph nodes are less common presenting features. Weeks or months may elapse before any other symptoms appear.

There is an acute type of the disease which may be associated with generalised superficial lymph node involvement or the deep lymph nodes may be principally and primarily involved. The clinical state may simulate an acute infection such as miliary tuberculosis. The most difficult cases to diagnose are those of primary involvement of the intra-abdominal lymph glands alone.

**Course.**—Two groups of symptoms develop in the more insidious case—the general symptoms of the disease and those referable to pressure and infiltration of the lymphadenomatous masses in different organs and tissues of the body. The most prominent symptom is generalised weakness and if the mediastinal glands are involved or the patient be anæmic, breathlessness on exertion may also be a feature. Loss of weight, pyrexia and pruritus which may be intractable, are common. This is the stage of the disease which is frequently seen on first admission to hospital, and the clinical condition may simulate tuberculosis. The pyrexia may have a characteristic undulant character, and its recognition is of great importance in diagnosis. It is a feature commonly missed, particularly in domiciliary practice. Sometimes the fever follows a regular pattern—waves of pyrexia of 4 to 14 days' duration alternating with periods of apyrexia. Such pyrexia is referred to as the "Pel-Ebstein" type. In rapidly progressing cases with widespread involvement a continuous type of pyrexia may be present, making it necessary to differentiate the condition from the enteric group of diseases.

Because of the widespread nature of the disease a multitude of local symptoms and signs may be present. For example, mediastinal pressure may cause a distressing dyspnoea and cyanosis, laryngeal palsy may be present and if bilateral may necessitate tracheotomy. Enlargement of the hilar glands and invasion of the peri-bronchial tissues may produce collapse of the lungs, pleural effusions or lung abscess. Masses in the liver may cause obstructive jaundice and ascites. In the later stages of the disease the bones may be extensively involved. Paraplegia has occurred as the result of involvement of the meninges.

**THE PERIPHERAL BLOOD PICTURE.**—Though there is a marked deviation from normal in cellular elements of the blood, there are no special features to help in establishing the diagnosis of lymphadenoma. A variable degree of hypochromic, or much more rarely normochromic anæmia develops in a large proportion of cases, particularly in the late stages of the disease. The pathogenesis of this anæmia is uncertain; in some cases it is obviously due to involvement of the bone marrow but this is not invariably so; hypersplenism, see p. 781, may be the cause. In rare cases there is severe hæmolytic anæmia simulating acquired hæmolytic anæmia. In these cases there may be pseudomacrocytosis and increased fragility of the red cells. There is a wide variation in the white cell picture in the peripheral blood. Marked fluctuation in the white cell count may occur in a short period of time without apparent cause. Persistent leucocytosis is extremely frequent though a persistent leucopenia may occur. The most significant change in the differential white cell count is a relative or absolute increase in the percentage of neutrophil polymorphonuclear cells. In 10 to 15 per cent. of cases the absolute eosinophil count exceeds the upper limit of normal (400 per c.mm.). In spite of much that has been written on the importance of eosinophilia in the diagnosis of Hodgkin's disease, a very high eosinophil count suggests that it should be reconsidered. Monocytes are frequently increased in

number. A normal blood sedimentation rate is usually found in patients in a chronic phase of the disease and a rising rate usually indicates that the condition is rapidly spreading. An exception to this rule is found when the liver is massively involved.

**Clinical Diagnosis.**—Cases often present in one of three ways—patients with localised lymphadenopathy, those with generalised lymphadenopathy, and those with constitutional symptoms associated with little or no enlargement of the superficial nodes.

When confronted with localised lymphadenopathy, the condition has to be distinguished from other neoplastic conditions such as lymphoma, lymphosarcoma, reticulum-cell sarcoma as well as from tuberculosis, infective mononucleosis, syphilis and leukaemia. The two diseases which are confused with Hodgkin's disease most commonly are tuberculous adenitis and lymphosarcoma. Biopsy is the only sure means of establishing the diagnosis, and even then the tissue examined may not show the characteristic changes.

When generalised lymphadenopathy is present the condition most commonly confused with the disease is leukaemia.

The febrile type, in which no superficial lymph nodes are enlarged, presents great difficulty, and the diagnosis is arrived at principally by exclusion. Marrow biopsy is justifiable under these circumstances. The diagnosis is sometimes not made until necropsy.

**Treatment.**—There is no specific treatment for the disease but there are a number of therapeutic measures which will alleviate symptoms if not prolong life. Whenever possible a biopsy should be performed prior to therapy and a detailed clinical and radiological examination carried out.

Radiotherapy is the most valuable form of treatment available. Close collaboration between the clinician and the radiotherapist is essential for the best results. The form of treatment, local or wide field therapy and the dosage and frequency of treatment have to be decided in each case. Usually the first course of therapy lasts 2 to 3 weeks, treatment being given daily. The patient's general health has to be carefully watched during therapy. Frequent blood examinations should be carried out to detect any signs of bone marrow depression. "Nitrogen mustards" should be reserved for cases where further irradiation is contraindicated or for the acute form of the disease. Apart from these measures treatment is symptomatic.

## LYMPHOSARCOMA

**Definition.**—Lymphosarcoma is a highly malignant tumour composed of mature or immature lymphocytes. Neighbouring structures are invaded at an early stage in the disease. Widespread metastases are uncommon except in those cases in which leukaemia develops.

**Ætiology.**—This is unknown.

**Pathology.**—The site of origin is usually in the cervical lymph glands, less commonly in the tonsil, mediastinal glands or the lymphoid tissue of the intestine. The tumour may vary greatly in appearance. Sometimes the outline of the lymph nodes is still recognisable, while in other tumours it is not. The colour of the tumour is white or pinkish and areas of necrosis are not infrequent. The section has a homogeneous appearance and histologically it is composed of mature lymphocytes or lymphoblasts. Neither giant cells nor multi-nucleated cells occur and the reticulum of the glands is not increased.

The greatest difficulty in differential diagnosis is to distinguish lymphosarcoma, especially of the lymphoblastic type, from reticulum cell sarcoma. In reticulum cell sarcoma, the cytoplasm of the cells is rather more abundant, the nuclei are usually slightly larger than those of an adult lymphocyte, and are irregular in shape. The reticulum is greatly increased, occurring in fine strands around groups of cells and

between individual cells. In the later stages of both diseases distant metastases occur in the lymph nodes, the spleen which is not often enlarged and throughout the body. Distant metastases are probably commoner in reticulosarcoma.

In children lymphatic leukaemia may be preceded by a local lesion with the characters of lymphosarcoma.

**Symptoms.**—Initial symptoms of lymphosarcoma are rather strikingly different in the young and in the old. The disease is commonest in the first two decades and in the elderly. In childhood enlarged cervical lymph glands are frequently noted first. The children are often pale and petechiae may be present in the skin, and in fact these children are usually found to have an acute leukaemia. In adult cases the patients may remain well for quite a time and complain only of a mass in the neck, a sore throat or cough. The peripheral blood picture shows nothing characteristic. Fever is much less common in these adult cases.

**Course.**—The disease progresses steadily to death. In children this occurs within a few months, though in the elderly the patient may live for 3 or 4 years.

**Treatment.**—Great alleviation in symptoms and marked temporary improvement in general health may result from radiotherapy. Localised masses will disappear with the greatest rapidity but the cases in which the most satisfactory response occurs are often those in whom relapse is also rapid.

## RETICULUM CELL SARCOMA

**Synonym.**—Lymphosarcoma, reticulum cell type.

Many still regard reticulum cell sarcoma as a variety of lymphosarcoma. There are, however, many differences between the two types of neoplasm. As mentioned above, a number of cases of lymphosarcoma are accompanied by lymphatic leukaemia: if leukaemia occurs in relation to reticulum cell sarcoma it is of monocytic type. Reticulum cell sarcoma of bone is also an important variety of primary bone tumour, whereas lymphosarcoma of bone is never primary. Whereas lymphosarcoma is common in early years of life, reticulum cell sarcoma occurs chiefly in the fifth, sixth and seventh decades. When it does occur under the age of 20 the disease is always a primary disease of bone.

**Symptoms.**—The commonest initial symptom is pain, which is often constant and is resistant to radiotherapy. It is most common in the neck or in the abdomen. Enlarged lymph nodes usually in the cervical region are frequent early in the course of the disease and they are occasionally painful. In sharp contrast to Hodgkin's disease, these enlarged lymphatic glands are fixed to the underlying tissues and tend to be stony hard rather than of rubbery consistence. In reticulum cell sarcoma neither the mediastinum nor the lungs are involved nearly so commonly as in Hodgkin's disease or in lymphosarcoma. The liver and spleen do not enlarge to the same degree as in Hodgkin's disease. Involvement of the pharynx is common in reticulum cell sarcoma and rare in Hodgkin's disease.

**Course and Prognosis.**—Loss of weight and pain are the commonest features of the course of the illness and both may be extreme. Pronounced fever, on the other hand, unless due to sepsis, is rare and the so-called Pel-Ebstein fever does not occur in this condition. The disease progresses at very different rates and in some cases surgical treatment and radiotherapy of the "metastatic" masses may prolong life for years. In others the end comes rapidly.

**Diagnosis.**—The clinical diagnosis of reticulum cell sarcoma cannot be made with certainty and a biopsy is necessary. The disease may be indistinguishable from Hodgkin's disease on histological section.

**Treatment.**—Radiotherapy offers the only hope of improvement. Response to therapy is not always so marked as in lymphosarcoma.

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## SECTION XII

# DISEASES OF THE CARDIO-VASCULAR SYSTEM

### GENERAL CONSIDERATIONS

The function of the heart and blood vessels is to supply all tissues of the body with adequate oxygenated blood. The cardiac output is the effective volume expelled by each ventricle in a minute, and it varies between 4 and 6.5 litres per minute at rest with an average of 5.3 litres. The output with each beat averages between 70 and 80 ml. when the heart rate is 72 per minute. An increase in heart rate or an increase in stroke volume causes an increase in cardiac output. Blood is ejected into the great vessels against peripheral resistance thus creating arterial pressure, and each separate ventricular systole causes a pulse pressure wave. The resistance offered in the systemic circulation is much higher than that in the pulmonary circulation; thus the arterial pressures differ in each circulation by a corresponding degree, although the output of the two ventricles is equal; the difference in the thickness of right and left ventricles reflects the difference in resistance against which each works.

The cardiac output varies greatly under physiological conditions; changes in venous return are largely responsible for significant changes in cardiac output, which are brought about by alterations in stroke volume and heart rate. Cardiac output decreases with a change to the upright position because of a fall in venous return; it increases with emotion and may increase fivefold or more on exercise in a trained athlete. The arterial pressure remains relatively constant because these physiological variations in cardiac output are balanced by reciprocal changes in the tone of the peripheral vascular system. The cardio-vascular system functions as a whole; changes in one variable factor are offset by alterations in others and there is integration of the whole system through the autonomic nervous system.

The heart beat is initiated at the sino-auricular node, from which the auricles are activated by the stimulus which passes over them in a cephalo-caudal direction to the auriculo-ventricular node. The auricles function as low-pressure receiving reservoirs and they augment ventricular filling by contraction at the end of diastole. Systole of the right and left auricles is almost simultaneous, and the left functions at a slightly higher pressure than the right. The clinical manifestations of auricular contraction are an "a" wave in the jugular venous pulse, a soft auricular sound which forms the early vibrations of the first heart sound, and the "P" wave of the electrocardiogram.

The cardiac stimulus passes through the junctional tissues of the auriculo-ventricular node and is conducted to the ventricles by the right and left branches of the bundle of His, and the Purkinje network. The function of the ventricles is to eject blood into the high-pressure arterial systems. In systole the auriculo-ventricular valves are closed, and each ventricular chamber and its outflow tract to the aorta or pulmonary artery behaves as a smooth continuum; after the peak pressure is reached relaxation follows and the semilunar valves close, preventing the regurgitation of blood and thereby creating a diastolic arterial pressure. The clinical manifestations of ventricular systole are the arterial pulse wave, the "c" wave in the jugular venous pulse, the lift of the apex beat, the first heart sound and the QRS complex on the electrocardiogram. The second sound which occurs at the end of systole is normally split into two sounds from asynchronous closure of the semilunar valves. When the

intraventricular pressure has fallen low enough for the auriculo-ventricular valves to open, ventricular filling starts and it is completed by auricular systole. Impulse formation and its conduction over the heart is further described in the section on arrhythmia (see p. 819).

The normal basal systemic arterial pressure is between 100 to 145 mm. Hg. in systole and between 60 to 90 mm. Hg. in diastole. Considerably higher figures may be recorded in normal subjects at a casual examination, but after rest and reassurance the blood pressure falls. The elasticity of the normal aorta damps the initial systolic thrust so that as the aorta loses elasticity with increasing age, systolic pressures tend to rise. The normal pulmonary artery blood pressure is between 15 and 25 mm. Hg. in systole and between 6 and 10 mm. Hg. for the diastolic level. The pulmonary capillary pressure may be obtained by passing a cardiac catheter into a branch of the pulmonary artery to the point of blockage, and in this wedged position the pressure and pulse wave forms appear to be a direct reflection of the dynamics of the left auricle.

**SYMPTOMS IN HEART DISEASE.**—There are relatively few symptoms of cardio-vascular disease but it is most important to obtain a detailed account of each; in most cases this necessitates a searching enquiry by direct questions, the results of which can only be interpreted with a knowledge of the patient's emotional state and level of intelligence. *Dyspnoea* on effort is the first and most sensitive indication of cardiac failure. It is due to diminished vital capacity, congestion of the pulmonary vascular bed and reflexes arising therein which abbreviate the depth of respiration and increase its rate. Dyspnoea may be due to primary lung disease or obesity, but a carefully taken history will often reveal a subtle but significant change when cardiac dyspnoea is superimposed on dyspnoea due to these other factors. Respiratory symptoms associated with psychoneurosis, such as sighing and tachypnoea, are readily distinguished from those due to organic disease. *Pain* in heart disease is mostly due to cardiac ischaemia, pericarditis or psychoneurosis. The type of pain, its site and radiation, provoking and relieving factors and natural history must be known before a diagnosis and full assessment can be made. *Palpitation* is an awareness of the heart beating due to an increase of rate, force or an arrhythmia. It is a frequent symptom of neurotic ill health, but is common in heart disease and thyrotoxicosis. *Fatigue* and weakness are often symptoms of neurosis, but may also be due to a low cardiac output from chronic valvular disease. *Syncope* is loss of consciousness due to acute systemic arterial hypotension. An adequate history usually distinguishes syncope from unconsciousness due to primary cerebral causes. Simple fainting is vasovagal syncope which, like other symptoms of cardiac disease, may be associated with psychoneurosis. *Giddiness* is the term used by patients to mean various sensations such as vertigo, a sensation of dimmed vision, a pressure on the head, general weakness or even local weakness in the legs. This symptom thus always requires careful analysis with particular reference to near syncopal reactions and true vertigo.

**PHYSICAL EXAMINATION IN HEART DISEASE.**—Examination should include a general inspection of the patient, a detailed examination of the cardio-vascular system and of any other systems indicated. Appearance and demeanour may reveal anxiety or depression; other signs such as dyspnoea, wheeziness, cyanosis, obesity, malnutrition, pallor, icterus and goitre may be observed whilst obtaining the history. The hands and skin should be inspected, structural abnormalities of the hands may be associated with congenital heart disease; coldness, pallor and blotchy cyanosis indicate peripheral vascular constriction, whilst hot, moist hands with pulsation of digital vessels may indicate anxiety or a state of high cardiac output: hyperidrosis is also a feature of the rheumatic state, when a diffuse swelling of digital joints and nodules may be found. Inspection of the nails may show such important signs as clubbing, undue pallor, capillary pulsation, koilonychia or splinter haemorrhages. Changes in texture of the skin are important pointers to disturbed water balance, endocrinopathy and



collagen diseases. Skin rashes are obviously important and are often related to previous medication.

**EXAMINATION OF THE CARDIO-VASCULAR SYSTEM.**—Arterial and venous pulses should be examined first, then the peripheral signs of heart failure should be sought and the examination is completed with inspection and palpation of the præcordium and auscultation of the heart. *The venous pulse* should be examined with the subject reclining at approximately 45°; in normal subjects it appears just above the clavicles in this position. The upper limit of a normal pulse wave is 3 cm. above the sternal angle. Normally there are three positive waves: a sharp "a" wave due to auricular systole; a small "c" wave due to ventricular systole and largely transmitted from the adjacent carotid; and at the height of auricular filling a blunt "v" wave whose apex just precedes the opening of the auriculo-ventricular valves, signified by a steep trough in the venous pulse. The venous pressure may be generally elevated in heart failure, pericardial tamponade, constrictive pericarditis and mediastinal obstruction, or individual waves may be augmented, diminished or absent. The jugular venous pulse is distinguished from the carotid arterial pulse by the following features: (1) triple wave form, (2) the diffuse undulating nature of the pulse which is seen over a relatively large area, (3) an upper level of pulsation (which, however, may not be seen when the venous pressure is very high), (4) variation of the level of pressure with respiration and an increase in the distinctiveness of the separate waves with inspiration, (5) elevation of the level of the venous pulse in the neck by hepatic pressure, and (6) obstruction of the venous pulse by relatively gentle pressure at the root of the neck. The auricular "a" waves have a sharp, "flicking" form and are presystolic in time. They are augmented in conditions which cause auricular systolic hypertension and thus are largest in tricuspid stenosis and when auricular systole is obstructed by closed auriculo-ventricular valves, as in the occasional coincidence of auricular and ventricular systole in heart block; "a" waves are also augmented in conditions of right ventricular hypertension such as pulmonary stenosis and pulmonary hypertension. Large fused "cv" waves coinciding with ventricular systole, having a large pulse volume, appearing to rise rather slowly and followed by a diastolic collapse, are characteristic of tricuspid incompetence and may be confused with a Corrigan pulse in the carotid arteries.

*The arterial pulse* is traditionally examined at the wrist, but both radial pulses and the brachial vessels should be palpated, and where there is any difference in these pulses, or if hypertension is present, the subclavian, carotid and femoral pulses should also be felt. The pulse pressure and volume determine the size of the pulse; the level of the blood pressure is difficult to determine without a sphygmomanometer, although a rough estimate may be made by compressing the brachial artery with the thumb whilst the fingers of the right hand are used to detect the point of obliteration. Pulse volume is increased when the stroke output is increased in high cardiac output states, in aortic incompetence, and, to a lesser degree, in mitral incompetence. The pulse appears full and bounding and often pulsation can be felt as far as the digital arteries; the hands are warm and often moist. The pulse is diminished in low cardiac output states and when there are obstructive lesions such as aortic stenosis and mitral stenosis. Aortic valve disease causes a change in the pulse wave form, apart from an alteration in its volume; aortic stenosis causes a notched and flattened wave—the anacrotic pulse, whilst aortic incompetence (and other causes of a rapid leak from the arterial system such as patent ductus arteriosus or arterio-venous aneurysm) causes a water-hammer pulse. Combined aortic stenosis and aortic incompetence produces a deeply notched pulse—the pulsus bisferiens. An absent peripheral pulse may be due to very low pulse pressures from an arterial obstruction (e.g. peripheral embolism or coarctation of the aorta), but the diastolic pressure and the resting blood flow to the area concerned may be within normal limits. The state of vessel walls is assessed by digital examination; the brachial vessels are always

thickened in established hypertension and further evidence of the state of the smaller vessels may be obtained by ophthalmic examination.

*Heart size and shape* are most accurately determined by radiological methods. Percussion of the chest and palpation of the apex may be illusory; however, the position of the apex beat is a reliable guide to heart size when its displacement is not due to deformity of the thorax, fibrosis of lung, or pleural effusion, and when apparent displacement is not due to great overactivity as in thyrotoxicosis. Percussion of the præcordium reveals relatively gross changes in size to right or left, and is helpful when the apex cannot be felt when emphysema is present, but many physicians now regard evidence from percussion of the heart with suspicion.

Abnormal *pulsations* of the heart may be detected by observation and palpation, and are of great significance in diagnosis. The hyperdynamic heart of anxiety, thyrotoxicosis and other high output states causes an increased pulsation of the whole præcordium and apex. In conditions with a left to right shunt, such as auricular septal defect, the increased activity may become very great, affecting the whole præcordium, or it may be more or less confined to the intercostal spaces over the right ventricle and pulmonary artery. Equally significant but much more difficult to appreciate is the quiet heart of a pericardial effusion, myxœdema or a primary cardiopathy. In left ventricular hypertrophy the apex beat is strong and appears to be sustained, but when ventricular dilatation develops the beat eventually loses its heaving quality. Right ventricular hypertrophy is characterised by a systolic heave or lift in the parasternal region and præcordium; this is felt by placing fingers in the intercostal spaces or placing the flat hand along the parasternal region over the right ventricle and pulmonary artery; sometimes it is best appreciated by placing the fingers high in the epigastrium and directed towards the right ventricle. In right ventricular hypertrophy the apex beat is rather localised and is still formed by the left ventricle which appears to tilt forward on the enlarged right ventricle. Pulsation of the right ventricle merges into that of the pulmonary artery at the level of the third interspace. The vibrations caused by heart sounds and murmurs can be palpated when of sufficient intensity, and they are often superimposed on the pulsations described above. The tapping quality of the apex in mitral stenosis is due to left ventricular systole together with an appreciation of the loud and sharp first heart sound. In pulmonary hypertension the diastolic shock of valve closure may be felt as well as the systolic thrust of the tense pulmonary artery.

*Heart sounds and murmurs* are vibrations set up by the main events in the cardiac cycle and are essentially recognised by auscultation, but when of sufficient intensity they may be appreciated by palpation. Heart sounds and murmurs may be recorded by phonocardiography (see below). *Technique of auscultation.* The stethoscope should have well-fitting earpieces and moderately thick tubing between 10 and 15 in. long—chest pieces are of two types, bell and diaphragm, and available in a combined form; the bell end is better for low-pitched sounds and murmurs, the diaphragm for high-pitched ones. On auscultation it is essential to listen to one sound or murmur at a time, and with practice the other sounds and murmurs may be actively excluded. The ear is more sensitive to higher frequencies than to the lower ones—low frequency vibrations must be of much greater intensity to bring them within the range of audibility. *Heart sounds.* The timing, pitch, intensity and site of maximal intensity should be noted for all sounds. The first heart sound is due to ventricular systole and the closure of auriculo-ventricular valves. It is best heard in the mitral area and is preceded by a soft sound due to auricular systole. It often appears to be split and is soft when the P-R interval is long, and it is loud and short when the P-R interval is short, and when there is tachycardia; it also becomes very loud in mitral stenosis. Systole is normally silent and terminated by the second heart sounds, which are due to the closure of the semilunar valves. Although usually referred to as the second heart sound, there are essentially two components, aortic and pulmonary, which are

slightly asynchronous. The second heart sounds are best heard in the second left intercostal space, where slight splitting, increased by inspiration, is physiological. The aortic second sound is the first component, and, being louder, is widely heard, and is the second heart sound at the mitral area. The later component is pulmonary and is softer. It follows that augmentation of either component reflects a rise of pressure in the vessel concerned; conversely when the pressures are low, valve closure is delayed and less violent, *i.e.* in pulmonary stenosis P2 is significantly late and soft. Asynchronous contraction of the ventricles due to bundle branch block leads to wide separation of the second heart sounds which is proportional to the degree of delay of systole in the affected ventricle. The third heart sound is the most important additional heart sound. It is associated with ventricular filling and occurs in early diastole. It is a low-pitched, soft thud, best heard at the mitral area (except in the case of right ventricular failure) and with light pressure of the bell-ended stethoscope. It is physiological in the young, its incidence diminishes up to the age of 40, and thereafter it is pathological; it occurs in all forms of heart failure, and when the heart rate is normal or slow it produces a protodiastolic gallop rhythm (triple rhythm). The third sound may become the loudest of the heart sounds in heart failure and when the heart rate is increased there is summation of the third heart sound and the next auricular sound, producing a presystolic gallop rhythm. In constrictive pericarditis the third heart sound is shortened and sharpened and occurs rather earlier in diastole than is usual; this may be due to the very high venous pressure and restriction of ventricular filling by the pericardium. In mitral stenosis rapid ventricular filling is prevented by the mitral obstruction so that a third sound is not heard; however, in pure mitral incompetence there is a free and augmented flow to the ventricle so that a third heart sound is usual. An additional sound, the opening snap, is heard in mitral stenosis. It is due to the diastolic opening movement of thickened inelastic mitral valves, but it disappears when such valves are completely rigid and calcified. It is short and sharp and best heard above and inside the apex. Added sounds in systole are not uncommon; their significance is not well understood but it appears that most are innocent. It has recently been shown, however, that a short sharp sound in early systole is associated with ejection when the great vessels are dilated beyond the semilunar valves.

*Murmurs* are due to a more prolonged series of vibrations than sounds. The timing, duration, pitch, intensity, variations with posture and respiration, site of maximal intensity and radiation should be observed in all murmurs. *Systolic murmurs.* It is customary to classify systolic murmurs in the first instance as either innocent or organic. The distinction has been largely based on loudness, but it is doubtful whether this is justifiable, since most loud organic systolic murmurs presumably start as soft ones; duration and quality are probably more important. Many systolic murmurs are related to deformities of the chest or very minor abnormalities in the heart, and as such they are of entirely benign significance but not necessarily innocent in the sense that there is no structural or haemodynamic cause for their existence.

Many children have a soft, mid-systolic, parasternal murmur, especially when there is tachycardia—this is of no significance and may disappear in adult life. Soft, mid-systolic murmurs in the parasternal region and over the pulmonary artery are not uncommon in adults; some are due to an increased blood flow into the great vessels, *e.g.* in pregnancy, thyrotoxicosis and auricular septal defect, and others are associated with sternal depression or kyphoscoliosis. A soft, mid-systolic murmur may occur in the parasternal region without evidence of an hyperdynamic circulation or heart disease, and these often diminish greatly with a change from a reclining to an upright posture and are regarded as innocent. The systolic murmurs of aortic stenosis, aortic sclerosis and pulmonary stenosis are also of maximal intensity in mid-systole—those arising in the aortic valve are best heard in the second right intercostal space and radiate to the neck and downwards towards the apex; those

arising in the pulmonary outflow tract are best heard in the third left intercostal space and radiate upwards to the left, and downwards. The systolic murmurs due to regurgitation from the ventricles, *i.e.* mitral and tricuspid incompetence and ventricular septal defect, tend to be heard throughout systole (pan-systolic). In the case of mitral incompetence the murmur may be so loud and long at the apex that the second heart sound cannot be distinguished there, and it tends to radiate towards the left axilla. In tricuspid incompetence the murmur is not usually as loud as in mitral incompetence; it is heard best at the lower end of the sternum and varies with respiration.

*Diastolic murmurs.*—All indicate heart disease. Incompetence of the aortic or pulmonary valves is shown by an early diastolic murmur which is high pitched and diminishing, starting immediately after the second heart sound and often loudest in the third or fourth left intercostal spaces. These murmurs are best heard when the patient is in an upright position with the breath held in expiration. A diaphragm chest piece is superior to the bell for the detection of soft, early diastolic murmurs. The murmur of mitral stenosis is of much lower pitch and its onset is delayed well after the second sound; it is heard best at the apex and aptly described as a rumble. The presystolic murmur, or more accurately the auricular systolic murmur, follows the mid-diastolic murmur of mitral stenosis; it is short and brisk, and its crescendo rises to the first heart sound. Mid-diastolic murmurs also occur in conditions associated with an increased flow through the auriculo-ventricular valves, *e.g.* auricular septal defect, ventricular septal defect and patent ductus arteriosus. Mid-diastolic murmurs are best heard where the patient is reclining and half-turned over to the left side, and by using light pressure over the apex with a bell end piece to the stethoscope. Continuous murmurs occur when the pressure on one side of a vascular fistula is higher than that on the other throughout the cardiac cycle. A continuous rushing noise is produced, usually loudest in systole. Murmurs are often described in such terms as "blowing", "musical", "harsh", "machinery", "seagull", etc. There is little place for such inaccurate and unsatisfactory adjectives if murmurs are described in terms of loudness, pitch, duration and site of maximum intensity. *Phonocardiography* is a graphic method of registration of heart sounds and murmurs. By means of sensitive microphones, valve amplifiers and multiple galvanometers, synchronous records from various sites on the præcordium may be made and the characteristics of human hearing with the stethoscope may be represented. By this means permanent records of auscultatory findings at particular times in the natural history of the disease may be made, heart sounds may be accurately timed and identified, and the special features of various murmurs may be determined. At present the methods do not lend themselves to routine use, for considerable technical skill and care is required, and quiet undisturbed conditions are necessary in order to obtain useful records.

*Electrocardiography.*—When heart muscle contracts the polarised state which exists between the cell membrane and its cytoplasm is disturbed and total depolarisation follows; recovery is associated with repolarisation. These phases of ionic reorientation are accompanied by minute potential changes which are conducted in the surrounding medium. At maximal activity and at complete rest there is no change and no current flows. The heart is thus the source of electrical charges which are conducted through the surrounding medium in all directions to the body surface, and an electrocardiogram is the graphic registration of the surface potential changes by means of a galvanometer. Since the heart is completely surrounded by a varying electrical field, it follows that the potential changes may be registered at any point on the body surface, and at such points (or lead positions) the electrical changes represent the resultant electrical forces in the axis of the electrode.

In practice the electrocardiographic lead connections between the body and the galvanometer are of two types: (1) *Bipolar* when two electrodes are placed on different

points of the surface and the resultant potential differences existing between them are recorded. The standard leads of Einthoven are bipolar and obtained by connecting the left arm and right arm to form lead I, the right arm and left leg to form lead II, and the left leg and left arm for lead III. The apices of the hypothetical Einthoven triangle are formed by connections from the left arm, right arm and left leg, and the heart is considered to be lying in the centre and equidistant from each apex of the triangle. Bipolar chest leads are formed by connecting an exploring chest electrode and the right arm (CR leads). (2) *Unipolar* leads are formed by recording between an exploring electrode and an indifferent electrode which is formed by joining together three limb leads, each through 5,000 ohm resistances (Wilson). The exploring electrode may be used to record and measure the voltages from any point on the surface (V leads).

The horizontal components of the heart's electrical field are explored anteriorly by means of chest electrodes (either V or CR) at the following stations, which are conventionally designated 1 to 7 (CV or CR): 1 and 2 are at the level of the fourth intercostal space on the right and left sides of the sternum, 4 is at the level of the fifth left intercostal space in the mid-clavicular line, and 3 is half-way between 2 and 4. Numbers 5, 6 and 7 are also in the fifth left intercostal space in the anterior, mid and posterior axillary lines. CR leads show slightly greater voltages than V chest leads and when recording from the routine stations  $C_1$  to  $C_7$  the differences are insignificant. The components of the central electrical field in the frontal plane are recorded in Einthoven's standard leads and by means of the unipolar limb leads VR, VL and VF, referring to the right arm, left arm and left foot connections of the exploring electrode.

The normal electrocardiogram consists of a series of waves arising from an isoelectric baseline and associated with each heart beat. By convention positivity is recorded above and negativity below the baseline. The P wave is caused by activation of the auricles and is the first wave. It is upright in standard leads and in left-sided chest leads, but it is negative in VR and often inverted in  $V_1$ . The duration of the P wave is usually 0.10 second or less and its amplitude varies from 0 to 2.5 mm. P waves are followed by a small recovery wave (auricular T wave), but this is not usually recognisable in the ensuing isoelectric part of the PR interval. The PR interval represents the time taken by an impulse from the sinus node to reach the ventricles; it is measured from the beginning of the P wave to the beginning of the ventricular complex and varies normally from 0.12 second to 0.21 second.

The QRS complex is the second and major series of deflections of the electrocardiogram and is due to ventricular activation. Q refers to any initially negative wave. R waves are positive waves and S waves are negative waves following positive deflections. Left ventricular activity dominates the electrical field during the phase of ventricular activation and its resultant positive axis is directed downwards and to the left; the surface components of this field are thus positive over a wide area of the left chest and leads taken from this area are said to show left ventricular complexes. It is probable, however, that such deflections are the resultant effect of the electrical activity from the whole heart. Dominant "left ventricular" complexes (qR pattern) may be obtained in any one of the standard leads, but mostly in lead I, and in left chest leads  $V_6$ ,  $V_5$  and  $V_7$ . Normally there is a small initial Q wave in leads I, II,  $V_6$  and  $V_7$ ; it does not exceed 0.04 seconds in duration and is usually less than 2 mm. R waves in "good" left ventricular leads exceed 5 mm. and are usually more than 10 mm. high. The height of the R wave in the left chest leads added to the depth of the S wave in right chest leads should not exceed 35 mm. A short, brief S wave follows the R wave in leads I and  $V_7$  and this wave deepens and widens as right-sided lead stations are approached. In right-sided chest leads  $V_1$  to  $V_3$ , the ventricular complex is usually of an RS form, the height of R wave being from 1 to 5 mm. and the depth of the S wave from 5 to 15 mm. in  $V_1$ . The R waves gradually increase across the chest to  $V_6$  or  $V_7$  and the S waves;

diminish. The total duration of the QRS complex is usually 0.08 second and should not exceed 0.10 second.

The direction of the greatest electrical potential in the frontal plane may be assessed from the direction of the main deflections in the standard leads. When the QRS is mainly positive in lead I, and mainly negative in lead III there is left axis deviation, which indicates a rather horizontal position of the electrical axis; this is found in thickset subjects with a high diaphragm, and often in patients with left ventricular hypertrophy. When the main QRS deflection in lead I is negative and in lead III is largely positive there is right axis deviation, which is associated with the vertical heart of tall thin subjects, with emphysema and with right ventricular hypertrophy.

The QRS complex is followed by the S-T interval and T waves. The S-T interval represents total activity of the myocardium and should thus be isoelectric; usually there is a slight upward curving slope from the end of the S wave to the T wave, but general deviation of the S-T segment from the baseline of 1 mm. or more is pathological, and smaller deviations than this may be significant when taken in conjunction with the clinical and other electrocardiographic findings. The T wave is associated with recovery of the myocardium. It is normally upright in all standard leads but it may be inverted in lead III when the heart is horizontal, as in patients with obesity, and a high diaphragm; on deep inspiration, which moves the heart to a more vertical position, such negative T waves tend to become upright. The T wave is also often negative in lead  $V_1$ , and in children the negativity of T waves from the right chest may extend to the left as far as  $V_4$ . T waves are normally positive when the ventricular complex shows a left ventricular qR pattern. The Q-T interval indicates the total duration of ventricular excitation and recovery; it is normally an inverse function of heart rate and varies from 0.39 to 0.41 seconds at 70 beats per minute. The Q-T interval is prolonged by carditis and hypocalcaemia and shortened by digitalis. The U wave is a small deflection which follows the T wave and is positive in left ventricular leads, where it is best seen.

The abnormal electrocardiogram shows abnormalities of two different kinds. Firstly, disorders of the sequence of auricular and ventricular contraction and the time relations between successive cycles may be shown—these are the arrhythmias—and here the electrocardiogram confirms accurately abnormalities which may be detected by clinical examination. The electrocardiogram in the cardiac arrhythmias is described in the section on this subject. Secondly, a different type of information concerning the qualitative changes of individual QRS and T waves may be shown; such changes are due to alterations in the relative order in which different areas of myocardium pass through stages of excitation and recovery, and the abnormalities referred to in this group are associated with various clinical conditions but they have no direct clinical counterpart, e.g. there is no physical sign corresponding to a negative T wave. *Abnormalities of the P wave.* P waves become tall (up to 5 mm.) and sharp in right auricular hypertrophy, and are best seen in leads II and III, and in  $V_1$  to  $V_3$ , e.g. in congenital heart disease and pulmonary heart disease. Pathological P waves due to left auricular hypertrophy are seen in mitral stenosis; they are notched and widened and the two peaks correspond to right and left auricular activity respectively. When activation of the auricle starts at its caudal end, the direction of activation is reversed, and P waves become inverted in lead III, VF and left chest leads, e.g. in nodal rhythm.

*Abnormalities of the QRS-T complex.—Left ventricular hypertrophy.* The first electrocardiographic sign of left ventricular hypertrophy is an increased height of left ventricular R waves. At a further stage the duration of the QRS is slightly prolonged and the T waves in left ventricular leads become flattened; in more extreme degrees the ST segment is depressed below the isoelectric line and it merges into an inverted T wave. Ultimately when ventricular muscle is greatly damaged, the voltage becomes lower, the duration longer and a left bundle branch block pattern with in-

verted T waves may emerge. The changes of left ventricular preponderance are best seen in lead I, VL and left-sided chest leads. The tall R waves in I and deep S waves in III are due to left axis deviation which is mostly present, but occasionally the electrical axis may be more vertical (especially in aortic stenosis) and then the QRS-T changes of left ventricular preponderance are best seen in leads II, III and VF. *Right ventricular hypertrophy.* The normal preponderance of the left ventricle masks early right ventricular preponderance which is often difficult to detect without additional leads taken from the right side of the chest. The R waves of right pectoral leads are of increased amplitude and S waves tend to diminish. The R wave from hypertrophy of the right ventricle tends to occur slightly after the normal initial R wave in  $V_1$ , so that a positive secondary R wave, producing a notched complex, appears in  $V_1$  to  $V_3$  and resembles the pattern of right bundle branch block. Right ventricular hypertrophy is reflected in  $V_5$  to  $V_7$  by a deepening of normal S waves and the standard leads generally show right axis deviation. In extreme degrees of right ventricular preponderance the R wave is not followed by an S wave in  $V_1$  to  $V_3$  and it exceeds the R wave in  $V_5$  to  $V_6$  and is followed by inversion of the T waves from  $V_1$  to  $V_3$  or  $V_4$ .

*Bundle branch block* (intraventricular block) (see also p. 833). The essential feature of the electrocardiogram of bundle branch block is an increased duration of the QRS time; it is due to lesions of the intraventricular septum and also occurs as a transitory functional phenomenon in acute dilatation of the heart, e.g. in pulmonary embolism. Left bundle branch block is always associated with heart disease, whereas right bundle branch block may be innocent. *In left bundle branch block* the ventricular septum is stimulated from the right side, and activation of the left ventricle is delayed so that the normal initial Q wave of left ventricular leads ( $V_5$  to  $V_6$ ) is replaced by a small R wave from the septum, which is followed by a delayed R wave due to activation of the left ventricular muscle. This is reflected in late wide S waves after an initial R wave in right chest leads. The S-T segment is usually depressed below the iso-electric line and the T wave is secondarily inverted in leads showing the left-sided pattern. *In right bundle branch block* the initial deflections of the QRS are normal since the septum is normally stimulated from the left side. Leads  $V_1$  to  $V_3$  show that the small initial R wave is followed by a second and taller R wave from the right ventricle.  $V_5$  to  $V_6$  show the normal qR pattern followed by a wide S wave which reflects delayed right ventricular activation.

*Myocardial injury.*—Damage to the myocardium is shown in changes of the ventricular complex of the electrocardiogram. The cause is mostly ischaemia with or without infarction, but inflammation, infiltration, intoxication and trauma may occasionally produce similar changes. The degree and extent of damage may be assessed approximately from abnormalities of the T wave, S-T and QRS deflections and from the leads in which these changes are seen to occur. *The T wave* may become flattened and inverted in left ventricular leads from ischaemia and other injurious processes. The change is non-specific and reversible. In coronary disease the T wave inversions tend to be sharp and form a symmetrical triangle below the iso-electric line. Inversion may be transient and produced only by effort in the first instance, or a spontaneous transient inversion may be the only evidence of a small restricted infarction. *The S-T segment.* Deviation of the S-T interval may represent more severe degrees of injury and, though reversible, recovery may be slower than in the case of a fleeting T wave inversion. Injury to the endocardial layers of muscle causes S-T depression in surface leads "facing" the lesion, whilst relatively superficial injury causes an S-T elevation; the former change is seen in severe attacks of angina pectoris and in coronary insufficiency and S-T elevation is seen in pericarditis and in recent cardiac infarction. Leads recording from the opposite surface of the body to that which is adjacent to the underlying lesion show reciprocal changes in the S-T deviation, though these are usually of slighter degree, e.g. in posterior

cardiac infarction ST elevation is seen in lead III and VF, but præcordial leads frequently show S-T depression. *The QRS deflection.* Potential changes are not produced by necrotic muscle so that an area of cardiac infarction does not contribute to the R wave and in leads "facing" an area of infarction large negative waves (pathological Q waves) appear and are the result of positive potentials arising in remaining normal muscle and directed away from the exploring electrode. Pathological Q waves are of more than 0.04 second duration and usually more than 2 mm. deep, they may occupy the whole QRS time (QS waves) or be followed by an R wave. The Q wave is a permanent abnormality but with time it may become smaller and the number of leads which show it may become fewer. Since few conditions other than infarction are responsible for local muscle death and replacement, it follows that the pathological Q wave is almost specific for this condition.

In acute cardiac infarction S-T elevation is often the first abnormality; it soon regresses but may persist. Q waves may appear within minutes or several hours after the onset of pain, but the T wave inversion often only becomes apparent as the S-T segment subsides towards the iso-electric level. This pattern of cardiac infarction is always essentially the same, but these changes may occur in any lead, depending on the site of the lesion in the heart and the position of the heart in the thorax.

The common sites of infarction may be recognised by the following patterns:

1. *Anterior cardiac infarction.*—Characteristic Q waves and T wave inversion are present in leads  $V_3$  to  $V_6$  with more or less distinctive changes in leads I, VL,  $V_5$  and  $V_6$ .
2. *Posterior cardiac infarction.*—The deep Q waves and T inversion are found in leads II, III and VF. Physiological Q waves in lead III are not accompanied by changes in other leads and on deep breathing normal Q waves are diminished.
3. *Lateral infarction.*—The changes of infarction are found in leads I, VL and  $V_7$  and may be combined with anterior or posterior patterns.
4. *Septal infarction.*—Q waves are present in  $V_1$ ,  $2$  and  $3$  (i.e. QS waves in these leads) and may be combined with either anterior or posterior patterns of infarction.

**RADIOLOGY IN HEART DISEASE.**—Three important methods are used in radiological diagnosis of heart disease; radioscopy (X-ray screening), telerradiography (films taken at a tube distance of 6 ft. or more) and angiocardiology. Less frequently used methods are electro-kymography and roentgen-kymography, by means of which pulsations may be recorded, and tomography, which is a method of investigating structures at various depths in the thorax.

The radiological silhouette of the mediastinum shows the following structures from above downwards: on the right border a soft straight line, the superior vena cava, joins the sterno-clavicular joint to a gentle convexity due to the ascending aorta, at the lower end of which the hilar vessels protrude into the right lung shadow; below this a larger convexity due to the right auricle extends to the diaphragm below, where a soft straight line often interrupts the sharp angle between the auricle and diaphragm, and is due to the inferior vena cava. On the left border the aortic arch forms a smooth, semicircular knob (diameter from 2 to 4 cm.) just below the sterno-clavicular joint; this meets a second and somewhat longer convexity—the pulmonary arc, due to the main left branch of the pulmonary artery. Below this the short, flatish segment of the left auricular appendage joins the bold sweep of the left ventricle which meets the shadow of the diaphragm at a variable angle. On radioscopy all of these structures are moving. In systole the left ventricle moves sharply inwards and so does the right border formed by the right auricle, whilst the pulmonary artery and aorta above move outwards. Pulmonary vessels form the hilar shadows and on



screening slight pulsation is normally seen in the main branches. Films taken at a fast exposure time are necessary to study the smaller lung vessels in detail—a fine arborisation of vessels may be seen almost as far as the pleura.

The oblique views provide further useful information. After screening in the antero-posterior position, the patient is rotated to the left so that the right chest is applied to the screen (the first or right oblique), the right arm is moved backward and the left forward; these adjustments are made by the operator and, with experience, a satisfactory view is soon obtained. In this view the anterior border of the mediastinal shadow comprises the aorta (the circumference of the arch may be seen) and a gentle curve due to the pulmonary artery, the upper part of the right ventricle, and the border of the left ventricle below. The posterior border may be outlined by a barium swallow and comprises: aorta, a lighter region due to the left main bronchus, and below this a slight gentle curve due to the left auricle, and a variable small part of the right auricle followed by a short, straight line due to the inferior vena cava. The second oblique or left oblique position is obtained by rotating the patient so that the left shoulder and chest are pressed to the screen; the arms are moved again to give a clear view. The anterior border is formed of two bold convexities, that above being due to the ascending aorta and that below due to the right auricular appendage and the right ventricle. The ascending aorta may be followed in a continuous backward curve over the arch to the descending aorta behind. Below the arch of the aorta a second arch, due to the pulmonary artery and its left main branch, extends from the base of the heart shadow to intersect the shadow of the descending aorta. Below this there is a large backward convexity due to left auricle above and left ventricle below—the latter extends backwards to reach the line of the descending aorta, and when the patient takes a deep breath the ventricle is separated from the anterior line of the dorsal spine by a short space. The point of intersection of the ventricle with diaphragm below is near the interventricular sulcus. In the frontal view the aortic valve lies almost in the centre of the heart shadow and slightly to the left of the mid line, whilst the mitral valve lies somewhat lower and slightly farther to the left. During radioscopic examination it is most important to view the whole chest, noting any deformity of the thoracic cage which may influence an assessment of heart size through displacement of the heart within the thorax.

The apparent size and shape of the heart vary greatly in normal individuals. Deformities of the thorax such as funnel depression of the sternum and kyphoscoliosis often produce gross deviations (usually to the left) which may be mistaken for enlargement. Radioscopy in all views, however, usually indicates the nature of the condition. Minor degrees of apparent enlargement may be found when there is bradycardia, in obese subjects when the diaphragm is high and the heart tends to be horizontal, and when there is epicardial fat seen as a soft triangular shaped shadow beyond the true apex. Very small hearts are seen in long lean individuals and as a result of wasting disease.

**RADIOLOGY OF THE ABNORMAL HEART.**—Investigation of cardio-vascular disease by radiology is largely concerned with the assessment of enlargement of the whole heart or its separate chambers and with changes in the vascular shadows of the lungs. *Pulmonary vessels.* Gross changes in the level of blood flow to the lungs are recognisable by radiology. Small, quiet branches of the pulmonary artery and generally light lung fields indicate a diminished blood flow (*i.e.* oligæmia); large, pulsating branches and a generally increased opacity of the lungs due to increased vascular markings indicate an increased blood flow (*i.e.* plethora or pleonæmia). Congestion of the lungs from heart failure is more common than plethora, the hilar regions are dense, the separate vessels become indistinct due to interstitial œdema, and the general increase of density extends for a varying distance into the lung fields and the vessels do not pulsate vigorously as in pulmonary plethora. Prominent interlobar fissures and effusions of varying sizes are also found in association with congestion.

*The pulmonary artery.*—Enlargement of the main pulmonary artery shows as a bulge on the left border in the anterior view and as a large oval opacity below the aortic arch in the left oblique view. An enlarged main pulmonary artery may be associated with either plethora or oligæmia of the lung fields. In the young, in subjects with a vertical narrow heart, and in deformities of the thoracic cage with rotation of the heart, a normal pulmonary artery may appear enlarged.

*The aorta.*—Dilatation of the aorta due to syphilitic aortitis may be diffuse, or local and aneurysmal (see also p. 858). In the anterior view, enlargements of the aorta cause a widening of the superior mediastinum from bulging of the ascending aorta on the right or dilatation of the arch and descending aorta on the left side. A similar widening or localised bulging of the mediastinal shadow may be produced by unfolding of the aorta in hypertension, tortuosity of the aorta from degenerative changes and by mediastinal tumours. Calcification in the wall of the aorta is often helpful in the diagnosis of these conditions. A barium swallow outlines the posterior border of the arch and is an aid to assessment of its diameter. Irregularities of the descending aorta may also be outlined by deviation of the barium-filled œsophagus. Localised pulsation, though not expansile, is sometimes transmitted to tumours; on the other hand, an aortic aneurysm when filled with clot may show no pulsation. Excessive pulsation of the whole aorta is usually due to aortic incompetence, but may be due to a high cardiac output. When due regard is paid to the appearance in all views, it is usually possible to distinguish syphilitic dilatation from other conditions, but when doubt remains, angiocardiology can show clearly the course of the aorta and the calibre of its lumen. Coarctation of the aorta may be recognised by the absence of a normal aortic knuckle, rib notching and enlargement of the ventricle. Here also angiocardiology is necessary if accurate anatomical details are required.

*The auricles.*—The enlarged right auricle bulges from the lower half of the cardiac shadow into the right lung field and meets the diaphragm at a variable angle. The right auricle is often greatly enlarged in congestive heart failure, especially when there is tricuspid incompetence; it is usually associated with enlargement of other chambers but it is selectively enlarged in organic tricuspid valve disease. An enlarged left auricle also bulges on the right border, but at a higher level than the right auricle, and when both are enlarged the right border of the heart below the aorta is formed by two graceful, intersecting arcs. The left auricle is also seen as a characteristic hump below the pulmonary arc on the left border of the heart, and sometimes the whole contour of this chamber may be seen through the heart shadow. Its size and minor degrees of enlargement are best assessed in the right oblique view, with a barium swallow. As the barium is followed down, it changes its course by turning backwards just below the level of the bronchus at the upper end of the left auricle; it continues in a gentle curve almost to the lower margin of the heart shadow—the patient should be turned to and fro in this oblique position until the maximum backward displacement of the barium is best seen. A small left auricular curve is often seen in normal subjects, but this can be straightened with a deep inspiration. In some patients, when the barium-filled œsophagus appears as a straight line in the right oblique view, a large left auricle can be best seen in the left oblique view. Expansile pulsation of the left auricle in ventricular systole is seen in severe degrees of mitral incompetence. In the anterior view both right and left borders of the auricle are seen to protrude beyond the cardiac shadow when the ventricle moves inwards in systole.

*The ventricles.*—The right ventricle does not form a distinctive border of the heart in any view on radioscopy so that its enlargement is not easily recognised. With considerable right ventricular enlargement the heart may appear relatively normal sized in the anterior view, but the apex is often high and the left border rather straight above and below it. In the left oblique view the angle between the aorta and the anterior border of the right heart is sharpened, producing a more

globular heart shadow. The left ventricle enlarges backwards as well as outwards. In the anterior view the ventricular part of the left border develops a bold curve, and extends farther to the left; in the second oblique view the left ventricle extends backwards, often well into the vertebral shadow. An acute angulation or local bulging on the left ventricular border indicates a ventricular aneurysm, and on screening the swelling may bulge outwards as the apex is withdrawn in systole.

**ANGIOCARDIOGRAPHY.**—Radiography of the heart chambers and great vessels after an injection of radio-opaque substance is known as angiocardiology. Several types of apparatus are used. Manually operated X-ray film cassette changers have the disadvantages of inaccurate timing and slow speeds (rarely two pictures per second may be obtained); mechanical cassette changes allow a more rapid sequence of film exposures but cinematography provides a more continuous picture of the passage of dye through the heart and will probably replace other methods. Oblique or lateral views are often necessary, but it is desirable to eliminate a second injection of dye by some form of simultaneous two-plane cassette changer. The radio-opaque substance which is most widely used is 70 per cent. diodone. The dye is injected through a wide bore needle or catheter to facilitate a rapid injection, which should take less than 2 seconds. Forty to 50 ml. are required for adults and 10 to 30 ml. for children. The dye is non-toxic in these doses. The patient should be recumbent. All children should be anaesthetised and there is much to be said for using a general anaesthetic in adults. The procedure is not without risk and the overall mortality is approximately 0.5 per cent., but most of the deaths have occurred in severe cyanotic congenital heart disease.

The normal angiocardigram shows the right heart chambers as a "U"-shaped curve, and on the right side the column of dye in the superior vena cava is seen entering the right auricle, and in the centre the tricuspid valve may sometimes show as a notch. On the left side of the "U" lies the right ventricle, a ragged chamber, the size of which will depend on whether the picture is taken in systole or diastole. The pulmonary outflow tract is well seen towards the periphery of the cardiac silhouette at the base of the right ventricle, as the terminal portion of the "U". The main pulmonary artery does not form the pulmonary arc. In the left anterior oblique view, the superior vena cava is superimposed on shadows of right auricle and right ventricle, which are seen anteriorly. The pulmonary artery curves backwards, forming an arch, the terminal downstroke of which is formed by its left main branch. The bifurcation of the pulmonary artery is usually seen about the centre of the arch. The pulmonary arteries and veins are well seen in both anterior and oblique views. In the anterior view, the pulmonary veins are seen draining into a central oval opacity, which is the left auricle. Superimposed upon the auricle is the base of the left ventricle; the apex of the ventricle projects downwards to the left. The left ventricular cavity varies considerably in size with the phase of the cardiac cycle. The root of the aorta is obscured in the cardiac shadow, but the dye-filled aortic arch is seen above it. The chambers of the left heart are best seen in the left anterior oblique view where the left auricle is seen above the shadow of the left ventricle. The aorta arises almost in the centre of the cardiac shadow and arches antero-posteriorly. At the origin of the aorta, which is deep in the heart shadow, the sinuses of Valsalva appear as a bulbous dilatation. In the normal adult the progress of the dye through the right heart and pulmonary arteries is seen in pictures taken between  $\frac{1}{2}$  and 4 seconds after the beginning of the injection of dye; and that through the left heart and aorta is seen in pictures taken after 6 seconds.

Angiocardiology can show abnormal anatomy of the heart chambers and great vessels, and if the passage of the dye is recorded with sufficient continuity some aspects of the dynamics of the circulation may be studied. Angiocardiology is especially valuable in congenital heart disease where shunts from the right to the left side are shown by premature opacification of the "left side", but shunts in the

reverse direction are not readily seen. In addition, the size, position and abnormalities of the aorta and its branches may be seen, information which is of value to the surgeon when planning operations for coarctation of the aorta or anastomotic operations for the treatment of cyanotic congenital heart disease. Aneurysms of the great vessels may be distinguished from other masses in the mediastinum.

**CARDIAC CATHETERISATION.**—Three kinds of information can be obtained by means of cardiac catheterisation—(1) pressures may be measured in the right heart and the pulmonary artery; (2) samples of blood for gas analysis may be obtained from these sites; and (3) by means of X-ray screening the passage of the radio-opaque catheter may reveal abnormal channels and heart chambers. Cardiac catheterisation is safest and likely to provide the most useful information when carried out by an experienced team comprising an operator, with one assistant and technicians.

**Technique.**—The plastic catheter is very flexible, radio-opaque, and has a slight curve a few centimetres from the tip: it is filled with heparinised saline from a 10 ml. syringe attached by an adaptor. The tip is introduced into the cubital vein which has been exposed and opened by a small cut after adequate infiltration of the skin and surrounding tissues by a local anaesthetic. Subsequent manipulations of the catheter should be checked by X-ray screening. The catheter is gently manoeuvred up the arm vein to the thoracic inlet where it curves into the superior vena cava to gain the right auricle. By various manoeuvres the operator may now move the catheter through the tricuspid valve to the right ventricle, the pulmonary artery and its branches. If observations on the pulmonary capillaries are required, the catheter may be pushed into the smaller lung vessels to the point of blockage.

Blood samples are withdrawn through the catheter at various points and preserved under paraffin for gas analysis with a Haldane or Van Slyke apparatus. Pressures should be measured by means of an electromanometer and an adequate device for recording graphically the pulse pressure curves.

**Applications.**—The cardiac output may be calculated from the Fick principle as follows: cardiac output (litres per minute) = total oxygen consumption in ml. per minute divided by the arterial oxygen saturation minus the oxygen saturation of mixed venous blood in ml. per litre. Oxygen consumption is obtained by means of a spirometer, arterial samples are obtained by femoral artery puncture, and samples of mixed venous blood from the pulmonary artery by catheterisation.

Intracardiac shunts may be detected by obtaining blood samples of high oxygen saturation from the right heart and pulmonary artery, e.g. in the septal defects and patent ductus arteriosus. X-ray visualisation of the passage of the catheter through these channels into the left heart or aorta is of diagnostic importance when the shunt is in the reverse direction.

Pressure measurements and pressure curves help in the diagnosis and assessment of various conditions, especially pulmonary hypertension and pulmonary stenosis. In right heart failure the diastolic pressure in the right ventricle is raised and this is reflected in a general elevation of pressures in the right auricle. Cardiac catheterisation has provided much information during the past decade concerning the haemodynamics of heart disease. Diagnosis is now more accurate and the indications for cardiac catheterisation are diminishing and are largely confined to the obscure forms of congenital heart disease.

## CIRCULATORY FAILURE

In circulatory failure the body receives an inadequate supply of blood. There are two forms; one is acute, causing shock or syncope, and is sometimes due to heart disease but often to extracardiac causes; the symptoms are mainly due to low cardiac output and systemic arterial hypotension. The second form, generally known as heart failure or congestive heart failure, is almost always due to cardiac

disease; the clinical picture is largely the result of secondary and compensatory effects of a chronic inadequate cardiac output, with the maintenance of a relatively normal blood pressure.

### HEART FAILURE

The ultimate cause of heart failure lies in the physiology of heart muscle, but the clinical causes of heart failure include all the known forms of heart disease. More than one cause is often present—thus systemic hypertension and myocardial disease often coexist, whilst rheumatic valvular disease is often accompanied by active rheumatic myocarditis. The causes of heart failure may be classified as follows : 1. Primary myocardial disease (*e.g.* inflammation, ischæmia, etc.). 2. Increased resistance to systolic ejection (*e.g.* hypertension). 3. Increased stroke volume (*e.g.* aortic incompetence, mitral incompetence). 4. Increased heart rate (*e.g.* prolonged tachycardia in infants). Generally loads due to increased volume are tolerated better than those due to increased pressure, and tachycardia is tolerated extremely well, but persistent high rates operative over a long period may lead to failure.

The essence of heart failure lies in the inability of the heart to deliver an adequate blood supply to the tissues under all circumstances. In other words the cardiac output is inadequate and fails to meet all requirements of the individual. The site of this failure may be primarily located in one or other ventricle or in the heart as a whole. Lewis emphasised that the level of cardiac output as a measure of circulatory efficiency is significant only when considered in relation to the demand on the circulation, *e.g.* in thyrotoxicosis or anæmia the cardiac output required for adequate oxygen transport at rest may be double that of the normal subject.

Under physiological conditions the heart responds to increased venous filling by a greater liberation of energy and increased output. At the level of the muscle fibre this means that increased stretching, resulting in increased surface area, results in more powerful contraction; more energy is stored in diastole and more is liberated on contraction. The isolated muscle strip or heart-lung preparation responds in this way up to a critical point beyond which a further load results in a diminished response (Starling's principle). This critical point is never reached in healthy man, but in heart failure it is reached and passed; there is then an inadequate systolic ejection into the great vessels, some blood is retained in the chambers and dilatation and hypertrophy follow. Compensatory hypertrophy is a long-term adaptation to these adverse factors. The diastolic filling pressure rises and auricular contraction becomes more forcible. Up to a point output may be restored but ultimately this is permanently reduced. The difficulty of deciding what is cause or consequence dominates all the problems in heart failure. It is still not certain whether venous hypertension behind the failing chamber is a merely passive phenomenon or whether it is positive and compensatory. Hæmodynamic changes occur very rapidly and an unstable equilibrium is soon established, so that the exact sequence of events is difficult to analyse.

Corvisart (1812) considered that the clinical phenomena of heart failure were due to the increased size of the heart pressing on the lungs and obstructing the circulation. Hope (1830) introduced the back pressure theory which has been elaborated and maintained to the present day. Starling's work with the heart-lung preparation appeared to support the back pressure theory but it should be remembered that there is no chronic dilatation or hypertrophy in the heart-lung preparation, no long-standing œdema and no elaborate system of reflexes in the central nervous system and clinical heart failure is a relatively chronic process, often lasting years. In the back pressure theory venous congestion is paramount in the formation of œdema, but there is now much evidence to show that œdema formation depends on other factors. Mackenzie and Lewis assumed that the inadequate blood supply to the organs

the important abnormality; this theory of forward failure is supported by modern researches, but the older theories cannot be abandoned lightly. It is probable that neither theory explains all the facts.

In all forms of heart failure the cardiac output is subnormal at rest in the late stages, but in the early stages output may be normal at rest and only inadequate during exercise; in other words, the cardiac reserve is diminished. An inadequate supply of blood results in its redistribution in the circulation as a whole. There is some evidence to show that the fall in renal blood flow is selective and relatively greater than the fall in cardiac output. Lowered renal blood flow results in diminished glomerular filtration and greater tubular resorption of water and salt; this appears to be a vital process and under circumstances other than congestive heart failure the mechanism has homeostatic features. The retention of water and salt leads to hæmodilution, hypervolaemia and ultimately an increase of extravascular fluid volume and the accumulation of œdema. Oliguria results from the retention of water and urine analysis at this time shows a falling salt content. Man's habitual high intake of sodium chloride is of no consequence when renal excretion is normal and unlimited, but in heart failure a deteriorating situation is potentiated. Hydrostatic factors, increased capillary permeability, increased accumulation of tissue metabolites and malnutrition probably also play a part in accumulation of œdema. Whatever the true importance of the various factors in heart failure, the importance of salt retention is emphasised by the remarkable improvement which may be achieved by salt depletion using dietetic, diuretic or ion exchange methods. Any mechanism causing further salt retention aggravates heart failure.

Venous hypertension is the most important sign of heart failure. It is possibly due to a reflex venopressor mechanism together with increased circulating blood volume, but when venous hypertension occurs behind an insufficient or stenosed auriculo-ventricular valve, this seems to be a true backward effect. In the early stages of failure and in high output states, it is possible that systemic venous hypertension is compensatory but later the adverse effects of increased venous hypertension in heart failure are shown by the effects of the recumbent posture and by blood transfusion, whilst the beneficial effects of a reduction in venous pressure are shown by venesection and change from a lying position to a more upright one. The elevation of systemic venous pressure in heart failure is responsible for the distension of the liver which must be considered of secondary importance. Even here there is some evidence that the damage to liver cells is the result of diminished blood flow rather than venous congestion.

When heart failure arises primarily on the left side, pulmonary venous hypertension develops. This is probably due to a temporary imbalance between the output of the left and right sides of the heart and this state is adversely affected by fluid retention. Pulmonary arterial pressure also rises in left heart failure and this is probably a direct consequence of the pulmonary venous congestion. Pulmonary œdema occurs when hydrostatic pressure in the capillaries exceeds the osmotic pressure of plasma. Dyspnoea is the most common symptom of heart failure and results from pulmonary congestion, cardiac dilatation which further reduces vital capacity, and an increased sensitivity of pulmonary reflexes.

There are many variable factors in the mechanisms which determine the passage from a normal circulation to one of unresponsive congestive heart failure and no one theory at present explains all of the facts. It appears that the clinical picture is produced by a series of relatively slow and only partially adequate adjustments to the diseased heart.

**Clinical Features.**—From the clinical point of view it is convenient to assess cardiac failure in terms of left-sided heart failure and right ventricular failure. Both conditions occur as isolated phenomena, or they may appear together, or more often right-sided failure follows left after a variable period when it is more satisfactory to

use the general term congestive heart failure. Whilst most cases of left heart failure are due to ventricular failure, it should be noted that in pure mitral stenosis the left ventricle is unaffected, although the clinical picture is left-sided in the early stages.

**LEFT VENTRICULAR FAILURE.**—Dyspnoea refers to the distress accompanying increased effort in breathing. It is the essential symptom of left heart failure. Cough is also common and is sometimes accompanied by hæmoptysis. Every grade of dyspnoea is encountered from the first detectable departure from physiological dyspnoea on effort to severest degrees which occur at rest and restrict all effort. Acute phases of dyspnoea, not necessarily provoked by effort, are common and range from orthopnoea, mild cardiac asthma, mild and severe paroxysmal nocturnal dyspnoea to pulmonary oedema.

At first *effort dyspnoea* occurs only with the more severe exertion; it is often only possible to detect a departure from the physiological by careful interrogation. Gradually the threshold of effort producing dyspnoea is lowered. It is often worse later in the day; undressing may provoke breathlessness, but a night's rest brings relief in the morning. Sooner or later breathlessness is present at rest and readily increased by speech, emotion and the slightest effort. Breathing is shallow, quick and obviously troublesome, being accompanied by much effort. It is never sighing and deep and is not relieved when attention is diverted. Obesity and diffuse pulmonary disease may produce a similar picture but it is rarely as severe. *Orthopnoea* commonly appears early in left heart failure. Here recumbency causes an increase of dyspnoea which is relieved by sitting or standing up. These patients sleep propped up by pillows or even prefer to spend nights in an armchair. It occurs in mitral stenosis and bronchial asthma as well as in patients with left ventricular disease.

*Paroxysmal cardiac dyspnoea.*—Paroxysmal dyspnoea and *cardiac asthma* are synonymous. Although often occurring before *effort dyspnoea* and *orthopnoea* have appeared, paroxysmal attacks usually arise later in the natural course of the disease and they may be of any degree of severity. Most attacks occur at night and it is probable that change in posture to a more horizontal level is the immediate cause, although there is often a history of an anxiety dream immediately before the attack. A particularly strenuous day's work, large meals and a greater salt intake during the preceding day may be factors which precipitate an attack during the night. Attacks commence with a sense of suffocation and dyspnoea. The patient is compelled to sit up or often to get out of bed. Characteristically patients seek an open window. There may be a sense of constriction in the chest, cough, and the expectoration of blood-tinged watery mucus. Breathing may become extremely difficult, wheezy and accompanied by very great distress. Relief is mostly spontaneous and usually occurs within an hour. Anxiety is an especial feature of nocturnal attacks and the pressor response accompanying this probably increases the severity and duration of the attacks. *Pulmonary oedema* constitutes a more severe and acute stage of left ventricular failure. Dyspnoea is worse and there is often præcordial pain, respiration is noisy and accompanied by coughing and expectoration of much watery mucus which is often pink with blood. Cyanosis develops from asphyxia caused by the transudate. Mental confusion may supervene and sometimes there is amnesia after the attack. After the pulmonary congestion has subsided, there is usually no deterioration in the patient's condition. Cough is a common symptom accompanying dyspnoea at any stage of left heart failure. Occasionally it is the dominant symptom and leads to erroneous diagnosis. *Hæmoptysis* and staining of sputum occur commonly with the severe forms of congestion. Occasionally a large hæmorrhage occurs.

**Signs.**—*Examination of the lungs* may show the presence of adventitious sounds ranging from fine basal crepitations in the early stages, to extensive coarse crepitations over all of both lung fields in pulmonary oedema. The intensity of these signs parallels the level of dyspnoea. Unilateral or bilateral hydrothorax as shown by diminished air entry and dullness to percussion may occur in pure left heart failure. The pleura is

drained by the pulmonary veins, as well as the systemic circulation. However, pleural effusions are more common in combined right and left heart failure. *Cheyne-Stokes respiration* frequently occurs in the late stages of left ventricular failure, especially in the elderly. Periods of heightened respiration alternate with depressed respiration or even apnoea. *Examination of the heart* may reveal the underlying cause of the heart failure, e.g. aortic incompetence, but of greater importance in relation to the question of heart failure *per se* is the presence of triple rhythm (or gallop rhythm). "*Gallop*" *rhythm*. This is due to the addition of a third sound, similar in timing and quality to the third heart sound heard in children and young adults. It is intimately related to ventricular filling—it may be that filling becomes audible under the impact of auricular hypertension and in the presence of damaged ventricular muscle. It is heard as a low-pitched sound shortly after the second sound, it is most easily heard at or near the apex, and when using a bell-type stethoscope. These low-pitched vibrations can often be palpated and perhaps more often seen. If the apex is observed from one side, then the lift of systole may be seen to be followed by a small after wave, coincident with the third heart sound. Tachycardia commonly accompanies heart failure. It will be readily appreciated that as diastole shortens with the increased heart rate, the third sound will approach the first heart sound; it may coincide with the sound of auricular systole which is thereby augmented and the gallop sound now appears late in diastole, giving rise to presystolic or summation gallop rhythm. Thus the essential feature of these triple rhythms, whatever the apparent cadence, is the addition of a filling sound. In some patients with early left ventricular failure the augmented systole of the hypertensive auricle can be appreciated by the presence of a loud auricular sound.

*Cardiac enlargement* accompanies heart failure. Left ventricular enlargement due to hypertrophy may be recognised by the apex which develops a sustained heaving character. As failure and dilatation increase the apex beat becomes more diffuse and loses some of its force. These qualities of the beat are more important than its position in the chest. Murmurs are of no consequence in the diagnosis of heart failure but a systolic murmur often develops with increasing cardiac size and is due to functional incompetence of the auriculo-ventricular valves.

During attacks of left ventricular failure (cardiac asthma, pulmonary oedema) the blood pressure is elevated, and there may be alternation of the pulse, which is best detected by using the sphygmomanometer but may be felt at the radial pulse. Weak beats alternate evenly with the strong; this sign should not be confused with bigeminal pulse where the weak ectopic beat is close to the preceding strong beat. In attacks of left ventricular failure there is often intense peripheral constriction shown in pallor of the skin and coldness of the extremities.

Patients with great left ventricular enlargement occasionally present with the picture of right ventricular failure and are able to lie flat. This is said to be due to mechanical embarrassment of the right ventricle, through bulging and hypertrophy of the interventricular septum which prevents the development of lung congestion (Bernheim's syndrome).

**RIGHT VENTRICULAR FAILURE.**—The commonest cause of right heart failure is pulmonary hypertension and congestion due to left heart failure. Dyspnoea is therefore a prominent symptom in congestive heart failure, but its severity and paroxysmal nature tend to subside when right heart failure supervenes. In the relatively uncommon condition of pure right ventricular failure dyspnoea is not a prominent feature, although it may be severe when parenchymatous lung disease is responsible for the right heart failure. Patients with pure right heart failure do not have orthopnoea and are often able to lie flat.

Fatigue and exhaustion are common symptoms in congestive heart failure; fatigue becomes a more prominent symptom when dyspnoea is relieved by the development of right heart failure and tricuspid incompetence. Generally dyspnoea is more in-



capacitating and unpleasant for the patient, so that fatigue is not noticed because of the limitations imposed by dyspnoea. Discomfort in the right hypochondrium from hepatic congestion is often present; it may become severe after effort and is rather slowly relieved by rest. This hepatic pain is not infrequently mistaken for gastrointestinal disease. Anorexia usually accompanies congestive heart failure, nausea and vomiting sometimes follow; similar symptoms are sometimes caused by digitalis or morphine rather than the heart failure.

Severe heart failure may cause temporary amnesias and slight confusion, but the more serious psychotic reactions are rare. Slight jaundice is often present and is due to hepatic congestion or to hæmolytic following extensive pulmonary infarction. Cardiac cirrhosis occurs in 2 to 5 per cent. of patients with heart disease and especially when there is chronic congestive heart failure with tricuspid incompetence.

**Signs.**—*Systemic venous hypertension* with congestion of both venæ cavæ and their tributaries invariably accompanies right heart failure. The appreciation of raised jugular venous pressure is the most important sign of heart failure. A partial mechanical obstruction often leads to apparent congestion of the external jugular vein which is thus unreliable for estimating central venous pressure and it should not be used unless a free venous pulse is seen. Pulsation of the internal jugular veins can be seen when there is heart failure with the patient reclining at an angle of 45°. The height of the venous pressure should be measured from the sternal angle. When the pressure is very high, congestion of veins is obvious even in the periphery. The recognition of jugular venous hypertension is difficult when there is tricuspid valve disease (see p. 877). In tricuspid incompetence a large "cv" wave rises in the neck with each ventricular systole; although this is often associated with congestive heart failure, it is not necessarily so. *Hepatic tenderness and enlargement* should be sought. Careful palpation of the abdomen usually reveals hepatic enlargement in congestive cardiac failure; systolic pulsation of the liver occurs when there is gross tricuspid incompetence. Gentle firm pressure over the liver will cause a further elevation of the jugular venous pressure; this manoeuvre may aid in the determination of the height and form of the venous pulse wave.

*Oedema* occurs in the dependent parts, at the ankles of ambulant patients, and over the sacrum, at the backs of the thighs and in the genitalia of bed patients. It is usually symmetrical—a gross difference between the degree of oedema of the ankles may indicate the presence of a local vascular lesion, particularly phlebo-thrombosis. Other manifestations of the dropsical state are pleural effusion, pericardial effusion and ascites. Oliguria and increased weight parallel the accumulation of oedema, and diuresis with a fall in body-weight is a good guide to the effectiveness of therapeutic measures. *Cyanosis* is not an essential feature of heart failure, although *peripheral cyanosis* from peripheral arteriolar constriction and stasis is often the result of low cardiac output; the hands, feet, tip of the nose and lobes of the ears are cold and blue, but the arterial blood is normally saturated with oxygen. Central cyanosis, when present, is related more directly to the underlying cause of heart failure: there are two causes—pulmonary disease producing anoxæmia, and congenital heart disease causing central mixing of the venous and arterial blood streams. Central cyanosis is more generalised and the blueness is as obvious in the mouth, tongue and retina as in the periphery. Arterial oxygen saturation is subnormal.

*Radiology of heart failure* (see also p. 803).—All degrees of vascular congestion of the lungs occur. A slight increase in the density and enlargement of the hilar shadows is found in early left ventricular failure; later the congestion extends to the peripheral lung fields. A soft diffuse haze which blurs the outline of hilar vessels extends out for a variable distance and is due to oedema. In pulmonary oedema massive shadows extend from the hilar regions over the mid zones of the lung (resembling the wings of a butterfly); the apices and bases are normally clear in acute pulmonary oedema. In left ventricular failure small effusions may appear at the bases

and in the interlobar fissures, and large effusions are commonly seen in congestive heart failure. Wedge shadows, linear shadows and other local opacities often show the presence of pulmonary infarction. The heart shadow is usually enlarged in heart failure and there is widening of the superior mediastinum due to distension of the great veins. Changes in the contour of particular cardiac chambers largely depends on the underlying disease which is responsible for the heart failure.

**Urine analysis.**—Oliguria is related to the severity of heart failure. Urine is concentrated but the sodium chloride content is low. Slight albuminuria is usually present. **Blood chemistry.** Sodium and chloride ions tend to be subnormal but plasma potassium is usually normal. Blood urea may be moderately raised when urine output is low. Gross deviations of blood chemistry may be associated with excessive therapeutic salt depletion (see pp. 416, 816). *The erythrocyte sedimentation rate* is slowed in heart failure and is therefore not a reliable guide to the course of rheumatic carditis, bacterial endocarditis and other infections in the presence of heart failure.

**TREATMENT OF HEART FAILURE.**—Heart failure presents a clinical picture of varying severity which is largely independent of its underlying cause. Likewise the treatment of heart failure follows general principles which may be applied independently of the cause. Firstly the work of the heart must be reduced by physical and mental rest. Secondly the force of the heart beat should be improved by the use of digitalis and thirdly the tendency to accumulate water and salt should be treated by diuretics, low salt diet and occasionally by the mechanical removal of fluid. Treatment of the underlying cause of heart failure is of fundamental importance, but this is rarely possible. However in some conditions, such as mitral stenosis, thyrotoxicosis and anemia, the cause may be removed or profoundly modified and this is described in the appropriate sections.

**Rest.**—Physical and mental rest diminishes cardiac work and is the most important therapeutic measure in cardiac failure. The duration and degree of rest required for any patient depends on the severity of the illness. A single attack of cardiac asthma may require little more than a few days in bed, whilst 2 or 3 weeks of partial bed rest is advisable for the mildest cases of congestive heart failure; such patients should be allowed up for toilet purposes. In more severe degrees of congestive cardiac failure bed rest in a semi-upright position (obtained by pillows, a back rest or a special cardiac bed) should be maintained for at least 3 weeks or until the signs of congestion have subsided. Most patients may be allowed to move about in bed, feed themselves and receive visitors, but it is occasionally advisable to restrict all activities; continuous nursing care is then required. Mental rest should be promoted by reassurance, explanation and the use of sedatives.

Thrombosis in the deep leg veins with subsequent pulmonary infarction are hazards of prolonged strict bed rest in any condition, but they are especially common in patients with heart disease. Some physicians have advocated an armchair régime to overcome this and the other adverse features of bed rest; the armchair position is good from the physiological point of view, but patients are tempted to increased physical activities and it seems best to reserve the armchair for a stage after a period of initial bed rest.

The important considerations in deciding the mode of rest and its duration are the severity of circulatory failure and the patient's general physical and mental state; the domestic and economic circumstances of the patient usually determine the availability of nursing help and therefore the advisability of home or hospital treatment. It is better to err on the side of too little than too much rest in elderly patients, especially when the condition of the heart is such that little improvement can be expected. When some degree of ambulation has been permitted throughout, the transition to convalescence is facilitated.

**Diet.**—One of the advantages of bed rest is that food requirements are less, so

that cardiac work is further diminished. In severe heart failure anorexia limits food intake, but in other cases meals should be small and as attractive as possible, with a maximum daily intake of 1000 calories during the initial rest period. A low salt diet is a most effective method of relieving the symptoms of heart failure. Dietary sodium should be reduced to 500 mg. a day, but this is not always possible for psychological, gustatory or domestic reasons; it is impossible in unintelligent or unco-operative patients outside hospital and attempts to reduce sodium should be abandoned in favour of other methods of producing hyponatraemia. It is not easy to achieve levels of 500 mg. of sodium daily and probably most patients on a well-managed low salt régime receive nearer 1 g. All food must be prepared and served without the addition of salt or soda. Foodstuffs must be carefully selected, bearing in mind that most protein foods (milk, eggs and red meat) have a relatively high sodium content. Certain proprietary foods high in protein and low in sodium are available if it is necessary to augment protein intake. The following rules should be observed. (1) Use salt-free bread (obtainable from many bakers), salt-free butter or margarine (if not obtainable it may be prepared by washing free of salt), salt-free fat or arachis oil for roasting and frying purposes. (2) Use plain flour and a special baking powder containing potassium bicarbonate instead of sodium bicarbonate for cakes, puddings and scones, which may help to vary the diet. (3) Restrict milk to half a pint daily and eggs to one per day. (4) Avoid the following foods with a high salt content: ham, bacon, sausages, tinned meat, meat extracts, smoked and salt fish, tinned fish, cheese, pickles, tinned vegetables and soup, chocolate, junket and dried fruits (except prunes). (5) Use vinegar, mustard, pepper and sodium-free salt substitutes for seasoning purposes. There is no necessity to restrict fluids on a low salt diet; water, tea, coffee and alcohol are allowed. Beer contains from 75 mg. to 130 mg. of sodium per pint. Many patients find that a low sodium diet is flat and monotonous, particularly in the first weeks of treatment, but most consider these unpleasant features worth while after experiencing relief from distressing symptoms. There are often difficulties in obtaining a regular low salt diet, especially for those who must feed in canteens and restaurants.

A diet of rice, sugar, fruit and water is worthy of trial in patients with intractable congestive heart failure, and especially where hypertension is the cause. Few patients keep to the diet for more than a few weeks, thereafter they are often happy to receive an otherwise unpalatable low sodium diet which may effectively maintain any improvement initially achieved by the rice diet. Obesity, which is almost invariably due to chronic habitual overeating, should be corrected in patients with heart failure by an appropriate drastic reduction in the calorie value of all food.

Tobacco should be discouraged except where its withdrawal causes much mental stress. Alcohol is permitted in moderation; it is a satisfactory sedative and diminishes anxiety. An ounce or two of whisky at night promotes sleep, and a glass of champagne may elevate morale and create a sense of well-being during the day.

*Drugs.*—*Morphine* may be used in all forms of heart failure except in pulmonary heart disease, where its depressing effect on a sensitive respiratory centre may be fatal. Morphine is the drug of choice in acute left heart failure. It allays anxiety, reduces mental and physical tension, secures sleep and possibly causes a fall in venous pressure—all factors which tend to diminish cardiac work. Most patients with heart failure tolerate morphine well; it is better to err on the side of large doses than inadequate ones and the drug should never be withheld when there is great distress in terminal heart failure. If, as in acute left ventricular failure, morphine is required urgently, it may be given intravenously (gr.  $\frac{1}{4}$  in 5 ml. saline), but otherwise oral or subcutaneous doses (gr.  $\frac{1}{2}$  to 1) are effective and may be repeated in 2 hours if there is no improvement.

*Digitalis.*—Withering published his *Account of the Foxglove and Some of Its Medical Uses* in 1785. Digitalis is still the most important drug in the treatment of heart

failure. Many preparations are available and the pharmacological effects of the whole leaf or any of the glycosides are similar.

*Mode of action.*—It is reasonably certain that the beneficial effects of digitalis are mainly due to a direct action on heart muscle causing stronger contractions. An increased cardiac output and elevation of arterial tension follow, whilst congestion and high pressure in the venous or filling side of the heart are reduced. It is probable that a less important peripheral action also tends to lower the venous pressure. Digitalis also causes a beneficial slowing of the heart, particularly when there is tachycardia associated with heart failure and auricular fibrillation. Slowing is effected by direct central vagal stimulation and by a depression of the intracardiac conducting tissues. It is probable that even this slowing effect is largely due to a direct myocardial action which causes stronger contraction and increased refractoriness during recovery. Furthermore, as the cardiac output improves, reflex vagal action also causes slowing. Improvement of the circulation leads to a reversal of all the adverse factors accompanying heart failure. Thus renal blood flow is increased and diuresis follows. Congestion in the lungs subsides, heart size diminishes and vital capacity increases. All other organs, including the liver which becomes smaller, are relieved of congestion and there is a fall in circulating blood volume. Variability of response to digitalis has long been a matter for speculation and research. It appears that the best effects are achieved when failure is accompanied by a normal or low output and venous congestion, and less effect is obtained where the congestion of failure is largely compensatory and the cardiac output is normal or high.

*Administration.*—In most cases of heart failure it is advisable to obtain the greatest optimum effect of digitalis as soon as reasonably possible by giving large initial doses (digitalisation). This may be achieved very rapidly by the intravenous route, but in most cases the oral method is satisfactory and it is safer. After digitalisation the blood levels of digitalis are kept up (and hence the effectiveness of the drug) by smaller maintenance doses.

The powdered leaf of digitalis purpurea (digitalis folia B.P.) is the most widely used preparation for oral use. Tablets contain gr. 1 (or gr.  $\frac{1}{2}$ ) and digitalisation may be effectively carried out by giving on three successive days gr. 3 t.d.s., gr. 2 t.d.s. and gr. 1 t.d.s.; gr. 1 to 3 daily is usually required for maintenance. An alcoholic solution of the leaves of digitalis purpurea (tinctura digitalis B.P.) has no advantage over the tablets and doses are more likely to be inaccurate. Bio-assay is necessary for standardisation. Relatively pure glycosides of digitalis purpurea (digitoxin and Nativelle's digitaline) are available, but are not widely used in Great Britain. These glycosides may be standardised by weight and potency is relatively constant, but they are slow to act and elimination is prolonged. Local gastric irritation is less than with the whole leaf preparations.

Digoxin is a glycoside obtained from the leaves of digitalis lanata; it should not be confused with digitoxin from *D. purpurea*. It is a pure substance and can be standardised by weight. Tablets contain 0.25 mg. and the daily maintenance dose is usually 0.5 mg. Rapid digitalisation usually requires from 2 to 4 mg. in 24 hours. It is available for intravenous use. One ml. contains 0.5 mg. of drug and this should be administered slowly after appropriate dilution. Lanatoside C is also derived from digitalis lanata; it acts quickly and excretion is very rapid; it may be given by mouth or intravenously.

*Outcome.*—Digoxin is derived from strophanthus gratus and is usually reserved for emergency use. Its action and excretion are very rapid and digitalisation is usually achieved more rapidly than with the slower-acting oral preparation; 0.5 mg. should be injected.

Digoxin is used in heart failure whatever the cause and whatever the response varies and depends on many factors.

factors, the most important of which is the underlying cause. Great care should be exercised if it is used in the presence of recent myocardial damage, *e.g.* in recent cardiac infarction or rheumatic carditis, when other drugs should be tried first, and it should never be used in diphtheritic carditis. Digitalis may be used with caution in the presence of heart block if failure supervenes, and is unresponsive to other drugs. Intravenous digoxin or ouabain have a pressor effect and are best avoided in acute left ventricular failure.

*Overdosage of digitalis.*—The first and most common symptom is anorexia, which may progress to nausea and vomiting. Difficulty arises when these symptoms may be due to continuation of congestive cardiac failure. Extrasystoles are the most common cardiac sign of overdosage; they frequently follow each regular beat, producing *pulsus bigeminus* (coupled beats): digitalis should then be omitted for 1 day and thereafter reduced, but there is no necessity to change the form of digitalis or stop it altogether. Extrasystoles occurring before treatment is started are no contra-indication to digitalis. With more serious intoxication multifocal ventricular ectopic beats may be so frequent as to cause tachycardia; paroxysmal ventricular tachycardia may appear, and even ventricular fibrillation. Excessive slowing of the heart is a common sign of digitalis overdosage. The vagal action of digitalis causes sinus bradycardia and even sinus arrest; nodal rhythm may appear and complete auriculo-ventricular dissociation has been observed.

Digitalis causes profound changes in the electrocardiogram which may be indistinguishable from those produced by disease of the myocardium. These effects should not be regarded as an indication to reduce dosage for they are routine when a therapeutic effect is obtained and may occur when the heart is normal. The S-T interval is lowered and may become slightly coved, but it is more often depressed in a straight sloping form. The T waves may be blunted, lowered or even inverted. The PR interval may be prolonged and in more serious levels of intoxication depressed conduction with or without extrasystoles may be seen.

*Diuretics.*—The organic mercurial compounds are the most effective diuretic agents available at the present time and they are now widely used. Other diuretics such as *urea*, *hypertonic solutions*, *acidifying agents*, *xanthines* and *uracil compounds* which have been used in the past are not indicated in heart failure.

The organic salts of mercury are more soluble and less toxic than inorganic ones, but their action is the same. Therapeutic doses of injected organic mercurials are rapidly cleared from the blood through the kidneys and the protein bound circulating mercury does not diffuse into other tissues; excretion in the urine continues over a prolonged period. There is considerable evidence that therapeutic mercury acts by causing slight reversible damage to cells of the lower nephron (large toxic doses produce necrosis of tubular cells). This tubular damage results in the selective rejection of certain electrolytes, of which sodium and chloride are blocked to the greatest extent. Water excretion follows as an osmotic effect of the increased electrolyte content of glomerular filtrate. Urine volume increases within 3 hours and the diuresis persists for 12 hours, the magnitude of which depends on the state of the circulation, the dose, the rate of absorption of mercury, and on the degree of oedema. The overall effects are a reduction of excess sodium, reduction of oedema and blood volume with consequent improvement in heart failure.

*Administration.*—Many preparations are available, mersalyl (Salyrgan), Neptal, Novurit, Esidrone and Thiomerin. Intramuscular injection (2 ml.) is satisfactory and safe and may be repeated in 5 to 7 days or sooner if there is much oedema and a good diuresis has been obtained with the first injection. It is usually safe to continue with a weekly injection for as long as required, but routine prescription should never be given without observation of the patient. Thiomerin may be given subcutaneously. Tablets for oral use and rectal suppositories are less effective than intramuscular or intravenous injection.

*Indications.*—Organic mercurial diuretics are indicated in all forms of heart failure except when there is severe renal disease or a known sensitivity to mercury; it is not always necessary to use them when rest and digitalis are rapidly effective, but when œdema is gross a mercurial diuretic is always advisable. Early left ventricular failure responds well to mercurial diuretics and in this condition a weekly injection may prevent loss of work and loss of sleep from cardiac asthma. Mercurial diuretics are particularly useful when a low salt régime is not practical.

*Toxic manifestations.*—Mercurials are relatively safe drugs, but a variety of untoward reactions may occur. The most important ill effects are those due to excessive diuresis and electrolyte depletion; they are likely to occur when mercurials are given frequently for long periods, especially when combined with a low salt diet. The resulting clinical states are often insidious and may readily pass undiagnosed or they are incorrectly attributed to heart failure. It is often possible to recognise one dominant pattern due to loss of a particular electrolyte, but mostly the clinical picture results from the disturbance of several factors. Weakness, malaise and apathy progressing to drowsiness are common symptoms, whilst headache, cramps, vomiting and confusion occasionally occur. By assessing the clinical state and blood electrolyte pattern, it is usually possible to recognise one of the following:

1. *Hypochloræmia* is probably the commonest disturbance, but is less likely to occur when ammonium chloride is used with mercurial therapy. Alkalosis and uræmia may develop. 2. *Low salt syndrome* resulting from excessive excretion of salt and water may progress to acidosis and uræmia. 3. *Hypokaliæmia* is rarely a significant factor. Tetany and vitamin deficiency have also been reported. These conditions should be corrected by administration of the appropriate ion and modification of the diuretic regime.

Chronic mercury poisoning (mercurialism), as shown by stomatitis, gingivitis, gastro-enteritis and dermatitis, is not encountered with modern preparations. Acute hypersensitivity reactions, such as a transient skin rash with pruritus, are rare and mild, but severe reactions may follow intravenous administration of the drug. Symptoms suggesting excessive digitalisation due to a mobilisation of digitalis from œdema fluid occasionally occur and are of little consequence.

*Oxygen.*—In most cases of heart failure the oxygen content of arterial blood is normal. If, however, this is lowered because of pulmonary insufficiency, oxygen is indicated. Oxygen is of great value in patients with anoxic pulmonary heart disease (see pp. 857, 1000) and when heart failure is due to other causes but complicated by pulmonary œdema, extensive pulmonary infarction, or broncho-pneumonia. Various methods of administration are available and selection usually depends on individual preference and available apparatus; however, an efficient oxygen tent is considered the most satisfactory.

*Venesection* lowers venous pressure and relieves congestion. It is of value in congestive heart failure whatever the cause, but mostly other therapeutic methods are preferred and it should not be used when there is anaemia or severe hypotension. It is most effective in cases of acute left heart failure and should be used more often in this condition. In patients with chronic right ventricular failure with great venous congestion which is responding poorly to drug treatment, a venesection may "break into" the vicious circle of failure and lead to a steady improvement with an increasing response to other drugs; 350 to 750 ml. should be removed from the antecubital vein with a wide bore needle, using a sphygmomanometer cuff to increase the local venous pressure and enhance the flow. A similar effect to venesection can be produced by occluding the venous return from both legs by means of thigh cuffs inflated above the venous pressure but below the arterial pressure; symptoms may be relieved but they are likely to recur when the cuffs are released. This method is not advocated.

*Acupuncture* should be used to remove extensive œdema which is resistant to more usual therapy. The patient should be placed in an armchair position for 24

hours before puncture so that maximal accumulation of œdema occurs in the legs. Southey's tubes are introduced into subcutaneous tissues and small attached rubber tubes drain the fluid. An injection of 500,000 units of depot penicillin prevents sepsis which, however, should not occur if an adequate antiseptic technique has been used. *Paracentesis abdominis and thoracis*. Large effusions in the pleural sacs embarrass respiration and hinder recovery and should be removed by tapping.

### SYNCOPE AND SHOCK

*Syncope* is a transient interruption of consciousness due to acute failure of the circulation; *shock* is a more protracted form of acute circulatory failure resulting in a depression of all vital activity and having characteristic clinical features. Systemic arterial hypotension is an essential feature of both conditions. These hypotensive states are sometimes referred to as peripheral circulatory failure, but this term is misleading because the whole cardio-vascular system is involved.

Arterial tension is the product of cardiac output and total peripheral resistance; changes in cardiac output are compensated by reciprocal changes in arteriolar tone so that arterial blood pressure remains relatively constant. When fall in cardiac output, whether of physiological or pathological degree, is incompletely compensated by peripheral constriction the resultant hypotension leads to syncope, shock or sudden death.

### SYNCOPE

Syncope is usually brief, transient and totally reversible, but when serious trauma or disease is the cause, shock or sudden death may follow. The cause of unconsciousness is sudden arterial hypotension with resulting loss of support to the brain substance and cerebral anæmia. A fall in cardiac output is the initiating event in all cases; this may be physiological, as occurs in the upright posture, but may remain uncompensated by an unstable vasomotor nervous system (vaso-vagal syncope) or rarely the autonomic nervous system may be diseased (see below). In other cases a severe pathological fall in output may be due to hæmorrhage or heart disease (cardiogenic syncope) and remain uncompensated by relatively normal vasoconstrictor reactions.

**VASO-VAGAL SYNCOPE (FAINTING).**—Simple fainting is common and the clinical features are characteristic. The patient is usually in an upright posture and syncope is preceded by a feeling of "faintness", rapidly developing pallor, sweating and tachypnœa. Bradycardia accompanies the sudden fall of arterial pressure. Unconsciousness is brief, but rarely convulsions may follow. Recovery occurs when the patient is recumbent; there is no mental confusion after the attack and there are no abnormal signs in the nervous system. Pallor and bradycardia may persist for an hour.

Many interacting factors cause fainting; the more important ones are (1) the upright posture leading to venous pooling below the heart (functional hæmorrhage), increased by prolonged quiet standing and lumbar lordosis, (2) an instability of vasomotor control leading to sudden vasodilatation in the muscles, (3) hot weather and a stuffy atmosphere which increase peripheral vasodilatation, (4) ill health—fainting is common during convalescence from illness, (5) psychic factors—intense emotional situations, fright and characteristically the sight of blood. Many subjects who have a tendency to recurrent fainting also show other features of psychoneurosis. Fainting is common in pregnancy; lumbar lordosis and the tendency to increased venous pooling below the heart are probably causal factors. In late pregnancy fainting may occur in the recumbent posture when a sudden fall in venous return may be caused by the uterus pressing on the inferior vena cava; equilibrium is rapidly restored by

turning to one side. Severe hæmorrhage commonly causes syncope which has similar features to other forms of vasovagal fainting.

Postural hypotension severe enough to cause fainting occurs when the sympathetic system is paralysed by bilateral sympathectomy, spinal anæsthesia and the ganglionic blocking of drugs of the methonium halide series; it also rarely occurs in association with certain chronic diseases of the nervous system such as tabes dorsalis and syringomyelia. A rare form of syncope occurs in middle-aged males where the essential feature of postural hypotension is associated with anhidrosis and impotence. Faintness comes on shortly after standing and the blood pressure falls steeply. Normal vasoconstriction is lacking, and the disease appears to be due to a gradually developing paresis of the sympathetic nervous system possibly originating in hypothalamic centres; once the disease has reached a certain degree, there is no further deterioration and fatalities have not been recorded. The *carotid sinus syndrome* is rare. The carotid sinus is hypersensitive and pressure upon it caused by movement of the neck, external pressure, or a tumour, may lead to profound hypotension and loss of consciousness.

**CARDIOGENIC SYNCOPE.**—A transitory sudden loss of consciousness is not uncommon in heart disease and it is due to a sudden fall of cardiac output. The usual premonitory symptoms of vasovagal syncope are absent and in most cases the attack comes without warning. There is usually pallor and, if unconsciousness is prolonged, convulsions may occur. Consciousness is regained without confusion and incontinence is rare. The causes are (1) a change of rhythm—syncope may occur at the onset of any arrhythmia, (2) heart block—see Stokes-Adams disease, p. 831, (3) very rapid ventricular rates, (4) cardiac infarction, (5) aortic stenosis, (6) aortic incompetence (rarely), (7) severe pulmonary hypertension, (8) severe pulmonary stenosis, (9) ball valve obstruction of the mitral valve. In aortic stenosis and in pulmonary hypertension syncope may be the result of effort, and in the latter condition it appears to be due to acute right ventricular failure. Effort syncope in heart disease should not be confused with the syncope which may come on after the cessation of effort in hot weather, when the cause is extreme muscle vasodilatation. Syncope due to ball valve thrombus in the mitral orifice is sudden, and produced characteristically by a change to the sitting or standing position; the prognosis is grave.

**Treatment.**—Attacks of syncope are terminated by lying flat. The treatment of recurrent fainting depends on the cause and is described in the appropriate section. Chronic postural hypotension is best treated by the sympathomimetic drugs given orally and at least four times daily; ephedrine (30 mg.) or amphetamine (5 to 10 mg.), or paredrine (20 mg.), or phenylephrine (5 to 10 mg.) should be tried and the most effective drug or combination of drugs selected.

### SHOCK

The essential features of the shock state are arterial hypotension and a depression of all vital activities causing weakness, subnormal temperature, sweating and apathy. Consciousness is generally maintained without confusion, but syncope may occur. The skin is pale and cold, the arterial pulse is weak and rapid, and the venous pressure is low. Some patients are restless but most are quiet and lie still.

**Ætiology.**—The fundamental cause of the shock state, whatever the immediate cause, is a relatively acute severe reduction in cardiac output. Intense sympathetic action causing vaso-constriction follows and maintains the perfusion pressure of arterial blood, although at subnormal levels, to the head and other vital organs. The pallor and sweating is the result of compensatory sympatheticonia. It is probable that many homeostatic mechanisms are operative in the compensation of shock; the sympathetic nervous system and adrenal medulla are responsible for vaso-constriction; selective renal vaso-constriction causing a reduction in renal blood flow is responsible



for fluid and electrolyte retention. Some degree of oliguria is always present in shock. If the shock state is prolonged it becomes irreversible and it is possible that the products of tissue anoxia are responsible for this.

The immediate causes of shock are severe external trauma and internal disasters to the major organs of the body. In the first category hæmorrhage, crushing and burning are important factors causing loss of fluid and a fall in circulating blood volume; pain and possibly the products of tissue damage exert a further depressor action. The second category includes perforation of the gut, peritonitis, pancreatitis, acute severe diarrhoea and vomiting, overwhelming septicæmia and massive pulmonary embolism, but damage to the heart itself by cardiac infarction and acute pericardial tamponade is especially likely to cause shock because there are not only the factors of pain and tissue damage, but also the direct reduction of cardiac output through damage to the pump.

**Treatment.**—Shock is a medical emergency, and treatment should be started as soon as the condition is diagnosed or before it occurs, if it can be anticipated. The immediate cause of the condition should be remedied if possible and as soon as possible, e.g. hæmorrhage should be stopped or a perforated viscus repaired.

The patient should be kept warm but not hot, and sufficient morphine should be given to stop pain. Hæmorrhage and all forms of traumatic shock are best treated by transfusion of blood, plasma or a plasma substitute such as dextran. Saline or glucose saline solutions are useful but not as effective. The newer vaso-constrictor drugs such as l-noradrenaline raise arterial pressure and should be used if there is no sign of improvement after a few hours (see p. 846). Cortisone appears to be effective in some cases, but its place in the treatment of shock is not yet established. *Prognosis* depends on the nature and severity of the underlying cause, the response to treatment and upon the duration of the shock state.

## CARDIAC ARRHYTHMIA

### INTRODUCTION

Myocardium has an inherent rhythmicity, but certain specialised areas become dominant foci of stimulus formation. All myocardium has the capacity to conduct these stimuli and cause excitation of adjacent muscle, but this function also is carried out by specialised tissue bundles. This section is concerned with disorders of the rate and rhythm of impulse formation and disorders of stimulus conduction over the rest of the heart.

The cardiac impulse arises in the sino-auricular node which is situated in the right auricular muscle near the entrance of the superior vena cava and it produces normal heart rhythm known as sinus rhythm. The artery to the sino-auricular node arises from a coronary artery, usually the right one, near its origin from the aorta. The rate of impulse formation depends not only on spontaneous rhythmicity but also on neurogenic and humoral factors. Sympathetic cardio-accelerator fibres and vagal inhibitory fibres have a dominant influence. The natural rate of impulse formation at the sinus node (70 per min.) is rather higher than the inherent rhythmicity of lower centres. Excitation from the node spreads rapidly over the auricles in all directions, inducing activity of the auricular myocardium which then stimulates the auriculo-ventricular node. This focus is in the auriculo-ventricular junctional tissues immediately to the right of the auricular septum, and is also influenced by the autonomic nervous system. Its own slower rhythm (60 per min.) is blocked normally by the higher frequency of the sino-auricular node. Conduction continues at a slower rate through the node and the ventricular muscle is reached by the bundle of His which divides into left and right bundle branches in the upper part of the

septum. Each branch lies in the immediate subendocardium of the septum and subsequently breaks up into a network of fine conducting fibres (Purkinje fibres) which remain in the ventricular subendocardium. Excitation of the ventricular muscle appears to spread from the endocardium to the epicardium. The inherent rate of impulse formation of foci in the ventricular muscle is 40 per min., but these are blocked by the higher rate of stimuli from supraventricular centres. The arrhythmias may be classified in various ways. The following order is adopted here:

1. Sinus rhythm :  
tachycardia, bradycardia, sinus arrest and phasic arrhythmia.
2. Ectopic beats and ectopic rhythm :  
auricular, nodal and ventricular.
3. Tachycardias; paroxysmal and otherwise :  
paroxysmal tachycardia (auricular);  
auricular flutter;  
auricular fibrillation;  
ventricular tachycardia;  
ventricular fibrillation.
4. Disorders of conduction.

#### SINUS RHYTHM

**SINUS TACHYCARDIA.**—Tachycardia means a fast heart rate. Normal resting rates lie between 50 and 90 beats per minute. In sinus tachycardia the increased rate is due to increased rhythmicity of the sinus node and this is largely due to diminished vagal tone or sympathetic stimulation. Sinus tachycardia emerges imperceptibly from the physiological response to effort, emotion and digestion into the pathological, and tachycardia is only significant when considered in relation to its cause.

**Etiology.** Tachycardia is found in all forms of heart failure, where it appears to be caused by the failure in some general way or by local damage to the myocardium. In some forms it may be compensatory in maintaining a higher than normal cardiac output but mostly it makes failure worse by diminishing the period of myocardial rest and recovery. Sinus tachycardia occurs in all conditions with a high cardiac output, such as thyrotoxicosis, arterio-venous aneurysm, anaemia, beriberi and anoxic cor pulmonale. Here it is a factor in maintaining the high output. Tachycardia accompanies most infectious diseases, especially those accompanied by cirrhosis.

Tachycardia may be caused by excessive use of tea, coffee, tobacco, alcohol or certain drugs, especially those affecting autonomic activity, e.g. atropine and adrenaline. Simple tachycardia is a common symptom in patients who are convalescent after prolonged illness. Psychoneurosis is a common cause of tachycardia especially when emotional disturbance is expressed through the cardio-respiratory system (see Cardiac Neurosis, p. 903).

**Symptoms.**—Sinus tachycardia is mostly asymptomatic but sometimes patients are conscious of the rapid heart action.

**Treatment** is not indicated apart from that of the underlying cause.

**SINUS BRADYCARDIA.**—Bradycardia means a slow heart rate. Some people have a naturally slow pulse and the well-trained athlete may have a heart rate of 45 to 50 a minute. Sinus slowing is due to increased vagal tone and diminished sympathetic tone. It may be induced by carotid sinus massage.

**Etiology.**—Sinus bradycardia occurs (1) during convalescence from some infectious fevers, especially influenza, dysentery, typhoid and typhus; (2) in certain toxic conditions such as jaundice, diabetes and anaemia; (3) in hypothyroidism;

(4) occasionally in organic heart disease such as *aortic stenosis*; (5) as a result of certain drugs, *e.g.* digitalis, opium and its derivatives; (6) in increased intracranial pressure, especially in patient with cerebral tumours; (7) in vaso-vagal fainting-reactions.

**Diagnosis.**—Sinus bradycardia may be distinguished from the various forms of heart block by clinical correlation of the arterial pulse, the venous pulse and heart sounds (see p. 831). The heart rate is increased by effort, emotion, fever, the nitrites and atropine in sinus bradycardia, but not in heart block. The electrocardiogram is diagnostic.

**SINUS ARREST (SINO-AURICULAR BLOCK).**—The sinus node may be inhibited by increased vagal tone so that the whole heart is stopped for one or more beats. These dropped beats may occur at irregular or regular intervals. If normal conduction is not soon resumed, nodal or ventricular escape beats occur. As in sinus bradycardia, carotid sinus pressure may induce the condition, and atropine abolishes it. Occasionally a transient dizziness or even syncope may occur.

This condition occurs in normal individuals and should be regarded as an extreme example of sinus bradycardia. It may be caused by digitalis or quinidine poisoning. Treatment is not usually indicated (see Heart Block, p. 832).

**SINUS ARRHYTHMIA.**—The sinus node sometimes shows phasic activity, which is due to variations in vagal tone. The regular arrhythmia is most often related to respiration and the heart rate increases during inspiration and gradually diminishes during expiration. Phasic arrhythmias are most apparent in the young, in the presence of sinus bradycardia and when digitalis is used.

Diagnosis is usually obvious. An electrocardiogram is confirmatory when there is doubt. This condition should be disregarded. Its significance is in the differential diagnosis from serious arrhythmia.

### ECTOPIC BEATS

**Synonym.**—Extrasystoles, Premature Contraction or Premature Systoles.

Ectopic beats are premature contractions arising as the result of impulse formation at a site other than the sino-auricular node. They may arise in the auricles, auriculo-ventricular node or the ventricles. Most ectopic beats are followed by a diastolic pause which is longer than normal (compensatory pause) because the following sinus impulse falls on refractory tissues. Occasionally the ectopic beat occurs early in the cycle and muscle recovers in time for the next sinus beat to occur without a pause—this is then a true "extrasystole" and is referred to as an *interpolated beat*.

Ectopic beats are the commonest cause of arrhythmia and those of ventricular origin are the commonest variety. They may occur at rare intervals or may be frequent and irregular, or regular. When premature contraction follows each normal contraction, coupling is produced and the pulse shows bigeminy. Ectopic beats may occur in short runs and occasionally an ectopic rhythm may be established. Premature contractions may be very frequent and arise from different foci in the same patient. The prematurity of the contraction results in subnormal ventricular filling so that the stroke volume is smaller than normal. Thus the ectopic pulse wave is smaller and often insufficient to be felt at the wrist, resulting in an intermittent pulse although the ectopic heart sounds will be heard on auscultation. Sometimes the premature contraction is so feeble that closure of the aortic valves is not heard; in this way a group of three sounds (two normal and one ectopic) is heard.

**AURICULAR EXTRASYSTOLES.**—Here the ectopic focus is in the auricular myocardium and conduction to the ventricle follows a normal pathway thereafter. The compensatory pause is usually short. Occasionally the ectopic auricular sound may be heard preceding the first heart sound.

The electrocardiogram is diagnostic. As might be expected, the P wave is abnormal

and may be superimposed on the T wave of the preceding sinus beat. The premature ventricular complex has a normal or almost normal QRS; occasionally it is absent, the ventricle is refractory and the auricular ectopic stimulus is "blocked".

**NODAL EXTRASYSTOLES.**—Here the ectopic focus is in the auriculo-ventricular node and excitation passes in a retrograde fashion over the auricle and normally to the ventricle. The P wave is inverted in leads where it is normally positive and it may occur immediately before, during, or immediately after the ectopic QRS complex.

**VENTRICULAR ECTOPIC BEATS.**—The ectopic focus may lie anywhere in the ventricular muscle. The compensatory pause is long because the normal rhythm of the sinus node is not inhibited and the ventricle does not usually respond to the first stimulus after the ectopic beat; normal rhythm is resumed with the arrival of the second normal sinus impulse.

The electrocardiogram shows a premature and bizarre QRS complex often resembling bundle branch block. Right ventricular extrasystoles show a positive main deflection in left ventricular leads whilst left ventricular extrasystoles show the opposite.

**Ætiology.**—Ectopic beats occur at any age in either sex, but they are rare in childhood and increase in frequency throughout adult life; they are more common in men than women.

Most patients with premature beats show no evidence of organic heart disease; however, the diseased heart shows an increased tendency to form ectopic beats. When there is ventricular disease ventricular ectopics are common, and when there is auricular disease as in mitral stenosis, auricular ectopics tend to occur and may herald the onset of fibrillation, but the relationship is not a close one and all forms of premature contractions occur throughout the range of organic heart disease, particularly when the muscle is directly affected.

It is unusual to detect any cause for ectopic beats in patients without gross organic heart disease, but mental and physical fatigue increase their occurrence, as does excessive use of tea, coffee, tobacco and alcohol. Emotional stress and unusual physical effort are also common provoking factors. Premature contractions are especially apt to occur during rest following physical exertion, soon after getting into bed, with change of posture and after large meals; they not infrequently occur in association with attacks of migraine and digestive disturbances. Premature contractions may be caused by digitalis and pressor amines, and occur frequently during surgical anaesthesia.

**Clinical Features.**—Many individuals are unconscious of ectopic beats, even when examination shows gross irregularity. Others experience palpitation, a sense of missing a beat, a large thumping in the chest or a sensation of the heart "turning over", whilst some declare that the "heart stops". Occasionally more serious symptoms of faintness and even syncope may appear. The premature beat may be felt at the radial pulse or the pulse may be intermittent. When the ectopic pulse does not reach the wrist, auscultation reveals the sounds of premature contraction.

**Diagnosis.**—In most patients a correct diagnosis can be made by palpation of the pulse and auscultation. The premature beat and following pause may be detected at the wrist. On auscultation the first and second heart sounds of the normal beat are followed in a rapid cadence by one or two sounds of the ectopic beat. When the pulse is interrupted by a long pause, partial heart block is excluded by palpating or hearing an ectopic beat at the apex. However, the occasionally inaudible or blocked ectopic beat necessitates an electrocardiogram for diagnosis. Sinus arrest may also confuse.

Coupled extrasystoles (*pulsus bigeminus*) may be confused with *pulsus alternans* and occasionally with *pulsus bisferiens*. In *pulsus alternans* the alternating weak and strong beats are equally spaced and the rhythm is quite regular, whereas in coupling the weak beat is clearly premature. In *pulsus bisferiens* the pulse wave is split, and rarely this bifidity may be enough to resemble two close but separate waves; auscultation

tion reveals that a single heart beat is responsible and also reveals the presence of combined aortic stenosis and incompetence which causes a bisferiens pulse.

Frequent extrasystoles, especially if auricular in origin, may produce an extremely irregular pulse which may be difficult to differentiate from auricular fibrillation. Tachycardia induced by effort or drugs tends to diminish the frequency of ectopic beats but in all cases an electrocardiogram is diagnostic.

**Prognosis** depends on the nature of any associated heart disease.

**Treatment.**—As previously indicated, most premature beats are asymptomatic. When the arrhythmia is discovered in the course of examination, the patient should not be informed. Patients who are aware of the condition should be reassured firmly and they should be dissuaded from feeling the pulse. Many respond to reassurance and require no other treatment. Where anxiety and the ectopic beats persist, a sedative should be used. Occasionally when there is much anxiety and distress due to frequent extrasystoles, more intensive therapy is indicated. Smoking should be avoided or diminished, sedation with phenobarbitone in doses of gr.  $\frac{1}{2}$  to 1 t.d.s. should be given and quinidine sulphate in doses of gr. 1 to 5 three times daily may be tried with good effect. When there is associated heart disease, this should be reviewed and treated.

**Nodal rhythm** occurs when the auriculo-ventricular node becomes the pacemaker. The auricle is activated by a retrograde spread of the stimulus. The electrocardiogram shows the same changes in each complex as are seen in isolated nodal ectopic beats. This condition occasionally occurs in normal subjects, but it is more often associated with heart disease.

#### AURICULAR TACHYCARDIA (PAROXYSMAL)

**Synonyms.**—Auricular Tachycardia, Paroxysmal Tachycardia, Supraventricular Tachycardia.

This is the common form of paroxysmal tachycardia but it should be noted that other tachycardias may occur in paroxysms. In this condition there are repeated attacks of rapid beating. The onset and termination are sudden. The arrhythmia arises at a single ectopic focus which may be high or low in the auricle. The auricular rate is usually between 150 and 220 per min., and mostly there is 1:1 conduction to the ventricle which therefore contracts at the same rapid regular rate. The individual beats are essentially the same as isolated auricular ectopic beats, which may precede or follow the termination of an attack. Paroxysms may last for a few minutes up to a few days. They may recur rarely or with great frequency.

**Ætiology.**—The ætiology is unknown. As with extrasystoles, patients with normal or diseased hearts may be affected. Paroxysmal tachycardia may occur at any age; it is rare in infancy and increases in middle life, being less common after the sixth decade. Both sexes are equally affected. Paroxysmal tachycardia may occur in any form of heart disease but patients with mitral stenosis, hyperthyroidism and auricular septal defect are more commonly affected. It is not infrequently associated with anomalous auriculo-ventricular conduction (see Wolff-Parkinson-White Syndrome, p. 833).

Most attacks appear spontaneously but in some patients a sudden change of posture, excessive emotion, or physical exertion may provoke an attack. Tea, coffee, alcohol and tobacco may be aggravating factors.

**Clinical Features.**—The common complaint is of severe palpitation commencing suddenly with little warning. Sometimes a "heavy beat" or "lunge" of the heart signifies an ectopic beat which precedes the main burst of palpitation. Although cessation is equally sudden, this change to normal rhythm is not appreciated so frequently as the sudden onset. The rapid heart beat may affect the whole body with pulsation, some patients will say that the bed appears to shake. Attacks may be

accompanied by sternal discomfort and relative coronary insufficiency may develop, producing severe ischaemic pain. A sensation of faintness or giddiness is common and rarely syncope may occur. Many patients experience sensations of great anxiety and extreme exhaustion. There is often much flatulence and abdominal distension; vomiting may occur and this usually terminates the attack. Attacks of migraine are sometimes associated with paroxysmal tachycardia. With very fast rates a shock-like condition may appear, with coldness of the extremities, perspiration and extreme pallor and faintness. Rarely congestive heart failure may develop, especially in patients with pre-existing heart disease, in the very young and when paroxysms continue for long periods.

The physical signs are tachycardia (140 to 220) and those of any associated disease. If congestive heart failure develops, it rapidly improves with cessation of the attack, which is not infrequently followed by polyuria.

Diagnosis depends mainly on a history of repeated sudden attacks of tachycardia without cause. An electrocardiogram in the attack is diagnostic. Sinus tachycardia is distinguished by its slow onset, slow decline, variable rate and the knowledge of its cause. Carotid sinus pressure causes slight slowing in the sinus rhythm but in auricular tachycardia there is either no effect or a sudden return to normal rhythm.

Auricular flutter causes a similar fast heart rate and should be distinguished (see p. 825). Clinical recognition is sometimes possible if two auricular venous pulse waves to each ventricular systole can be detected. Auricular flutter may continue for weeks or months, whereas paroxysmal auricular tachycardia lasts for minutes or hours. Differentiation from the electrocardiogram may also be difficult. There is 1:1 conduction in auricular tachycardia but the alternate P waves in 2:1 auricular flutter may be buried in the QRS complex and therefore difficult to detect. When the pulse is irregular and fast, auricular fibrillation is the usual cause (see p. 826). Paroxysmal ventricular tachycardia is rare and associated with serious disease of heart muscle (for diagnosis, see p. 828).

**Prognosis.**—The outlook for individual attacks is good; cessation occurs spontaneously after a short period. However, when there is organic heart disease or when attacks are resistant to treatment and the tachycardia persists for a long time, congestive cardiac failure may develop. Persistent attacks occasionally cause coronary insufficiency and muscle damage. In infancy long attacks may be lethal from heart failure. From the long-term point of view, prognosis is very good for the vast majority of patients. Attacks may be infrequent and they rarely interfere with work and normal employment. They may cease as mysteriously as they started and the physician should invariably give an encouraging prognosis.

**Treatment.**—In most patients with paroxysmal tachycardia there is anxiety and attacks are often more frequent during phases of heightened emotional tension. Confident reassurance is thus essential, and it should be stressed that the heart is healthy and that sudden death is no more likely than in other people. In rare cases where the attacks are associated with serious organic heart disease and cardiac failure is present or a possibility, digitalis should be given indefinitely.

Many patients learn a simple method of terminating the attack, such as breath holding, drinking iced water or self-induced vomiting. Carotid sinus massage is, however, the most effective: with the neck extended in a reclining posture, the carotid sinus region is firmly massaged on one side only, and this procedure may be repeated on the opposite side; it should not be carried out in elderly, arteriosclerotic subjects. In severe, prolonged attacks, it is advisable for the patient to lie down and gr. 5 of quinidine together with gr. 1 of phenobarbitone, should be given. Most attacks then cease within 8 hours; whether this is spontaneous or due to quinidine or sedation is uncertain. Intravenous digoxin (1 mg.) (or Lanatoside C) should be tried, and is usually effective in attacks which continue after quinidine has been used without success. Cholinergic drugs have unpleasant side effects and are not advised unless

sedation, quinidine and digitalis have failed. Prostigmine is given intravenously or intramuscularly in doses of 1 mg. Acetyl- $\beta$ -methylcholine chloride (Mechoyl) may be given subcutaneously in doses of 10 to 20 mg. as it acts in less than 5 minutes, and often the gut and bladder are more dramatically affected than the arrhythmia. Hypotension is a serious toxic effect. Cholinergic action may be abolished by intravenous atropine (1 mg.) if any of the side effects is serious. It is emphasised that at least 95 per cent. of attacks may be terminated by less drastic methods. Patients having only occasional attacks need advice about the individual attack, but no long-term treatment other than reassurance and perhaps an occasional sedative. When attacks are frequent, gr. 3 to 5 of quinidine t.d.s., should be given for a trial period of 2 to 3 months and if the frequency of attacks is reduced and the drug is well tolerated, it should be continued indefinitely.

Paroxysmal tachycardia in infancy is serious and may lead to congestive heart failure; digitalis is indicated and is almost always effective.

### AURICULAR FLUTTER

Auricular flutter is a condition of rapid auricular pulsation of 180 to 360 beats per minute. The onset is sudden. In the majority of cases there is partial auriculo-ventricular block varying from 2:1 to 5:1, the former being more common. Ventricular rates are usually from 130 to 180 per minute. Investigations by Lewis suggested that flutter was due to a continuous circus movement of excitation in the auricular myocardium; more recent work indicates that there is rapid stimulus formation at a single focus from which waves of activity spread through the auricles in all directions.

The rate of stimulus formation in this condition is faster than in the auricular tachycardias and slower than in auricular fibrillation, but in each condition ectopic stimulus formation appears to be the fundamental disorder. Investigations by Prinzmetal show that the ectopic focus tends to be at the caudal end of the auricle in flutter and at the cephalic end in auricular tachycardia. Auricular flutter is much less common than either auricular tachycardia or auricular fibrillation. Paroxysms of flutter usually last much longer than those of paroxysmal tachycardia (auricular) and conversion to auricular fibrillation occurs readily; there is much overlap between the two conditions.

**Ætiology.**—Auricular flutter is almost always associated with either ischæmic or rheumatic heart disease. Men are most commonly affected. It may be responsible for tachycardia in infancy but otherwise is unusual under 40 years of age and most common after 60.

**Clinical Features.**—Auricular flutter may cause the same symptoms as paroxysmal tachycardia (see p. 823). Ischæmic heart pain may occur and a persistent attack of auricular flutter may precipitate congestive cardiac failure.

Heart rate is usually rapid and regular, but there may be sudden changes in rate due to a variable degree of auriculo-ventricular block. Exercise and emotional change leave the rate unaltered, but carotid sinus or eyeball pressure may result in a sudden rate change. When the degree of block is high (4:1) the ventricular rate may be normal. The loudness of the first heart sound may be variable when there is a varying degree of block. Sometimes the auricular waves ("a" waves) may be seen in the neck, and their regular relationship to the less frequent ventricular pulse detected.

**The electrocardiogram.**—P waves are regular at rates from 200 to 350 per minute. They are most readily seen in leads II and III or right-sided præcordial leads, especially CRI. The P waves often show a continuous undulating pattern without an iso-electric interval; this appearance is due to the auricular T waves. P waves are also abnormal in form, depending on the site of ectopic impulse formation. None of these criteria is absolute. The level of auriculo-ventricular block determines the

frequency of the QRS complex. When there is 1 : 1 conduction, P waves may not be distinguished and the appearance may be confused with ventricular tachycardia. Vagal stimulation leaves the P waves unchanged, whilst the QRS complexes may become irregular or recur at a regular slower rate.

**Prognosis.**—Prognosis depends largely on the nature of any underlying heart disease. Prolonged attacks may precipitate heart failure when there is pre-existing heart disease, but when the heart is otherwise normal, auricular flutter may be tolerated well for years. Attacks of auricular flutter tend to recur, but they are extremely variable in duration and in frequency of recurrence.

**Treatment.**—In all cases underlying heart disease should be reviewed and congestive heart failure treated by the usual methods. In the rare cases where natural heart block keeps the heart rate normal, there are no symptoms and no treatment is indicated, but in others digitalis is the drug of choice. Digitalis is given to slow the ventricular rate and to produce auricular fibrillation which is more easily controlled than auricular flutter and more readily converted into normal rhythm.

Digitalis folia (or other preparations of the physician's choice, see p. 814) should be given in doses of gr. 3 t.d.s., on the first day, gr. 2 t.d.s. and gr. 1 t.d.s. on the second and third days, with a maintenance dose of gr. 1 b.d. Auricular fibrillation frequently follows this régime. Many patients, however, remain in auricular flutter and in these the ventricular rate should be controlled by digitalis. Little is gained by using other anti-arrhythmic drugs, as in most cases underlying organic heart disease prevents the continuation of normal rhythm. Patients in whom auricular fibrillation has developed should be maintained on digitalis, but in some, where there is no serious organic heart disease, quinidine should be used (see treatment of auricular fibrillation, p. 828).

#### AURICULAR FIBRILLATION

Auricular fibrillation is the most common and one of the more serious of the persistent arrhythmias. Integrated auricular contraction disappears and is replaced by rapid irregular fibrillary twitching of the auricular muscle and there is irregular rapid ventricular contraction. Paroxysms may occur but mostly auricular fibrillation becomes a permanent condition.

As in the case of auricular flutter, Lewis came to the conclusion that auricular fibrillation was due to a single excitation wave travelling around a main circus path and giving rise to lateral "daughter" waves. This circus theory has been generally accepted but recent investigations, particularly by Prinzmetal and his associates, using the high-speed cinematograph and cathode ray oscillograms, have shown no evidence of circus movement, centrifugal waves or daughter waves. This recent work shows that auricular fibrillation is characterised by a chaotic disturbance of auricular muscle found only in this condition. There are asynchronous pulsations of minute segments of muscle, larger movements of larger areas of muscle and all intermediate varieties which may occur simultaneously or separately. It appears that the arrhythmia is initiated from a single ectopic focus but the larger movements arise from diverse foci and they pass over the auricle from 400 to 600 times a minute. These larger waves may pass in any direction during a given bout of fibrillation and they vary greatly in intensity of contraction.

With auricular fibrillation there is usually a degree of auriculo-ventricular block. Stimulation of the ventricle is irregular and the rate is usually between 100 and 180 beats per minute. Some patients, especially when there is long-standing mitral stenosis, show a high degree of A-V block and the rate may be normal. Digitalis is, however, mostly responsible for slow ventricular rates accompanying auricular fibrillation.

Auricular fibrillation diminishes the efficiency of the heart. There is good evidence



to show that cardiac output rises when normal rhythm is restored; however, from the clinical point of view the circulation may show little evidence of inefficiency if the ventricular rate is controlled by digitalis.

*The electrocardiogram.*—The characteristic feature of the electrocardiogram is the disappearance of P waves and their replacement by irregular waves of varying size called "f" waves, and usually best seen in right chest leads. The ventricular complexes are irregular and vary slightly in contour, but have the same general form as those found when the patient is in normal rhythm. If they appear to be regular, measurement of successive RR intervals reveals the underlying irregularity.

*Ætiology.*—Auricular fibrillation is mostly associated with organic heart disease. However, in 7 to 10 per cent. of patients the heart muscle and valves are apparently normal; these patients have a good prognosis.

Any type of organic heart disease may be associated with auricular fibrillation, but mitral stenosis, ischæmic heart disease and hyperthyroidism accounts for most cases. Auricular fibrillation occurs in the course of most patients with mitral stenosis, and the establishment of permanent arrhythmia may be preceded by frequent auricular ectopic beats or paroxysms of auricular fibrillation. Patients with great enlargement from mitral stenosis always have auricular fibrillation, but heart failure commonly occurs whilst there is still normal rhythm.

Auricular fibrillation may be continuous or paroxysmal in hyperthyroidism and its frequency increases with advancing years. Auricular fibrillation is common in chronic ischæmic heart disease and may be due to occlusion of the artery to the sinus node. Although many patients with hypertension develop heart failure with normal rhythm, auricular fibrillation sometimes occurs, particularly when coronary artery disease is also present. It is rare in malignant hypertension. Transient attacks of auricular fibrillation are common in patients with recent cardiac infarction. Constrictive pericarditis is associated with auricular fibrillation in at least one-third of the cases, but in other forms of pericarditis, arrhythmia is rare. Auricular fibrillation is sometimes associated with non-cardiac disease, especially in carcinoma of the bronchus and other neoplasms in the chest and mediastinum when there is involvement of cardiac nerves or direct invasion of the pericardium and heart. It occasionally occurs in apparently normal hearts. Sudden physical or mental shock may precipitate the arrhythmia in some patients whilst in others there is no apparent cause. Auricular fibrillation may occur at any age and in either sex.

*Clinical Features.*—Some patients are unaware of any irregular heart action but many experience palpitation. Dizziness, syncope and cardiac pain sometimes accompany an attack of auricular fibrillation. Heart failure may develop, symptoms are then determined by its severity, and the nature of the underlying heart disease.

Systemic and pulmonary emboli are common complications of auricular fibrillation and are especially likely to occur if the arrhythmia changes to sinus rhythm.

*Diagnosis.*—Auricular fibrillation is recognised by total irregularity of the pulse in rhythm and volume. Before treatment is given there is mostly tachycardia and some of the weaker beats may not be appreciated at the wrist so that a pulse deficit is usual. Frequent irregular ectopic beats may resemble auricular fibrillation, but in most cases the basic regularity of sinus rhythm can be recognised and exercise tends to produce a more regular pulse. A slow ventricular rate in auricular fibrillation from natural heart block or digitalis therapy may result in an almost regular pulse. When there is doubt an electrocardiogram is confirmatory.

*Treatment.*—The management of patients with auricular fibrillation depends to some extent on its cause, and in all cases the possibility of thyrotoxicosis should be borne in mind and excluded as an ætiological factor.

All cases with tachycardia, or any evidence of congestive cardiac failure, require digitalis which should be used in routine doses of the preparation of choice. Digitalis

folia is satisfactory and gr. 3 t.d.s. on the first day, followed by gr. 2 t.d.s., and gr. 1 t.d.s. on the second and third days, followed by a maintenance dose of gr. 1 b.d. which is adequate for most cases. Occasionally more rapid digitalisation is necessary, when intravenous digoxin or Lanatoside C may be used (see p. 814).

Conversion of auricular fibrillation to normal rhythm must be considered in all cases where auricular fibrillation is of functional origin, and where there is no evidence of serious organic heart disease. Conversion should also be attempted in successfully treated hyperthyroidism if spontaneous reversion has not taken place, it should also be attempted in cases of mitral stenosis after successful mitral valvotomy. Quinidine is the anti-arrhythmic drug of choice: it should be combined with digitalis in all cases where there is underlying heart disease and the possibility of heart failure. It is traditional to give a test dose of quinidine (gr. 2), but there is no evidence that this has any value. There are various recommended schedules for the oral administration of quinidine, the following one is satisfactory: gr. 5 four-hourly on the first day, gr. 5 two-hourly on the second day and repeated on the third day. The course is stopped when conversion to normal rhythm occurs or at the end of the third day, or if serious toxic effects occur. Toxicity is shown by vomiting, diarrhoea, hypotension and even syncope—the drug should be withdrawn if any one of these appears. Quinidine is an abortifacient drug and should not be used during pregnancy. If conversion to normal rhythm has occurred as a result of quinidine therapy a maintenance dose of gr. 5 t.d.s. should be continued for a few weeks.

#### VENTRICULAR TACHYCARDIA

Ventricular tachycardia is a condition of rapid regular rhythm which is initiated from a focus in the ventricle. It may be paroxysmal or continuous and is almost invariably associated with serious organic heart disease, affecting left ventricular muscle. Acute cardiac infarction is the cause in 75 per cent. of cases of ventricular tachycardia. Digitalis intoxication may be a precipitating or aggravating factor. Rarely there is no evidence of organic heart disease.

**Symptoms** are those of paroxysmal tachycardia; there may be little subjective disturbance or symptoms are submerged in those of cardiac infarction or heart failure. Ventricular tachycardia may be responsible for relatively sudden and rapid deterioration in the course of cardiac infarction. Examination shows a regular rapid heart rate between 150 and 300 per minute. Hypotension, peripheral constriction and sweating may indicate the development of shock.

The *electrocardiogram* shows abnormal QRS complexes which are widened and may resemble those of ventricular ectopic beats. There is slight irregularity of rhythm. P waves are rarely recognisable but during episodes of regular rhythm they are normal, whereas the QRS complexes usually show evidence of serious myocardial disease.

**Diagnosis.**—Paroxysms of tachycardia occurring during the course of serious organic heart disease suggest a ventricular origin, particularly in cardiac infarction, hypertension or aortic valve disease. The diagnosis is confirmed by the *electrocardiogram*. In supraventricular tachycardia the QRS complexes are frequently normal and regular, whereas in ventricular tachycardia the QRS is obviously abnormal and not quite regular. The *electrocardiogram* of supraventricular tachycardia with functional bundle branch block may not be distinguishable from that of ventricular tachycardia.

**Treatment.**—Quinidine is the anti-arrhythmic drug of choice. It should be given orally in the first instance as described for auricular fibrillation (see above). If oral quinidine is not effective or if deterioration in the patient's condition demands more urgent treatment intravenous procaine amide (5 to 10 ml. of 1 or 2 per cent. solution), or magnesium sulphate (20 ml. of 20 per cent. solution), or quinidien

lactate (gr. 10 of quinidine in 50 ml. of 5 per cent. glucose at a rate not exceeding 2 ml. per minute) should be given slowly and controlled by serial electrocardiograms where possible. The injection should be stopped if normal rhythm develops, or if serious toxic symptoms develop; oral quinidine should then be given in doses of gr. 5 t.d.s. for a few weeks.

Although the above measures are not without danger of serious toxic effects the gravity of ventricular tachycardia in cardiac infarction demands effective and urgent treatment.

#### DISORDERS OF CONDUCTION

Conduction of the excitatory impulse may be delayed or interrupted at any point during its passage from the sino-auricular node over the rest of the heart. The site and degree of delay may be determined and forms a basis of classification as follows:

- (1) Sino-auricular block.
- (2) Auriculo-ventricular block (usually known as heart block and including prolonged PR interval, partial and complete heart block).
- (3) Bundle branch block and intraventricular block.

#### SINO-AURICULAR BLOCK

Sino-auricular block is a relatively rare condition in which the whole heart fails to beat due to an impulse from the sino-auricular node not being generated, or possibly because auricular response to the stimulus is blocked. This condition is indistinguishable from sinus arrest (see p. 821).

#### AURICULO-VENTRICULAR BLOCK (HEART BLOCK)

In auriculo-ventricular block there is defective conduction in the auriculo-ventricular node or the bundle of His or both. The condition may be transient, paroxysmal or permanent. There are three grades: (i) Delayed conduction of the impulse from auricle to ventricle, resulting in a prolongation of the PR interval. (ii) Partial heart block with dropped beats due to intermittent failure of auriculo-ventricular conduction. (iii) Complete heart block when there is complete auriculo-ventricular dissociation.

Some authors group the first and second grades as partial or incomplete heart block, while other writers divide partial heart block into cases where there are irregular dropped beats and those where the conduction defect is regular.

(i) **PROLONGED PR INTERVAL (FIRST DEGREE HEART BLOCK).**—When impulses are delayed in passage through the auriculo-ventricular node and bundle there is a prolongation of the PR interval on the electrocardiogram (normal is 0.12 to 0.22 sec.). A prolonged PR interval may be transient, a stage in the development of more severe block, or permanent and non-progressive. The diagnosis is essentially electrocardiographic but the delay between auricular and ventricular events may be detected occasionally by clinical examination. Abnormal delay between jugular venous "a" waves and "c" waves or between auricular components and ventricular components of the first heart sound may be detected. As the PR interval is prolonged the first heart sound becomes softer. In mitral stenosis there may be a gap between the auricular systolic murmur and the first heart sound.

**Ætiology.**—First degree heart block occurs in all conditions which produce complete heart block (see p. 830). It commonly occurs in the course of carditis, especially in rheumatic fever where a prolonged PR interval indicates the presence of active carditis. A prolonged PR interval may be a permanent result of scar formation.

(ii) **PARTIAL HEART BLOCK.**—When the cardiac impulse fails to reach the ventricles,

through intermittent failure of auriculo-ventricular conduction so that dropped beats occur, the condition is spoken of as partial or second degree heart block. The dropped beats may be occasional, irregular or frequent and regular.

Wenckebach (1899) described a form in which the PR interval becomes progressively longer after each dropped beat until conduction fails again. In other cases the ratio between auricular and ventricular beats may be steady and regular but each second, third or even fourth ventricular beat may fail, producing 2:1, 3:1 and 4:1 ratios; the pulse may then appear to be grouped in runs of twos or threes. Ventricular rate depends on the auricular rate and the degree of block; thus at normal auricular rates and 2:1 block the pulse rate is slow (34 to 40 beats per minute), whereas with an auricular tachycardia and partial heart block the pulse may be rapid. Inspection of the jugular venous pulse may show an "a" wave corresponding to the dropped ventricular beats and an auricular sound may be heard at the same time, but an electrocardiogram is necessary for confirmation.

The electrocardiogram shows the frequency of absent QRS complexes compared with the frequency of regular P waves. Lead II or a right-sided chest lead should be examined when P waves are not clearly shown in other leads. A progressive lengthening of the PR interval followed by a dropped beat is the Wenckebach phenomenon.

**Ætiology** (see Complete Heart Block).

**Prognosis.**—Partial heart block nearly always indicates heart disease and implies damage to the myocardium. The condition may be transitional to complete heart block. Prognosis depends on the nature of the underlying heart condition.

**Treatment** depends on the nature of associated heart disease.

(iii) **COMPLETE HEART BLOCK.**—In complete auriculo-ventricular block the cardiac impulse fails to reach the ventricles which continue to beat in response to a focus which is situated in the conducting tissues of the ventricular septum. The inherent rhythmicity of ventricular foci is slow and slightly irregular, being almost totally uninfluenced by external stimuli so that fever and effort leave the pulse rate unaltered. There is some evidence that vagal activity has a slight effect. The condition is spoken of as complete auriculo-ventricular dissociation, and the ventricular beating as an idioventricular rhythm. The slow rate results in increased ventricular filling; the stroke volume is large and tends to maintain a near normal cardiac output at rest.

**Ætiology.**—There are many causes of delay in the conducting system; the higher grades of auriculo-ventricular block are usually associated with chronic serious heart disease, causing anatomical lesions of the conducting system, whereas in the lesser grades of block, which may be transient, the causative factors may be self-limiting, reversible and of a functional nature. The frequency of serious heart block increases with age and it is more common in men than in women. The more important causes are: *Ischaemic heart disease.* Chronic coronary athero-sclerosis leading to fibrosis of the A-V node and bundle is the commonest cause of complete heart block, which is then a permanent condition. Involvement of junctional tissues is usually part of widespread myocardial fibrosis, but occasionally the special artery to the bundle, which is a branch of the right coronary artery, is occluded and the lesion is more limited. Acute cardiac infarction sometimes causes transient heart block. *Calcific aortic stenosis* may be associated with various degrees of heart block. Calcification and fibrosis extends into the region of the bundle; associated coronary insufficiency is another factor in these cases. Rarely calcification may extend into the bundle from the mitral annulus in chronic mitral valve disease. *Rheumatic carditis* commonly causes first degree heart block, and less frequently severer grades of block. *Diphtheritic carditis* may cause any degree of conduction delay; complete block is more usual and indicates extensive and usually fatal myocarditis. *Syphilis* occasionally causes heart block; probably most cases are due to associated coronary insufficiency from

coronary ostial stenosis, or coronary athero-sclerosis; gummatous infiltration is a rare cause. Infiltration of the node and bundle by neoplasm occasionally produces heart block. Diffuse changes in the myocardium occur in Friedreich's disease and myotonia atrophica, and the bundle of His may be involved, causing an increase of the PR interval and even complete heart block. *Digitalis* is perhaps the commonest cause of the lesser degrees of heart block. The effect is due to vagal stimulation and a direct inhibition of the conducting tissues. Quinidine rarely causes conduction delay. *Congenital heart disease* may be associated with the various grades of heart block. Complete heart block is uncommon but occurs in some cases of ventricular septal defect, and occasionally where the septum is normal. It is very rare in cyanotic congenital heart disease. The ventricular rates tend to be considerably higher than in cases of acquired heart block.

**Clinical Features.**—The lesser grades of heart block do not usually produce symptoms. The dropped beats of partial heart block may produce unpleasant sensations in the chest; the long pause or the thud of the next beat may be felt and faintness may occur; however, it is with complete block that serious symptoms generally occur. Complete auriculo-ventricular dissociation is mostly associated with a slow heart rate, usually from 30 to 40 per minute. At this rate symptoms may be completely absent but with slower rates faintness is common. Attacks of sudden syncope (Stokes-Adams syndrome) occur in nearly 50 per cent. of cases.

**STOKES-ADAMS SYNDROME.**—This condition is characterised by sudden attacks of loss of consciousness associated with extreme bradycardia or periods of ventricular asystole. It seems that depression of the idioventricular focus resulting in very slow ventricular rates is mostly responsible (10 to 20 per minute). The auricle continues to beat at a normal rate whilst the ventricle is inactive.

Loss of consciousness is sudden and unaccompanied by any aura; attacks may last for a few seconds to 1 minute or more; recovery is unlikely after 2 minutes. As asystole continues extreme pallor develops and after some 10 to 12 seconds, movements commence and convulsions may follow. Breathing becomes stertorous and may be of the Cheyne-Stokes variety at the end of an attack. Ventricular fibrillation may supervene. When the ventricular beat is resumed consciousness returns, usually without any period of confusion, and flushing of the face is common. Bed patients have been observed in the course of conversation which has been resumed normally immediately after the syncope.

Attacks may occur at infrequent intervals or in rapid succession. They are particularly likely to occur at an early stage when complete heart block develops from partial heart block. It appears that the idioventricular rhythm becomes more stable when complete heart block is permanent. Rarely complete heart block causing Stokes-Adams attacks may be paroxysmal so that between the attacks there is sinus rhythm. Lesser grades of the syncopeal reaction such as giddiness and faintness may occur before and between attacks of complete unconsciousness.

Symptoms of circulatory insufficiency such as effort dyspnoea are common in heart block and depend on the nature and severity of the underlying heart disease.

The most important sign of complete heart block is bradycardia, but this may be minimal in congenital cases. The rate is not influenced by effort, emotion, fever, nitrites or, as a rule, by atropine. The jugular venous pulse shows "a" waves which are dissociated from the slow carotid pulse waves. From time to time auricular systole and ventricular systole happen to coincide, the auricle then contracts against closed valves, producing large regurgitant venous waves in the jugular veins (cannon waves). Auscultation may reveal soft auricular sounds between the sounds of ventricular systole. The intensity of the first heart sound varies depending on the proximity of auricular and ventricular systole. The peripheral arterial pulse wave is full and of a collapsing type; there is elevation of the systolic and a fall of the diastolic pressures. Ventricular hypertrophy can usually be detected; how-

ever, the size and shape of the heart is essentially determined by the underlying pathology.

**The electrocardiogram.**—P waves are regular or show slight variation and occur at a normal rate and are of normal form. The QRS complex occurs at a slow rate though usually at regular intervals; however, the PR intervals are totally irregular because there is no relationship between the auricular and ventricular complexes. The QRS complex is usually abnormal, being widened and similar to that seen in bundle branch block and ectopic ventricular beats.

**Diagnosis.**—The diagnosis of all forms of heart block must be confirmed by the electrocardiogram. A prolonged PR interval is not usually diagnosed by clinical methods. Second degree heart block may be diagnosed if attention is paid to ventricular activity as shown by the pulse, apex beat and the first heart sound, and to auricular activity by observing "a" waves in the venous pulse. It should be remembered that sinus irregularity, sinus bradycardia and ectopic beats may be confused with the dropped beats of heart block when attention is only given to the wrist pulse. Although most cases with a ventricular rate of 36 or under are due to complete heart block, a 2 : 1 partial heart block may occasionally cause difficulty when the auricular rate is normal.

Congenital heart block should be diagnosed only when a slow pulse has been found at an early stage and when there is other evidence of congenital heart disease.

Stokes-Adams attacks normally provide little difficulty in diagnosis when the presence of heart block is known. The suddenness of onset, absence of incontinence and absence of confusion afterwards help to differentiate from epilepsy. When heart block is paroxysmal, diagnosis is difficult between attacks and confirmation of the heart rate at the time of the attack is necessary.

**Prognosis.**—The prognosis depends mainly on the nature of associated heart disease and severity of the conduction defect. Thus first degree heart block is common in rheumatic carditis and the outlook depends on other factors. Complete heart block in diphtheria, on the other hand, indicates very severe carditis which is usually fatal.

In complete heart block due to slowly progressive ischemic fibrosis or calcification, a life of moderately reduced activity may be pursued for many years provided syncopal attacks are not present. When Stokes-Adams attacks are frequent the outlook is poor, and apart from the risk of a fatal termination during an attack, death may occur with the usual clinical picture of congestive heart failure. Transient block in acute cardiac infarction does not materially influence prognosis when compared with other factors such as shock and congestive heart failure. The progress of patients with congenital heart block depends almost entirely on the nature of the associated lesion.

**Treatment.**—Ephedrine and adrenaline are the only drugs of use in complete heart block. In chronic cases with Stokes-Adams attacks ephedrine may reduce their frequency. Grains  $\frac{1}{4}$  to 1 t.d.s. should be tried. If attacks are recurring at frequent intervals subcutaneous adrenaline may help and from 5 to 10 min. of 1 : 1000 solution should be given every few hours. Digitalis and quinidine should be avoided. It may be necessary to use the former for obstinate congestive cardiac failure.

In all cases a review of the associated heart condition is indicated. When syphilis is the cause, treatment should be started with relatively mild antisyphilitic agents and continued for a full effective course. Cures of heart block due to syphilis have been recorded.

Patients with Stokes-Adams attacks should be warned against the common dangers of an open fireplace, the highway, electrified railways and high places.

## BUNDLE BRANCH BLOCK

Activation of both ventricles occurs simultaneously in the normal heart. When there is delayed conduction of the impulse to one ventricle asynchronous contraction results. Unilateral delay may occur in the left or right branch of the bundle of His due to disease in the ventricular septum. In some cases there is no demonstrable disease of the septum and the delay appears to be of a functional nature. There are no symptoms or significant haemodynamic effects of this asynchronous contraction, and bundle branch block should not be considered apart from the condition of the heart with which it is associated. Although bundle branch block is essentially recognised by the electrocardiogram, its presence may be inferred by clinical recognition of ventricular asynchrony.

The normal second heart sound contains the almost simultaneous sounds produced by the closure of aortic and pulmonary semilunar valves. Inspiration accentuates the normal slight delay of pulmonary valve closure. When there is bundle branch block the asynchrony of ventricular systole is shown by an increased time interval between these two components of the second heart sound so that wide "splitting" results. This sign is most obvious in cases of right bundle branch block.

*The electrocardiogram* (see also p. 801).—Experimental work and clinical research has established clearly the cardiographic patterns associated with left and right bundle branch block. The P wave and PR interval are normal, but the QRS complexes are prolonged to 0.12 sec. or more due to the delayed activity of one ventricle. The diagnosis of left or right bundle branch block is best made from the præcordial leads.

In *left bundle branch block* the normal Q wave is absent from left-sided chest leads and is replaced by a small R wave, which is followed by a second R wave due to late excitation of the left ventricle. The complex tends to resemble an M. The initial R wave of right-sided chest leads is normal but there is a late S wave reflecting the delayed activity of the left ventricle. T waves are usually inverted in left præcordial leads.

In *right bundle branch block* right-sided chest leads show a delayed secondary R wave after the small normal initial R wave producing a characteristic RSR' complex. Left-sided chest leads show a normal left-sided qR wave, followed by a delayed S wave which is a reflection of the delayed right ventricular activity. T waves are frequently inverted in the leads showing an RSR' pattern.

**Ætiology.**—Left bundle branch block tends to occur in conditions producing left ventricular hypertrophy and left ventricular disease so that it is not uncommon in hypertensive heart disease, ischæmia and aortic valve disease. Cardiac infarction may produce right or left bundle branch block, which may be transient or permanent.

Right bundle branch block occurs in conditions particularly affecting the right heart. It occurs in some cases of mitral stenosis, chronic pulmonary heart disease and in 90 per cent. of patients with auricular septal defect. Massive pulmonary embolism commonly produces right bundle branch block. Bundle branch block may occur as a functional phenomenon in association with paroxysmal tachycardia. Right bundle branch block occurs in a few healthy individuals but left bundle branch block is always associated with heart disease.

**Clinical Features.**—Apart from the clinical recognition of asynchronous ventricular contraction described above, the clinical picture is determined by associated heart disease.

**Prognosis and Treatment** likewise depend entirely on associated heart disease.

**WOLFF-PARKINSON-WHITE SYNDROME.**—Although there is no conduction delay in this condition it is conventionally described with bundle branch block. The diagnosis is essentially by electrocardiogram. The PR interval is short (0.1 sec. or

less) and is followed by a QRS complex resembling bundle branch block. The short PR interval is compensated by the prolongation of the QRS complex so that the time between the P wave and the end of the QRS is normal. It appears, therefore, that there is premature ventricular excitation. This premature excitation wave probably travels by an anomalous pathway from auricle to ventricle. Anomalous bundles of tissue have been demonstrated occasionally by histological examination.

The condition may be permanent, transient or paroxysmal. Normal QRS complexes may alternate with pre-excitation ones. The heart is mostly normal but paroxysmal tachycardia occurs in 50 per cent. of cases.

## ISCHÆMIC HEART DISEASE

Ischæmic heart disease includes all conditions which are due to a failure of the coronary circulation to meet the demands of cardiac muscle. As a rule the coronary arteries are diseased, so that the term is almost synonymous with coronary heart disease, and in most cases atheroma is the cause. Angina pectoris is a clinical syndrome and is restricted to the diagnosis of paroxysmal cardiac pain due to coronary disease. Cardiac infarction indicates a clinical syndrome but also refers to pathology because it is essentially associated with necrosis of heart muscle. Coronary thrombosis refers to pathology and is almost synonymous with cardiac infarction, but occasionally either condition occurs without the other. Acute coronary insufficiency refers to an acute severe functional disturbance and may be recognised as a clinical syndrome having some of the features of angina pectoris and some of cardiac infarction. Such terms as coronary infarction, cardiac thrombosis, angina innocens, pseudoangina and angina minor should never be used.

The clinical picture largely depends on the rate of development and extent of myocardial ischæmia. The main syndromes, angina pectoris, cardiac infarction and coronary insufficiency, may occur in any sequence, in combination, or as isolated events. The slow development of ischæmic heart disease may rarely lead to impaired function and heart failure without cardiac pain. The disease should be regarded as a continuous process with cardiac infarction as the outstanding event responsible for deterioration in circulatory efficiency.

**Ætiology.**—All forms of ischæmic heart disease are manifestations of one disease process, the essentials of which are a discrepancy between the supply of oxygen and the requirements of heart muscle. Occlusive disease of the coronary arteries, usually atheroma, is the cause, but ischæmia may be relatively increased by the abnormal requirements of muscle hypertrophy or greatly increased external work.

The cause of coronary atheroma is unknown. There has been a great increase in the incidence of all manifestations of ischæmic heart disease during this century in modern Western states. This increase is real and cannot be accounted for by improved methods of diagnosis or a changing age distribution of the population. Ischæmic heart disease is the commonest single cause of death and probably accounts for 50 per cent. of all cardiac deaths.

Males are much more commonly affected than females; when hypertension, diabetes and other endocrine disorders are excluded, coronary disease is rare in women below 60 years of age. This sex difference must have an important association with the cause. Coronary artery disease is more frequent in the higher age groups, but it is not uncommon under the age of 40 in men, and conversely many aged people show little evidence of atheroma; indeed the absence of atheroma is a prerequisite of attaining great age. It is doubtful whether coronary atheroma leading to ischæmic heart disease should be regarded in any way as a part of the normal ageing process. Most authorities agree that hereditary factors are important in the pathogenesis of coronary disease. There is a relatively high incidence of coronary disease, hyper-



tension and degenerative vascular affections in the close relatives of patients with coronary disease; however, the relationship is by no means a close one and in general a common disease in the community is more likely to be due to environmental factors than genetic ones.

There is considerable evidence that abnormal lipid metabolism is a factor in the development of atherosclerosis (see p. 919). There is a higher incidence of atheroma in modern states where diets contain much more animal fat than those of primitive peoples, in whom atheroma is almost unknown. It is obvious that many other factors may be operative, and it has not yet been shown that decreasing the dietary intake of fats and cholesterol influences the severity or incidence of ischæmic heart disease. Further evidence for the metabolic theory comes from the laboratory, where atheroma may be produced in rabbits and chicks by feeding large amounts of animal fats and cholesterol; the conditions are not comparable with those in man and the lesions produced, though closely resembling human atheroma, are not identical. Many patients with coronary disease show rather high levels of blood cholesterol and certain other lipid substances. The high incidence of coronary atheroma in diseases associated with high blood levels of cholesterol, *e.g.* diabetes, myxœdema and familial hypercholesterolemia, strongly suggests that abnormal lipid metabolism is an ætiological factor in these conditions. Further evidence comes from the histopathology of the lesions in human atheroma, where deposits of cholesterol in the intima are invariably found. Excess cholesterol esters are thought to adhere to the intimal wall and to be deposited in it by macrophages, a connective tissue reaction is then provoked, with resultant scar formation.

When diseases such as coronary occlusion and peptic ulceration are not only common but especially prevalent in particular communities and groups within the community, it is probable that environmental factors play a considerable part in their ætiology. There appears to have been a fundamental change in the mode of life in civilised communities during the last half century. Coronary disease has shown a continuous tendency to increase during this period; it is possible that new conditions of stress especially affecting certain groups are an important ætiological factor. Those whose occupations are largely concerned with mental work, carrying responsibility, and whose lives are more individualised than the manual worker, are thought to be the special subjects of modern stress; they are the professional men, the managerial and executive classes who are often in tense competition with one another, and whose aims are set high yet are largely unattainable. These groups have numerically increased during the past century and coronary disease has selectively increased within these classes. Improved diagnosis, increased longevity and the diminution of previously prevalent infectious diseases do not account for the present status of coronary disease, and its cause must account for an increasing incidence and the great prevalence amongst middle-aged men. There is some evidence to show that diminished physical activity predisposes to coronary disease or conversely that coronary disease is less likely to occur in those whose occupation necessitates a vigorous outdoor life.

Less common causes of ischæmic heart disease are syphilitic coronary ostial stenosis (see p. 859), coronary embolism, periarteritis nodosa (see p. 931), thromboangiitis obliterans (see p. 921) and congenital abnormalities of the coronary arteries. Trauma to the præcordium is a rare cause of ischæmic heart disease; blunt, non-penetrating blows have been held responsible for coronary occlusion and infarction, but it is difficult to exclude pre-existing coronary atheroma even in young subjects (see p. 834). Penetrating injuries which damage the coronary circulation largely produce their effects through the development of hæmopericardium.

**Pathology.**—*The coronary arteries.*—All degrees of atheroma are found in the coronary arteries from small, infrequent, yellowish plaques on the intima to extensive thickening of the whole vessel with irregular large plaques encroaching upon the

lumen. Macroscopic calcification and ulceration of atheromatous plaques is common and the whole vessel may become a "pipe stem". Localised complete occlusion of the vessel may be due to large contiguous plaques of atheroma, fresh thrombosis on an ulcerated plaque, or more rarely to hæmorrhage in the intima. The morphology of the coronary circulation may be demonstrated by radiography of the heart after the injection of opaque media into the coronary arteries. Complete occlusion occurs in any branch but the commonest sites are in vessels supplying the left ventricle at a point to 2 to 3 cm. from their origin. The tendency to form collateral channels in the vicinity of an occlusion is well shown by this method and it appears to be a common finding. In long-standing cases the normal homogeneous vascular pattern is lost and replaced by ischæmic areas with a fine lace-work of vessels between. The major arteries show gross irregularities and narrowing of the lumen.

Microscopical changes are principally found in the intima. The smallest lesions show large lipoid-containing mononuclear cells, whilst in larger lesions and presumably older ones, masses of cholesterol are found outside the cells. The adjacent intima and the margins of atheromatous plaques are supplied by numerous capillaries, but the larger lesions appear to undergo central necrosis where a mass of lipoid and cells may form an atheromatous abscess which tends to break down with resulting ulceration. The elastic and muscle coats may be completely absent and replaced by fibrosis. Microscopic sections through an area of thrombotic occlusion sometimes show layers of thrombus in varying states of organisation, with a central fresh thrombus responsible for the final obstruction.

*The myocardium.*—All degrees of damage to the left ventricular myocardium are found in ischæmic heart disease. The right ventricle and auricles are rarely affected. When sudden death has occurred in the course of angina pectoris, the heart size and weight may be normal and the myocardium may show little macroscopic evidence of disease, whilst microscopic examination may show only an occasional patch of fibrosis. In other cases more widespread fibrosis is found either in frequent scattered patches or widely diffused throughout the muscle mass. This type of fibrosis probably represents a slow process of muscle death and replacement.

In recent cardiac infarction the heart may be of normal size, but it is usually dilated when there has been heart failure. A sero-fibrinous or sero-sanguinous pericarditis is common and occurs when the epicardium is involved. The pericardial sac is full of blood when cardiac rupture has occurred. The area of infarcted muscle varies in size but may involve a large part of the anterior wall and apical region, the septum, or postero-inferior wall. The infarcted area is pale, soft, friable and sometimes almost gelatinous. Hæmorrhagic patches are frequently seen in the necrotic zone and recent thrombi may be adherent to the endocardium beneath the area of infarction, which is sometimes surrounded by a reddish zone of hyperæmia. When the ventricular septum is involved, rupture may occur, leading to direct communication between the right and left ventricles. The papillary muscles are sometimes involved in cardiac infarction and occasionally one or more of the mitral valve chords may be fractured. In most cases of recent infarction a diligent search of the coronary vessels reveals a recent thrombus, but in some cases this is not so and it is presumed that intense prolonged ischæmia (acute coronary insufficiency, see p. 849) may result in necrosis. In such cases the necrosis is often patchy or in the sub-endocardial layers which are usually preserved in massive cardiac infarction due to acute occlusion.

Microscopical examination of recent cardiac infarction shows that the nuclei of muscle cells disappear first, followed rapidly by the disappearance of the whole cell structure and surrounding vessels and connective tissue. The necrotic mass becomes surrounded by a zone of reactive inflammation, with abundant leucocytes and extravascular red cells. Organisation involving resorption of necrotic cellular material and invasion by new vessels and fibroblasts begins within 7 days. Healing by fibrosis

and contraction of the scar continues for many weeks. In long-standing cases of ischæmic disease and cardiac infarction the heart is frequently enlarged. Dilatation is present when there has been heart failure. Hypertrophy of the good muscle is present when there is associated hypertension or valvular disease; it is doubtful whether hypertrophy occurs as a result of ischæmia and infarction alone.

The pericardium is often thickened and adherent over areas of old infarction and the ventricular wall is thin, hard and pale, due to dense fibrous tissue. Layers of organised thrombus are frequently found lining the ventricular cavity beneath the damaged area. Aneurysm formation occurs when an area of old infarction stretches and bulges under the influence of ventricular pressure. The aneurysmal cavity is usually filled with layers of partially organised clot. Calcification occasionally occurs in the scar tissue.

### ANGINA PECTORIS

**Synonyms.**—Angina of Effort; Heberden's Angina.

Angina pectoris was described by Heberden in 1768, but its relationship to coronary disease was not appreciated until the present century. Angina pectoris is essentially a clinical syndrome of characteristic chest pain produced by increased cardiac work and relieved by rest. The underlying cause in all cases is occlusive disease of the coronary arteries, which is mostly atheroma, sometimes syphilitic coronary ostial stenosis, and very rarely coronary embolism or congenital anomalies of the coronary vessels. Cardiac pain identical with angina pectoris may also be caused by aortic stenosis and less commonly aortic incompetence; it also occurs in patients with severe pulmonary hypertension and rarely in pulmonary stenosis. Anæmia, if severe, may cause cardiac pain, but rarely of the severity met with in coronary atheroma. Angina pectoris is often associated with myxœdema, rarely with thyrotoxicosis and frequently with diabetes mellitus, and in these conditions coronary atheroma is the underlying cause.

**Clinical Features.**—Paroxysmal chest pain caused by effort and other stimuli is the cardinal feature of angina pectoris. Although the pain varies in intensity, radiation, and the ease with which it is provoked, there is a constancy of the pattern which enables the disease to be recognised from the clinical history in the great majority of patients.

Anginal pain in most cases is situated in the front of the chest and mostly over the sternum. It tends to spread transversely from the sternum to the right and left pectoral regions. Occasionally the area of pain is small and it may be confined to the upper end of the sternum, or localised in the left pectoral region. It is more common on the left than the right side of the chest. Anginal pain tends to spread centrifugally to the arms, neck, jaws and epigastrium; the left shoulder and left upper arm are most often involved but frequently both arms are affected, and further spread down to the elbow, ulnar side of forearm and fingers is common. Many patients complain of numbness and a sense of great weakness in one or both arms. From the upper chest pain tends to spread to the neck, lower jaw, gums and teeth; occasionally it is experienced in the arm or jaws at first but in all cases the front of the chest is eventually involved. Less frequently pain is experienced in the epigastrium. Patients may feel that the pain is deep in the centre of the chest and often pain between the scapulae and across the shoulders accompanies the usual sternal pain. The extent of radiation of pain is roughly related to its severity. Ischæmic pain is characteristically described as constricting, crushing, vice-like or pressing. Sometimes there is a sensation of a weight on the front of the chest and some patients complain of a rawness or burning in the sternal region. The pain is steady during the attack, it does not stab, prick or shoot and is not related to chest movement or respiration.

Physical effort is the most common immediate cause of anginal pain. The first attack may be noticed with unusual effort, but sooner or later walking brings on the pain. An increase in pace, running or walking uphill diminish the threshold at which effort induces angina. A recent meal, cold air and worry also cause the pain to appear more readily. In some patients a meal, prolonged conversation, an argument, or any intense emotional situation may induce the pain without physical exertion. Rarely, and when ischæmia is severe, attacks of angina may be produced by lying down and, as with left ventricular failure, patients may be wakened from sleep. In such cases there is often a history of an unpleasant dream, but it would seem more likely that posture is responsible for these attacks, which are rapidly relieved by sitting up in bed. When physical exertion is the exciting cause, there is a remarkable constancy in the kind, rate or amount of effort which will probably, if not always, bring on an attack, and this also applies in a lesser degree to other exciting causes. Occasionally there is a clear history of a rapid increase in severity of the condition, threshold of onset is progressively lowered, pain becomes more severe and the frequency of attacks is greater. Such a history suggests impending cardiac infarction.

Attacks of angina rarely last for more than a few minutes. The pain rapidly reaches maximal intensity and subsides when the provoking stimulus is removed. In most cases the patient stops walking or slows below the critical point at which pain is produced. In very rare mild cases relief may come in spite of continued effort but in all severe cases pain brings the patient to a complete standstill—this immobility is enforced and is not a voluntary act to relieve pain. Even when pain has been largely abolished by a sympathectomy, a curious sensation is often experienced which demands immediate rest. With advanced disease the attacks may become very frequent, being evoked by the smallest effort. Although angina pectoris is essentially paroxysmal, sometimes a dull sternal ache persists between the attacks. Occasionally attacks are accompanied by a sense of anxiety out of all proportion to the severity of the pain and sometimes by a sense of impending dissolution.

The facial expression is often strained and anxious and there may be pallor at the time of the attack, but there are no important abnormal signs directly related to an attack of angina; the pulse-rate may change—in some patients it is increased, while occasionally it is diminished. The arterial blood pressure is usually somewhat increased. A few patients show a general pressor reaction associated with the pain; there is flushing of the face, sweating and a sharp rise of systemic blood pressure. When angina pectoris is due to disease other than coronary athero-sclerosis, there are associated symptoms and signs of the underlying cause (see appropriate sections).

*The electrocardiogram.*—The electrocardiogram should be obtained in all cases of suspected angina pectoris. There is no close agreement between various investigators concerning the frequency of a pathological electrocardiogram. However, if the electrocardiographic investigation includes standard leads, lead III on inspiration, unipolar limb leads and at least three præcordial leads, it is probable that 85 per cent. of patients will show some abnormality of the tracing. Those patients showing a normal electrocardiogram at rest should have further tracings taken at 2-minute intervals for 6 minutes, after moderate exercise. The amount of exercise is graded to the patient's capacity and should never continue after pain has started. It is obviously unnecessary to proceed with exercise tests if the resting electrocardiogram is abnormal. In angina pectoris the electrocardiogram may show such gross changes as left bundle branch block (see p. 833) or old cardiac infarction (see p. 801), but more often the changes are slight and these are: (1) depression of the S-T segment by 1 mm. or more, (2) unusual coving or winging of the S-T segment, (3) flattening or inversion of T waves, (4) inversion of U waves in left ventricular leads. Any one or all of these changes may be present when the patient is at rest or they may be produced by effort and recede with rest, or be produced by induced anoxæmia.

*Other investigations.*—The ballistocardiogram is pathological in a high percentage

of cases of angina pectoris but probably has little to add to the electrocardiogram from the diagnostic point of view.

Radiography often shows a normal sized heart but radiographic screening should be routinely carried out.

Further investigations are only necessary when disease other than coronary atheroma is the suspected cause, thus renal investigations are indicated for cases associated with hypertension, metabolic tests for those with hypothyroidism and a Wassermann reaction where syphilis is a possible cause.

**Diagnosis.**—(1) *The symptom.*—Angina pectoris is recognised by the clinical history, the most important features of which are the sternal site of pain, the relationship to effort and relief by rest. The constancy of the type, site and amount of effort required to cause the pain is an important feature of angina. Patients do not tell of other minor symptoms, their concern is with the one pain and they usually remember well the circumstances of a first attack, which is so often indelibly impressed on the mind. The relief of pain by nitrites may be misleading; many neurotics are relieved by drugs through suggestion and the relief of spasm of smooth muscle elsewhere, e.g. œsophago-spasm, may be relieved by nitrites. The results of physical examination are not helpful except where the presence of hypertension, and organic heart disease known to be associated with angina, is detected. Even in such cases it is on the characteristic features of the pain that diagnosis is made. The presence of ischæmia of the myocardium is confirmed by an electrocardiogram.

(2) *The cause.*—A diagnosis of angina pectoris is insufficient; it refers only to a symptom and contains no information concerning ætiology. In all cases a cause other than coronary atherosclerosis should be sought; in males from the age of 30 onwards coronary disease is by far the commonest cause, but in women this is not so. Most of the other causes of ischæmic pain, i.e. aortic stenosis, syphilitic aortitis, anæmia, myxœdema and pulmonary hypertension may be diagnosed readily by clinical examination.

*Other causes of chest pain.*—There are many causes and types of chest pain. Few should be confused with angina pectoris after a comprehensive history has been obtained by the art of firm interrogation. Pain associated with anxiety or other manifestations of psychoneurosis is the most common source of confusion. Neurotic patients often have numerous symptoms and the pain is usually beneath the left nipple; occasionally it is over the sternum and related to effort, but careful questioning usually shows that the relationship is inconstant or that the pain lasts for hours and comes on after the effort is over. It is frequently related to fatigue, both sexes may be affected and there are often obvious signs of anxiety. The electrocardiogram is normal before and after exercise. Pain arising from the œsophagus may cause difficulty. Here there is rarely any relation to effort although œsophageal pain may have the same quality and distribution as angina pectoris. Hiatus hernia produces a similar spasmodic pain, but there is no relation to effort, although a particular posture or particular movement may produce this pain. Hiatus hernia is not uncommonly associated with angina pectoris; both conditions occur with increasing frequency after middle life. Œsophageal spasm, œsophageal arrhythmia and hiatus hernia are diagnosed by radiological investigation. Pain referred from musculo-skeletal lesions may superficially resemble angina pectoris, especially if movement is confused with effort. Lesions of the cervical spine such as cervical spondylosis may cause pain over the upper chest and pain in the arms. Lesions of the upper dorsal spine may likewise cause neuritic pain in the front of the chest and a sudden movement of the chest or sneezing may produce it. Often there is no demonstrable musculo-skeletal lesion, but occasionally there is spondylitis or a prolapsed intervertebral disc. In these referred skeletal pains the electrocardiogram is normal. Especial care must be taken in the diagnosis of shoulder pain associated with chest pain.

Gall-bladder disease is said to cause confusion with angina pectoris; these

conditions often coexist and whilst gall-bladder disease may in some way lower the threshold for cardiac pain when there is coronary disease, it does not alone produce chest pain related to effort.

**Prognosis.**—One of the features of angina pectoris due to coronary artery disease is the varied course and uncertainty of outlook. Sudden death or cardiac infarction may occur early in the disease; on the other hand, attacks may subside in frequency and intensity and even completely disappear for years. However, in most cases the malady tends to be slowly progressive and the average duration of life is 8 years, but many live for 15 to 20 years. Hypertension, arrhythmia, diabetes mellitus, excessive weight and a strong family history of degenerative vascular disease adversely influence prognosis. The outlook is worse when attacks are caused by relatively slight exertion or excitement and when the pain is severe, widespread and persistent. A history of increasing severity indicates impending cardiac infarction, and if this episode is survived, subsequent effort pain may be less severe or even absent. Sudden death or cardiac infarction may supervene even in the mildest cases. The outlook for women is better than for men.

Prognosis in angina pectoris is affected by the underlying cause; it is good when associated with conditions which can be treated, such as paroxysmal tachycardia, thyrotoxicosis and anæmia. Cholecystectomy may favourably influence the outlook in cases where gall-bladder disease appears to be related to the attacks. When angina pectoris is associated with ventricular hypertrophy due to chronic valvular disease, pulmonary or systemic hypertension, the outlook is usually unfavourable. It is worse when syphilis is the cause of aortitis, coronary stenosis, aortic incompetence and ventricular hypertrophy. A good response to treatment in all cases of angina favourably influences prognosis, especially when life can be modified in such a way that attacks no longer occur.

**Treatment.**—Individual attacks of angina pectoris are relieved by rest. Most patients discover this in the first few attacks and all should be advised to cease exertion as soon as the first suggestion of pain is experienced.

**Nitrites** specifically relieve anginal pain by causing dilatation of coronary vessels; systemic arterioles are also relaxed, causing a fall in peripheral resistance. Therapeutic doses produce slight hypotension and tachycardia. Glyceryl trinitrate (trinitrin, trinitroglycerin) is the drug of choice; it is cheap, effective, administered in tablet form and is devoid of the more unpleasant side effects caused by amyl nitrite. Fresh tablets of glyceryl trinitrate (gr.  $\frac{1}{100}$ ) act in about 2 minutes when chewed and take longer when retained under the tongue. The effect lasts from 15 to 30 minutes. One tablet chewed at the onset of pain is usually effective, more may be taken if necessary. There are no long-term toxic effects and patients with angina pectoris should always carry a supply of fresh tablets. When it is necessary to undertake effort which is known to produce pain, a tablet should be chewed in anticipation and is frequently effective in preventing the attack. Glyceryl trinitrate sometimes causes a throbbing in the head and rarely a sense of giddiness or faintness.

Amyl nitrite is supplied in silk-covered glass capsules, which must be broken, and the malodorous vapour is then inhaled—an altogether unpleasant procedure. This drug acts somewhat more quickly than glyceryl trinitrate, but the side effects due to vasodilatation are more unpleasant. In view of the hypotensive action of amyl nitrite, it is advised for attacks of angina pectoris associated with a hypertensive reaction, but many find that glyceryl trinitrate is equally effective. Octyl nitrite is volatile and acts quickly but suffers the disadvantages of amyl nitrite. The longer-acting organic nitrites should not be used for separate attacks but are said to diminish the intensity and frequency of attacks (see below).

**GENERAL MANAGEMENT AND PREVENTION OF ATTACKS.**—Those situations which cause anginal pain are best avoided. Effort should be confined to levels below that which provokes pain, and if this is not possible, a tablet of trinitrin should be taken

prior to the expected pain. Hurry should be completely eliminated. Arguments, excitement or situations charged with emotional tension should be avoided and a quiet, philosophic attitude to life developed. It is advisable to avoid the spectacle of highly competitive sport, but quiet personal exercise of a steady kind below the level at which pain is caused should be encouraged.

Large meals are best avoided and exercise should not be taken after meals. When there is obesity, weight reduction is advisable, and this should be carried out by a low-fat, low-calorie régime. Weight reduction is most effectively carried out during a period of supervised bed rest in the first instance, when a 1,000 calorie diet may be used and salt restricted to 0.5 g. daily if there is associated hypertension. After an initial response the diet can be increased, but in all patients meals should be frequent, never large and low in fat and cholesterol.

Problems concerning hours of work, type of work, leisure time and holidays can only be resolved having due regard for the severity of the illness and individual economic and social responsibilities of the patient. In general it is better to remain in employment, but to reduce the number of working hours and diminish the physical and mental loads where these are heavy.

It is beneficial to have not less than 10 hours in bed per day and to spend most of one day per week in bed. A period of prolonged partial bed rest up to 4 weeks is advisable for patients seen soon after the onset of angina pectoris. Bed rest is also indicated when the disease is increasing rapidly in severity, for this suggests impending cardiac infarction. In such cases when brief attacks of pain begin to occur at rest, anticoagulant therapy (see p. 847) may be used with benefit.

Sedatives are advisable where emotional factors readily produce pain and for patients with secondary anxiety. It is especially important to ensure sound sleep and barbiturates should be freely used.

*Tobacco* smoking is best stopped altogether, if this can be done without causing too much mental stress.

*Alcohol* is not contraindicated. It is a sedative and possibly a mild coronary vasodilator. The admissibility of alcohol can be used to offset the withdrawal of tobacco, and even in total abstainers the news that it may be taken comes as relief when it is expected that the physician's advice will be entirely restrictive. An optimistic reassuring attitude should be adopted by the physician at all times.

When attacks are frequent and cause severe restriction of activity, the long-acting vasodilators may be tried. Erythrol tetranitrate and manitol hexanitrate (dose gr.  $\frac{1}{2}$  to  $\frac{1}{4}$ ) produce a vasodilatation in about 20 minutes which may last for some hours. The results are not impressive but the need for short-acting nitrites may be somewhat diminished. Khellin is extracted from the seeds of *Ammi visnaga*. It causes vasodilation and has been used with some success in angina pectoris. Undesirable side effects, particularly nausea and vomiting, are a disadvantage; khellin may be given orally or intramuscularly in doses of 40 mg. three times a day, this may be increased up to 100 mg. doses. Some 50 per cent. of patients are improved; fewer trinitrin tablets are used and pain is rather less severe and is caused by a greater amount of effort. There is always great difficulty in assessing the value of therapy in angina pectoris because suggestion, the enthusiasm of the physician and the psychiatric state of the patient play a considerable part in the severity of symptoms.

Tocopherol (vitamin E) has been advocated by some physicians, but the beneficial effect is doubtful and not yet confirmed.

The xanthine group of drugs, especially aminophylline, are often used in the treatment of angina pectoris. There is much disagreement about their value. It is certain that any effect is slight and xanthines, if used at all, should be invariably secondary to the nitrites. Aminophylline (theophylline-ethylene diamine) may be given in doses of 0.1 to 0.2 g. four times a day. A suppository of aminophylline at night is well worth a trial for patients having frequent nocturnal attacks. When

early left ventricular failure appears to be associated with angina pectoris, as in patients having nocturnal attacks of pain, sodium restriction and digitalis should be used (see treatment of heart failure, p. 812).

Antithyroid drugs, and in the past thyroidectomy, have been used to induce hypothyroidism and thereby lower the demands on the heart and circulation. It is doubtful whether the serious nature of the treatment is justified. Thiouracil drugs may cause toxicity and constant supervision is needed. Hypothyroidism may be associated with an increase in atheroma and many patients prefer angina pectoris to myxœdema. However, in cases where disability is great and even slight effort is attended by pain, propyl-thiouracil should be tried for a few months in doses of 200 mg. thrice daily at first and later reduced to 100 to 200 mg. daily.

Surgical treatment has been attempted during the last two or three decades. The object has been to cut the sympathetic nerves which conduct pain sensation or to improve the coronary circulation by producing coronary vascular anastomoses. Pain fibres are cut by either dorsal ganglionectomy and stellate ganglionectomy or posterior rhizotomy of the upper five dorsal roots. Some 50 per cent. of patients obtain considerable relief, but mortality is rather high and many patients complain that pain is replaced by an equally unpleasant but indefinable sensation often associated with giddiness which demands immobility.

The creation of an adhesive pericarditis has been carried out by introducing irritants into the pericardial sac in the hope that new vessels will develop between pericardium and epicardium and between end vessels of the coronary circulation. In practice either magnesium silicate or bone dust is used, and the procedure has enthusiastic advocates who claim considerable success. Further experience is necessary before the results of this method can be assessed.

The creation of an effective anastomotic circulation is a more rational procedure, but so far results have been disappointing. Various methods have been used. Earlier attempts, notably by Beck and O'Shaughnessy, involved the suturing of pectoral muscle or omentum to the heart. More recently branches of the internal mammary artery have been directly implanted in the myocardium and the coronary sinus has been anastomosed to the aorta; these latter methods are still in an experimental stage and the operative risks are great.

**TREATMENT OF THE UNDERLYING CAUSE.**—Unfortunately this is rarely possible, but in all cases the aetiology should be reviewed. The treatment for syphilitic aortitis, anemia, aortic stenosis, myxœdema, thyrotoxicosis and other causes of angina pectoris are described in the section concerned, but in addition to any specific treatment, all cases should be managed along the lines indicated above.

### CARDIAC INFARCTION

#### **Synonym.**—Myocardial Infarction.

The essential feature of cardiac infarction is acute necrosis of heart muscle. This is usually due to coronary occlusion which in most cases is due to coronary thrombosis, so that these terms have become almost synonymous by common usage. The aetiology of ischaemic heart disease and coronary atheroma has been discussed and similar factors are operative in cardiac infarction. There are no constant conditions which precipitate cardiac infarction; physical exertion and exceptional emotion do not appear to be important, and in many cases the onset is during sleep; it may occur at any time of the day or at any time of the year, but it is somewhat more frequent during winter months.

Cardiac infarction is said to be more common in short, obese individuals, but there is no doubt that it may occur in patients of any physical build or mental type. There are, in fact, no constant common features apart from the great preponderance of the disease in men. Coronary thrombosis is invariably associated with coronary



atheroma, but it is probably not the only ætiological factor, for advanced coronary atheroma is often found in patients who have never had manifestations of ischæmia; furthermore there is evidence from necropsy studies that whilst cardiac infarction has increased in frequency during recent years, coronary atheroma has remained unchanged; it is thus possible that an altered state of blood coagulability may be concerned with the pathogenesis of coronary thrombosis in addition to the presence of coronary atheroma. Coronary embolism, usually due to bacterial endocarditis, is a rare cause of acute occlusion and cardiac infarction.

Hypertension is frequently associated with coronary disease and it appears that coronary atheroma is more likely to become manifest as ischæmic heart disease when hypertension is present. Hypertension may be a factor in the pathogenesis of coronary atheroma, but it is also possible that both conditions are the result of the same common factors, which remain unknown.

Gall-bladder disease occasionally appears to precipitate ischæmic heart disease and it is possible that reflexes from the alimentary canal lower the threshold for cardiac pain. However, there is no evidence that gall-bladder disease or any other disturbance of the alimentary system is closely related to the cause of ischæmic heart disease.

**Clinical Features.**—*Pain* is the most prominent frequent symptom and it may be associated with shock or acute heart failure. There are prodromal symptoms in many cases. Brief attacks of pain may occur during the preceding 24 to 72 hours and sometimes there is a general feeling of malaise for a few hours before the major attack of pain. Patients having a long previous history of angina pectoris may recognise an increase in its severity during the preceding weeks and a few patients give a short history of angina pectoris which, from its onset, increases in frequency and intensity until brief attacks of pain at rest may herald a major attack of infarction. Many patients in this group seek medical advice before infarction occurs.

The onset of pain is rapid and it is independent of any exciting cause; it may occur at any time of the day or waken the patient from sleep. The maximal intensity of pain is soon reached; it is a steady pain and may be mild or of agonising intensity—among the severest of pains experienced by man. Its site, radiation and quality is the same as occurs in angina pectoris (see p. 837), but it tends to be more severe and lasts for hours or even days. Few patients remain motionless as in angina pectoris; most become restless and adopt various positions in an attempt to get relief; some walk about and I have known one patient who ran "to work off" the pain, and another who proceeded to exercise in a gymnasium in order to relieve the "acute rheumatism" in his chest. None of these manœuvres brings relief from the steady intense pain. Painless cardiac infarction is probably very rare. In some cases extreme shock and unconsciousness may be responsible for the early absence of pain, which, however, appears when the syncopal state passes off. The pain of past cardiac infarction may be forgotten when there is advanced cerebral vascular disease.

*Shock* is a common feature of cardiac infarction and all degrees occur, from those with symptoms of dizziness, weakness or faintness, sweating and vomiting, to those with severe degrees of shock which dominate the whole clinical picture. In severe cases there is great weakness; postural syncope may be the first symptom and this may be recurrent unless the patient is recumbent. The skin is pale, cold and moist, the face is greyish, drawn and anxious, and the mind is often clear. The skin of the extremities shows extreme vaso-constriction, being white or patchily cyanosed. The blood pressure is low and the pulse pressure may be so diminished that a radial pulse cannot be felt. Shock may persist for hours or even days. Pain, left ventricular failure or a general improvement may emerge as the shock state passes off.

*Heart failure* may occur alone or in combination with pain or shock at any time during the history of cardiac infarction. In the early stages of the disease heart failure usually appears as acute left ventricular failure; indeed the first symptom

may be an acute attack of cardiac asthma or even pulmonary œdema. Pain is usually present but the patient is sometimes overwhelmed by dyspnoea and a history of pain may not be obtained until later. Congestive cardiac failure may develop at any time, but usually after an interval of a few days. Cheyne-Stokes respiration is often present.

Nausea and vomiting are common features of cardiac infarction and may be combined with upper abdominal discomfort or epigastric pain. Morphine is often responsible for gastro-intestinal symptoms. *Arrhythmias* frequently develop in cardiac infarction, extrasystoles and brief episodes of auricular fibrillation being the commonest, but most patients are unaware of the irregularity and few complain of palpitation. Auricular or ventricular tachycardia may be paroxysmal or persistent and are often responsible for serious deterioration.

Cardiac infarction may or may not produce physical signs. Even with prolonged severe pain there may be no abnormal findings. Fever is common. It is of mild degree and lasts for a few days from the first or second day of the attack. A moderate leucocytosis and elevation of the erythrocyte sedimentation rate is usual. *Tachycardia* is often more than can be accounted for by fever and the *arrhythmias* mentioned above, including heart block, may be detected by examination of the radial arteries and jugular pulses.

*Pericardial friction* occurs early in some 10 to 15 per cent. of cases, especially in those with anterior infarction. It is often fleeting but may persist for days and indicates accompanying pericarditis. *Triple rhythm* due to the addition of a diastolic filling sound (third heart sound) is often audible. It may produce a protodiastolic or presystolic cadence of sounds, depending on the heart rate. It indicates severe muscle damage.

*Shock* is indicated by pallor, sweating, peripheral constriction and hypotension. When shock is absent, blood pressure may rise initially but tends to fall after 24 to 48 hours, and it may return to normal or near normal levels after a varying interval of days or weeks.

*Heart failure* is indicated by dyspnoea, orthopnoea, Cheyne-Stokes respiration or pulmonary œdema. A rise of jugular venous pressure is common but œdema, ascites and hepatomegaly are not usually seen in the early stages. Any of the signs of heart failure may be encountered at any stage of the illness, but the signs of shock are early. The signs of complicating thrombo-embolism should be sought and may appear at any time, but commonly in the first 3 weeks.

*The electrocardiogram.*—The electrocardiogram is of great diagnostic value. It is always abnormal in cardiac infarction although rarely it may remain normal for a few hours after the onset of pain. The ventricular complex is altered in three ways (see p. 801). (1) Large primarily negative waves (Q waves) appear in leads recording the main left ventricular potentials, i.e. where R waves existed before. These pathological Q waves are usually more than 0.04 sec. duration and may replace all of the QRS or be followed by the remnants of an R wave. The development of Q waves indicates muscle death, hence the change is usually permanent and is highly specific since coronary disease is almost always the cause of circumscribed myocardial necrosis. (2) Elevation and coving of the S-T segment in leads facing the damaged area (and reciprocal depression of the S-T segment in remote leads) are due to superficial injury involving the epicardium and pericardium. S-T elevation is maximal in the early phases of the attack and subsides after a few days. S-T changes are not as specific for cardiac infarction as Q waves, since the same changes occur in pericarditis from other causes. Persistent elevation of the S-T segment may be due to the development of a ventricular aneurysm. (3) Inversion of the T wave in leads where it is normally positive is usual in cardiac infarction. In the earliest days of the attack S-T elevation may be great and the isoelectric interval reached without the development of a separate T wave; however, sharp inversions of the T waves appear as the S-T elevation subsides. T wave inversion mostly occurs in combination with Q waves

and with S-T changes in cardiac infarction. Isolated T wave changes are not specific and occur as the result of many varied physiological and pathological changes in the muscle; however, when assessed with the clinical features, flattening and inversion of the T wave have great diagnostic value. The T waves may become positive after recovery and healing of cardiac infarction.

These pathological changes occur in leads related to the left ventricle and maximally in those "facing" the area of infarction, so that it is often possible to determine approximately its site and size (see p. 802). *Anterior infarction* is indicated by Q, S-T and T wave changes in anterior chest leads and in lead I. When the septum is involved, complete Q waves also occur in right anterior chest leads. *Posterior (or inferior) infarction* is indicated by the finding of Q, S-T and T wave abnormalities in leads from the left leg, i.e. in leads II, III and VF, which record potentials in the field facing the diaphragmatic surface of the heart. *Lateral infarction* is diagnosed when changes are found in the extreme left chest leads, i.e. V7, CR7 and VL. These changes may occur alone or in combination with an anterior or posterior pattern.

**Complications.**—Thrombo-embolic phenomena occur in more than one-third of necropsy examinations and are a clinical problem in some 15 per cent. of cases. Phlebothrombosis in the leg is the most common and is responsible for episodes of pulmonary infarction and for massive pulmonary embolism. Systemic emboli may involve any organ and arise from ventricular mural thrombi; however, there is much evidence to suggest that arterial thrombosis in the affected organ is often responsible. Cerebro-vascular episodes are common.

The infarcted area of myocardium may bulge, producing a local aneurysm, which, if large enough, causes a diffuse pulsation of the chest wall. Occasionally there appears to be a double apex; that due to the aneurysm is usually above and internal to the true apex, and a see-saw like movement occurs between the two pulsations. Ventricular aneurysms develop soon after the episode of infarction, which is usually of the anterior variety, but they do not necessarily influence the outcome. The cavity of the aneurysm often becomes partially obliterated by organised clot. Final diagnosis depends on radiological examination; a hump or bulge on the left ventricular silhouette which swells in systole is diagnostic. The electrocardiogram shows the changes of cardiac infarction.

Rupture of the heart at the site of the infarct is not uncommon; hæmopericardium follows and may cause sudden death. When the ventricular septum is infarcted, an internal rupture occasionally occurs, producing a left to right shunt and ultimately causing heart failure. The development of a loud systolic murmur in the mid-præcordium, associated with a rise of venous pressure, is suggestive of a ruptured septum.

"Frozen shoulder" and "the shoulder-hand syndrome" sometimes develop after cardiac infarction. Pain frequently occurs in either shoulder at variable periods from a few weeks to a few months after an attack of cardiac infarction, and in severe forms the shoulder may become stiff, painful and ultimately almost immobile. Less commonly the hand becomes stiff, swollen or shows trophic changes in the skin. The fingers become smooth and pale, resulting in a scleroderma-like condition. Spontaneous recovery after a variable period is usual.

**Prognosis.**—Cardiac infarction is an unpredictable disease. Sudden death may occur at any time and in the mildest cases, whilst others who are gravely ill during the acute stage may survive to live many years. There is no agreement about mortality rates but probably 25 per cent. die in the first attack; however, this figure is considerably lower for those receiving early, competent treatment. The greatest mortality occurs in the first 48 hours and remains high during the first 7 to 10 days. After 3 weeks there is an excellent chance of recovery from the immediate illness provided that there are no signs of heart failure.

Prognosis is adversely affected by increasing age, but sudden death from cardiac

infarction under the age of 40 is not uncommon. The prognosis for patients with a mild attack is relatively better than for those with symptoms and signs in addition to pain. The persistence of the shock over 24 hours is a grave sign and few recover when shock continues for more than 2 days. The early development of congestive heart failure is serious; however, many patients show a slight rise in venous pressure or signs of mild left ventricular failure for a few days, which does not necessarily affect the outcome. The disappearance of triple rhythm during the early weeks indicates improving ventricular function and a better prognosis than in those patients with a persistent third heart sound. Transient arrhythmias are common and prognosis is not adversely affected, but a persistent irregularity, especially when due to multiple ventricular ectopic beats, ventricular tachycardia, heart block or auricular fibrillation, is of grave significance.

Pulmonary infarction and other thrombo-embolic manifestations often cause deterioration and may adversely affect the outcome at any time during the first 3 weeks.

Hypertension and preceding angina pectoris do not materially alter prognosis, but a history of previous cardiac infarction does. The site, duration and intensity of pain, unless associated with shock, does not affect prognosis; nor does the anatomical site of the cardiac infarction.

As in all forms of ischaemic heart disease, women do better than men. The outlook improves with each week that passes free of complications, but after recovery from the acute illness, the ultimate prognosis depends on many factors. Prognosis is favourable when heart failure, cardiac enlargement, triple rhythm, hypertension, diabetes mellitus, obesity and angina pectoris are absent, and when the electrocardiogram shows recovery of the S-T segments and T waves. Under such circumstances many years of good health are probable, but the development of a further attack of infarction is always possible and unpredictable.

**Treatment.**—Treatment of cardiac infarction is based on four principles: (1) The relief of pain, (2) the treatment of shock and heart failure, (3) the reduction of cardiac work and (4) the prevention and treatment of complications. Immediate rest is indicated at the onset and the patient should be moved to bed as soon as possible.

Morphine is usually required to relieve the pain, but it should not be given routinely, and when the pain is slight a milder analgesic may be sufficient. Morphine should be given subcutaneously in doses of gr.  $\frac{1}{4}$  to  $\frac{1}{2}$ , and if the pain is especially severe gr.  $\frac{1}{4}$  in 5 ml. of sterile water may be given slowly into a vein, followed by subcutaneous doses of gr.  $\frac{1}{4}$  at intervals of 1 to 2 hours if severe pain persists. Vomiting, depression of respiration, and disturbances of the bowel are often due to morphine; synthetic morphine substitutes, which have few side effects, may therefore be used with advantage after the initial relief of pain.

**Shock** passes off under the influence of rest and morphine in most patients, but in some it is more severe and persistent. When acute hypotension is responsible for giddiness or syncope, patients must be nursed flat unless left ventricular failure appears when a more upright posture is necessary. Persistent shock carries a very high mortality; transfusions of glucose, plasma and blood have been advocated but they are of little value and may cause acute pulmonary oedema. Adrenaline and ephedrine raise systemic arterial pressure but tend to cause ventricular tachycardia or ventricular fibrillation and should not be used. The newer pressor amines act directly on peripheral vessels without increasing myocardial irritability and should be used if the shock state persists for more than 24 hours. Noradrenaline may be given as an intravenous drip infusion, sufficient dilution being obtained by adding 4 ml. of 1 : 1,000 noradrenaline to a litre of isotonic 5 per cent. dextrose. If hypotension persists, the concentration of noradrenaline may be increased to avoid the administration of too great a volume of fluid. The infusion may be continued for hours or days and its rate, concentration and duration judged by therapeutic effects.

*Heart failure* of any type and severity should be treated with a low salt diet and mercurial diuretics. Aminophylline given as a suppository at night may help to control nocturnal attacks of dyspnoea. Digitalis should be used for congestive heart failure in cardiac infarction, but it is advisable to give other methods a trial first unless the severity of the condition demands its immediate use. (For treatment of heart failure, see p. 812.)

*Arrhythmias* are often transient and do not then require special treatment. When extrasystoles are frequent quinidine in doses of gr. 3 or 5 four times a day may abolish them and prevent the development of a more serious arrhythmia. Ventricular tachycardia requires immediate treatment; 5-gr. doses of quinidine by mouth are given every 2 hours and if there is no response in 12 hours, the dose should be doubled. Intravenous quinidine or procaine amide may be used in the most serious cases, and, where possible, administration should be checked by serial electrocardiograms so that the drug may be discontinued immediately on restoration of normal rhythm (see p. 828 for details).

When pain and shock have been relieved, a full assessment of the patient's condition and home circumstances can be made. Gravely ill patients with shock or heart failure are best treated in hospital; others may be treated at home provided that there is freedom from domestic and business worries, and adequate nursing help is available.

Most patients require from 4 to 6 weeks bed rest, depending on the severity of the attack. From the physical point of view, the difference between complete and modified bed rest is slight, but morale and mental rest are benefited by the less exacting régime. Complete bed rest also increases the risk of peripheral thrombo-embolism. The recognised hazards of prolonged complete bed rest have led to the advocacy of armchair treatment during recent years. This method has its dangers and there appears to be no sound reason for abandoning bed rest provided that it is intelligently carried out. It is therefore recommended that (1) all cases rest in bed for at least 4 weeks and ideally none should return to work before 12 weeks. (2) Mild and moderate cases with no shock, no heart failure, no cardiac enlargement are allowed to use a commode, feed, wash and shave themselves and sit out of bed for short periods. After the third or fourth week, activity should be steadily increased. (3) More seriously ill patients should be rested in bed for 6 weeks or more if necessary. (4) Shocked patients should be nursed recumbent until the arterial pressure rises, whilst those with heart failure should be nursed in a more upright position. It is emphasised that at all stages the clinical condition of the patient should determine the nursing régime, the length of rest and the rate of convalescence.

*Diet.*—It is advisable to reduce the diet below 1000 calories daily for the first week in all cases. Thereafter more food is allowed but the separate meals should be small. Salt should be restricted to less than 1 g. daily in all patients with hypertension or any evidence of heart failure.

Constipation may become a problem and strenuous defæcation should be avoided by the use of liquid paraffin. Acute retention of urine is not uncommon in the elderly, and it is often advisable to allow elderly patients to sit out of bed for micturition during bed rest for cardiac infarction.

**ANTICOAGULANT THERAPY.**—In a disease where intravascular clotting is an essential part of the pathology and where thrombo-embolism is responsible for most of the complications leading to a high morbidity and mortality, there are strong theoretical reasons for using anticoagulant therapy and there is now abundant evidence of its value in the treatment of thrombo-embolic disease. The aims of anticoagulant therapy in cardiac infarction are the prevention of peripheral venous thrombosis and consequent pulmonary embolism, the prevention of intracardiac mural thrombosis and consequent arterial embolism and the prevention of further thrombotic occlusion in coronary vessels. It is probable that these aims are in part achieved without undue

risk of hæmorrhage if anticoagulant treatment is correctly regulated in an institution with adequate pathological services. Anticoagulant therapy should be used for cases of cardiac infarction where there is continued shock, heart failure or evidence of extensive muscle damage as judged by fever, sedimentation rate and the electrocardiogram. It is not indicated in mild cases and when there is a possible pre-existing source of hæmorrhage, e.g. peptic ulcer and cirrhosis of the liver. In most cases where urgent treatment is indicated, heparin is used for 48 hours and one of the oral preparations for reducing blood prothrombin is administered concurrently and then continued for 4 to 6 weeks. In less urgent cases the heparin may be omitted.

Heparin is the best anticoagulant drug available; it is effective within minutes of intravenous injection and when discontinued the coagulability of blood returns to normal in a short time. The necessity for frequent parenteral administration and its high cost are disadvantages. Administration is regulated by estimates of the coagulation time which should be prolonged to two or three times the normal. For short-term use before one of the coumarin drugs is effective, heparin is best given by intravenous injection in doses of 50 mg. (5,000 units) every 4 hours. Intramuscular injections may be given twice daily for a prolonged period in doses of 100 to 150 mg., and the immediate pain of injection may be abolished by the addition of 2 ml. of 1 per cent. procaine to 1 ml. of heparin, but delayed discomfort and extensive bruising at the site of injection are common and a serious disadvantage. Overdosage with heparin may be corrected immediately by 50 mg. of protamine sulphate given intravenously or by a transfusion of whole fresh blood.

Coumarin drugs affect the production of prothrombin by the liver and thereby prolong the prothrombin time of plasma, but they do not materially alter the coagulation time of whole blood. These drugs have the great advantage of being effective when given by mouth. Disadvantages are the necessity for control of administration by frequent estimation of prothrombin time, their relatively slow action and slow elimination. These drugs should not be used in the presence of liver disease, kidney disease or a serious blood dyscrasia.

Dicoumarol has been largely superseded by ethyl biscoumacetate (Tromexan) and phenylindanedione (Dindevan) which have a more rapid action and are more easily controlled. A daily estimation of prothrombin time should be made before the next dose is administered. Prothrombin time is estimated by the Quick method, in which oxalated blood plasma is mixed with an excess of calcium ion and an excess of thromboplastin. The clotting time is prolonged in proportion to decrease in concentration of prothrombin. In all cases the prothrombin time should be estimated before treatment, the normal is between 12 and 17 seconds and a safe therapeutic level is achieved when this is prolonged from 2 to 2.5 times, which corresponds to a prothrombin level of 15 to 30 per cent. Average doses for patients of medium weight are as follows: Dicoumarol 300 mg. first day, 200 mg. second day and thereafter 50 to 200 mg. depending on prothrombin times. Ethyl biscoumacetate 1500 mg. first day and thereafter 300 to 900 mg. Phenylindanedione 200 mg. on the first day and 50 to 150 mg. thereafter. Division of the daily dose produces a more even lowering of the blood prothrombin.

Inspection of a daily urine specimen for red cells is a useful adjunct to control by prothrombin time. Hæmorrhage due to overdosage is treated by transfusion if necessary. Vitamin K<sub>1</sub> oxide is an effective antidote; prolonged prothrombin time may be raised in 6 hours by an intravenous, or more slowly by an oral dose of 200 mg. Some physicians advocate the use of anticoagulants over long periods with weekly estimations of prothrombin time. The results are difficult to evaluate and the hazards considerable.

**TREATMENT OF COMPLICATIONS.**—*Phlebothrombosis* in the legs, with or without accompanying pulmonary infarction, is an indication for anticoagulant therapy (see above). The treatment of peripheral arterial embolism or thrombosis depends on

the site and severity of the resulting ischaemia (see p. 925). There is no treatment for ventricular aneurysm.

*Shoulder-hand syndrome* causing pain and stiffness tends to become permanent but many mild cases recover spontaneously or with the help of physiotherapy. A short course of cortisone in doses of 50 to 100 mg. by mouth cures some more resistant cases; when this fails, procaine block of the stellate ganglion is indicated.

**MANAGEMENT AFTER THE ACUTE ATTACK.**—Convalescence should be from 4 to 6 weeks. The degree of activity permitted thereafter depends entirely on the assessment of the clinical condition and its relation to the social and economic status of the patient. Many patients are able to return to their previous occupations and should be encouraged to do so. It is advisable to continue with small meals if there is a tendency to obesity. Smokers should reduce their tobacco consumption. Alcohol should not be prohibited. It is customary to advise moderation in all things and to reduce physical activities, but most patients are benefited by following their personal inclinations for work, exercise and leisure activities. There is evidence that restriction of activities beyond that imposed by diminished cardiac reserve not only fails to prevent further deterioration but may even hasten it. Angina of effort or heart failure require treatment and often cause permanent incapacity. The physician should maintain an attitude of optimism tempered by intelligent explanation and above all he should never cause unnecessary anxiety.

#### ACUTE CORONARY INSUFFICIENCY

Acute coronary insufficiency is not a clearly defined clinical syndrome; the term is used to indicate an acute disparity between the supply of oxygen and the demands of the myocardium, which is more prolonged than in angina of effort. On the other hand it excludes the clinical syndrome of acute coronary occlusion with cardiac infarction which is more severe and permanent. In acute coronary insufficiency the emphasis is on sudden abnormal increased demand or a sudden fall in blood supply due to factors other than complete coronary occlusion.

**Pathology.**—There is usually some degree of coronary atherosclerosis ranging from normal to severe, but there is no fresh thrombotic occlusion. Subendocardial necrosis or small patches of necrosis in deep layers of the muscle are usual, but massive necrosis involving pericardium and endocardium is not seen. Mural thrombosis and peripheral emboli do not occur.

**Ætiology.**—The sudden diminution of blood supply or greatly increased cardiac work required to produce acute coronary insufficiency is usually due to some degree of coronary disease associated with one or more of the following conditions: (1) Haemorrhage and other causes of shock and hypotension, (2) acute heart failure, (3) asphyxia and especially carbon monoxide poisoning, (4) acute severe pulmonary disease, (5) pulmonary embolism, (6) unusually severe effort or great emotional stress, (7) paroxysmal tachycardia and (8) acute hypertension.

**Symptoms.**—Pain is the usual symptom as in other manifestations of cardiac ischaemia; it lasts longer than in angina pectoris and it may occur under a variety of circumstances depending on the immediate cause. Shock, heart failure, fever and leucocytosis are not present. There are no signs of acute coronary insufficiency *per se*, but the signs of an associated precipitating cause may be present.

**The electrocardiogram.**—The electrocardiogram shows similar changes, but of greater magnitude than those found during an attack of angina pectoris. Great depression of the S-T segments in left ventricular leads is usual. T waves may remain flat or inverted for a few days after the attack. Pathological Q waves do not occur.

**Prognosis** largely depends on the nature of the immediate cause and whether there is evidence of severe coronary artery disease. The same general factors determine prognosis as for angina pectoris of effort.

**Treatment.**—During the attack trinitrin should be given as for angina pectoris (see p. 840), but it is usually ineffective and morphine may be necessary for the relief of pain. Heparin 50 mg. should be given intravenously and continued in similar doses every 4 to 6 hours for 48 hours. A full course of anticoagulant therapy should be given in those cases where a history of increasing angina precedes the attack of insufficiency and therefore suggests impending infarction. The precipitating cause, e.g. anæmia or hypertension requires treatment. A short period of bed rest is advisable.

## HYPERTENSIVE HEART DISEASE

Heart disease is the cause of death in approximately 75 per cent. of patients with established high blood pressure. In the great majority of cases the hypertension is of the essential and so-called benign variety. The transitions from asymptomatic systemic hypertension to compensated cardio-vascular hypertrophy and final decompensation is slow and mostly insidious, though sometimes interrupted by more or less acute cardiac or cerebral episodes; the point at which the heart becomes diseased is usually indefinable. The subject of hypertension is dealt with elsewhere.

**Ætiology and Pathology.**—The ætiology of hypertension is discussed on pp. 907, 908. Systemic hypertension is due to an increased total peripheral resistance with a normal cardiac output; the work of the left ventricle is increased, which leads to compensatory hypertrophy, and in the course of time dilatation of the ventricle occurs.

Disease of the heart in hypertension is essentially disease of the left ventricle. The ultimate failure of compensatory hypertrophy is probably due to failure of the coronary circulation to meet an increasing demand. Hypertension appears to accelerate the development of coronary atheroma which is present in all cases of long-standing hypertensive heart disease.

At necropsy there is hypertrophy of the left ventricle and the whole arterial system. In the majority of cases there is coronary atheroma and the myocardium shows varying degrees of ischæmic damage ranging from widespread fibrosis to more localised areas of infarction.

**Clinical Features.**—Cardiac symptoms are absent during the compensated stages of hypertension unless coronary sclerosis causes angina pectoris (see p. 837). During the phase of decompensation the symptoms are those of left ventricular failure and congestive cardiac failure (see p. 806). The onset of heart failure may be shown by increasing effort dyspnoea or by paroxysmal dyspnoea which is frequently of the nocturnal variety. Cardiac pain is often present and symptoms suggesting cardiac infarction may precede those of heart failure.

Examination during the compensated phase of hypertension shows varying degrees of arteriopathy in the fundus oculi, thickening of radial and brachial arteries, an apical impulse suggesting left ventricular hypertrophy, a loud second heart sound, sometimes an auricular gallop sound, occasionally an aortic diastolic murmur and always arterial hypertension. When heart failure has developed there is usually cardiac enlargement, a less forcible apex beat which, however, retains some of the sustained heave of hypertrophy, triple rhythm or a summation gallop, a variable apical systolic murmur due to functional mitral incompetence, together with the signs of pulmonary or systemic congestion in varying degrees. The blood pressure usually remains elevated, but as heart failure increases, the pulse pressure falls due to a greater drop in systolic pressure than in the diastolic level. Pulsus alternans may be present and Cheyne-Stokes respiration is common in the late stages. Auricular fibrillation occurs in about 25 per cent. of patients with hypertensive heart failure. In attacks of severe left ventricular failure and in the terminal stages of congestive cardiac failure, extreme peripheral constriction may occur.



*Radiographic examination* reveals varying degrees of pulmonary congestion when there are symptoms of left ventricular failure. The aorta tends to become "unfolded", causing a widening of the superior mediastinum; the aortic "knob" is unduly prominent and there are often scattered flecks of calcification in the wall. The left ventricle is enlarged and best seen in the left oblique view.

*The electrocardiogram* shows varying degrees of left ventricular hypertrophy associated with ischaemic changes. Characteristically the R waves in lead I, VL and V5 to V7 are tall and associated with some degree of S-T depression and T wave flattening or inversion in the same leads. In late stages left bundle branch block is common or the R waves become lower in voltage (see electrocardiogram of left ventricular hypertrophy, p. 800).

*Diagnosis* depends on the finding of raised blood pressure together with the signs of cardio-vascular hypertrophy. Gross hypertrophy of the left heart in the absence of the signs of valvular disease is generally due to systemic hypertension. When the signs of heart failure have supervened diagnosis may be more difficult, since the arterial tension tends to fall and the powerful thrust of a hypertrophied left ventricle diminishes. However, in such cases the diastolic tension usually remains elevated, whilst retinopathy and thickened brachial vessels indicate long-standing hypertension. Systolic murmurs may suggest organic mitral incompetence but the raised arterial tension and the clinical and electrocardiographic evidence of gross left ventricular hypertrophy indicate the true nature of the condition. Similar criteria serve to distinguish the cause of an early diastolic murmur associated with severe hypertension from that due to organic aortic incompetence. Angina pectoris associated with hypertension must be differentiated from cardiac pain due to other causes.

*Prognosis.*—During the compensated stage of hypertension the prognosis is worse in males than in females, and is adversely affected by high diastolic levels of pressure, evidence of myocardial disease and impaired renal function. When breathlessness develops the prognosis depends on the degree of cardiac damage; the presence of cardiac pain and evidence of ischaemia are adverse factors and triple rhythm, great cardiac enlargement, pulsus alternans and attacks of paroxysmal dyspnoea, occurring in spite of treatment, are of grave import.

*Treatment* is required for the hypertension and for heart failure when this is present. The treatment of hypertension is discussed on pp. 911, 916. It is emphasised that attempts to lower blood pressure with the various hypotensive agents and a low salt diet should be made after the development of heart failure or even when there is evidence of ischaemic disease in the myocardium, for hypertension is the fundamental error responsible for the disease. Heart failure should be treated on the lines indicated on p. 812. Regular periods of rest are advisable and an attack of cardiac asthma should be followed by a few days of bed rest. A low sodium diet (see p. 812) is probably the most satisfactory method of controlling both hypertension and heart failure and the action of the methonium halide drugs is potentiated by a low sodium régime. Acute left ventricular failure is best treated with morphine, aminophylline, oxygen if there is central cyanosis and a mercurial diuretic; a venesection of 250 to 500 ml. should be carried out if other methods are not rapidly effective; parenteral methonium halide has been tried with good effect in acute left heart failure, but further experience is necessary before this treatment can be satisfactorily assessed. Digitalis (*digitalis folia* gr. 1 twice daily) should be given to patients with hypertensive heart failure and maintained indefinitely irrespective of rhythm.

## PULMONARY HEART DISEASE

*Synonym.*—Cor Pulmonale.

Pulmonary heart disease may be defined as a disorder of the right heart, consequent upon disease of the lungs and of the pulmonary vasculature. It may be subdivided

into acute, subacute and chronic forms. Chronic pulmonary heart disease is common and may be due to lung disease, including bronchitis and emphysema, fibroid lung and pneumoconiosis, to vascular disorders of the lungs or to kyphoscoliosis. Acute pulmonary heart disease is due to massive pulmonary embolism and the subacute form to lymphatic or embolic carcinomatosis.

### ACUTE PULMONARY HEART DISEASE

**Synonym.**—Acute Cor Pulmonale.

**Definition.**—Acute pulmonary heart disease may be defined as a cardiac and circulatory disturbance resulting from rapid obstruction of the pulmonary circulation by one or more massive emboli.

**Ætiology.**—The immediate cause is sudden obstruction of the pulmonary artery by a large clot, which has become detached from its site of formation either in the systemic veins or in the right heart. Prolonged bed rest predisposes to the formation of clots, particularly in the leg veins. The thrombi in the calf muscle veins, giving rise to pulmonary emboli, may be locally asymptomatic or give rise to only minor symptoms (phlebothrombosis) although sometimes there is local tenderness, swelling and œdema. Pulmonary embolism may occur after operations, especially pelvic and abdominal, fractures and other serious injuries, and is most common in the second and third post-operative weeks. It may follow childbirth. Chronic congestive heart failure may be complicated by pulmonary embolism, since the poor peripheral circulation encourages the formation of clots, but pulmonary embolism is also associated with heart disease without failure, especially cardiac infarction, where reduction of clotting time seems to be a predisposing factor. It may occur in patients with carcinoma, especially of the stomach, and with hæmatological diseases. The act of straining at stool may sometimes be the immediate precipitating cause of displacement of the clot into the circulation.

**Pathology.**—The deep veins of the calf muscles are the commonest source of pulmonary emboli. Less commonly the pelvic veins may be the source or the chambers of the right heart.

Pulmonary emboli causing severe cardiac and circulatory disturbance are large and obstruct the main pulmonary artery and its branches. The large size of the embolus is caused by coiling up of a long thrombus into a compact mass after detachment from its site of formation. A common site of lodgement is the bifurcation of the pulmonary artery with complete occlusion of one branch and partial occlusion of the other. In other cases, in which death rapidly follows the symptoms of embolism, complete or almost complete occlusion of the main pulmonary artery has taken place. The obstructing pulmonary embolus may or may not be all of the same age, being in some cases formed of repeated smaller emboli and in others enlarged by local thrombosis. Smaller pulmonary emboli, insufficient to obstruct the main pulmonary arterial trunk, seldom give rise to serious general cardio-vascular disturbances, although they often cause pulmonary infarction.

If the patient survives the initial pulmonary embolism, pulmonary infarction may develop, depending on the site and size of vessel obstructed and the collateral circulation to the segment of lung involved. Embolism is more likely to give rise to infarction in the presence of pulmonary venous congestion from heart failure. Acute pulmonary heart disease, however, usually occurs without the development of pulmonary infarction, since the patient may die before the infarct develops.

The cardiac and circulatory effects of massive pulmonary embolism are due to mechanical circulatory obstruction and to myocardial ischæmia. It has been estimated that, in order to cause circulatory embarrassment, 50 to 70 per cent. of the cross-sectional area of the pulmonary arterial tree must be cut off. When this occurs, the output from the right heart is diminished with diminution of venous return to the

left heart and consequently the left ventricular output also falls. At the same time, acute right heart strain develops with dilatation of the right heart and a rise in systemic venous pressure. Myocardial ischaemia resulting in subendocardial necrosis, most severe in the left ventricle, is probably the result of diminished coronary flow (*i.e.* acute coronary insufficiency) resulting from a fall in left ventricular output and systolic pressure, associated with arterial anoxaemia, due to pulmonary asphyxia. Reflex coronary arterial spasm may also play a part in the production.

**Symptoms.**—The onset of massive pulmonary embolism is sudden. In some cases, however, smaller emboli precede the massive embolism and in these pre-monitory symptoms may be present.

The patient often complains of chest pain, frequently very severe, similar in type and distribution to that of cardiac infarction. This is accompanied by acute dyspnoea or tachypnoea. In addition there may be faintness, dizziness, restlessness, mental apathy or convulsions. Sometimes the pain is abdominal rather than substernal. Occasionally there is hæmoptysis and in some palpitation from an associated paroxysmal arrhythmia. The symptoms vary widely from case to case and may be relatively mild.

On examination there are usually signs of acute circulatory failure and shock, with a rapid, thready pulse, low blood pressure, pallor, coldness and sweating. In some cases deep black-blue cyanosis may be present from pulmonary asphyxia, which is probably reflex in origin. In contrast to the systemic hypotension, resulting from inadequate venous return to the left ventricle, in the right heart there are signs of pulmonary hypertension with systemic venous congestion. Triple rhythm, best heard at the left sternal edge or in the epigastrium is often present. The pulmonary second sound may be accentuated. There may be dilatation of the pulmonary artery, with a systolic murmur and thrill in the pulmonary area. The jugular venous pressure is raised and often associated with acute engorgement of the liver.

If the patient survives the massive pulmonary embolus, signs of pulmonary infarction may develop. There is usually pyrexia and leucocytosis: there may be pleural pain related to the side of the infarction: there may be cough with expectoration of bright red frothy sputum. Examination may reveal signs of consolidation over the infarcted area, sometimes accompanied by a pleural rub and there may be a pleural effusion, which on diagnostic aspiration is found to be blood-stained. The clinical picture, however, varies considerably and neither pain, cough nor hæmoptysis is necessarily present.

The *electrocardiogram* in massive pulmonary embolus usually shows a deep S wave in standard lead I and a Q wave with inversion of the T wave in lead III. In the V leads there is inversion of the T wave from V1 to V4, while in some cases transient right bundle branch block may develop. These signs may persist for days or weeks. With smaller emboli, on the other hand, the *electrocardiogram* usually remains normal.

**Radiography.**—The hilar shadows may be prominent and the main pulmonary artery large. In addition there may be evidence of pulmonary infarction with a triangular, ovoid or irregular shadow in the lung fields, often accompanied by a pleural effusion.

**Diagnosis.**—Collapse, præcordial pain, dyspnoea, tachycardia and cyanosis in a patient confined to bed after an operation, delivery or during a medical illness should at once suggest the diagnosis of massive pulmonary embolus. The diagnosis becomes even more probable if signs of phlebothrombosis or thrombophlebitis are present in the veins of the calf muscles. If, added to this, there are signs of right heart strain with elevation of the jugular venous pressure and characteristic electrocardiographic changes, then the diagnosis of acute pulmonary heart disease is established.

The differential diagnosis from cardiac infarction may be difficult, since pulmonary embolus may complicate cardiac infarction and since either may occur post-operatively. The *electrocardiogram* is usually diagnostic, but some cases of posterior

cardiac infarction may be difficult to differentiate in the electrocardiogram from acute pulmonary heart disease. The development of localising signs in the lung of pulmonary embolus may help to establish the diagnosis. Other conditions, which must be excluded, are pneumonia, pleurisy, post-operative shock and an acute abdominal emergency.

**Prognosis.**—The prognosis after massive pulmonary embolism resulting in acute pulmonary heart disease is extremely unfavourable and death occurs in over 80 per cent. of patients. Death is usually delayed for a number of hours or days, but may take place within a few minutes. Smaller emboli seldom cause death, but these are occasionally the precursors of larger emboli, which may prove fatal. In patients who survive a massive pulmonary embolus, the thrombus may undergo organisation and recanalisation.

**Treatment.**—The most important aspect of treatment in massive pulmonary embolus and acute pulmonary heart disease is prophylactic treatment. Unnecessarily prolonged periods of bed rest should be avoided and frequent changes of posture with leg exercises encouraged in chronic bed-ridden patients. In surgical cases, gentle handling at operation of the veins draining the lower extremities and avoidance of tight bandages obstructing the venous return are desirable. Since heart failure seems to predispose to venous thrombosis and pulmonary embolism, energetic and prompt treatment of failure may ward off these complications. If calf vein thrombosis develops and is recognised, a constant watch should be kept for the signs in any chronic bed-patient—two main forms of treatment are available, medical and surgical, in order to help to avoid pulmonary embolism. Anticoagulants may be given in order to prevent extension of the venous thrombus, or in cases where pulmonary embolus has already occurred to prevent growth of the pulmonary embolus by local thrombosis. The principles and details of anticoagulant therapy have already been discussed (see p. 847), and treatment is usually continued for 3 to 4 weeks.

Surgical treatment is by ligation of the femoral or common iliac veins or even of the inferior vena cava. This treatment is usually reserved for cases of recurrent embolism and where anticoagulant treatment is contraindicated.

Treatment of pulmonary embolism itself largely consists of supportive measures to tide the patient over the acute emergency. The patient should be nursed flat in order to encourage cerebral circulation in the presence of a low blood pressure. Oxygen should be given either by B.L.B. mask or in an oxygen tent. Papavarine hydrochloride (0.03 g.) intravenously has been recommended, but it is doubtful if it dilates the pulmonary artery. Venesection is contraindicated, since reduction in systemic venous pressure does nothing to relieve the cause, namely obstruction to right ventricular output. Surgical removal of an embolus from the main pulmonary artery (Trendelenburg operation) can only be carried out if a highly trained team is available and the operation carries a mortality of about 90 per cent.

#### FAT EMBOLISM

Acute pulmonary heart disease may rarely be caused by fat embolism, resulting from the entrance of fat globules into the systemic veins. The commonest cause of fat embolism is fracture of a long bone; orthopædic operations, blast injuries and burns may sometimes be responsible. Usually the fat globules are small and obstruct the smaller pulmonary or cerebral arteries. Sometimes, however, a large amount of fat may obstruct the main pulmonary artery with the production of acute pulmonary heart disease.

#### AIR EMBOLISM

The sudden entrance of air in large quantities into the systemic veins often results in death from heart failure. The commonest causes of air embolism are operations

on the neck, diagnostic or therapeutic procedures involving air insufflation, such as tubal insufflation or pneumo-peritoneum. The air entering the right heart, impedes the action of the right ventricle by its compressibility and may block the main pulmonary artery or result in widespread embolism of the pulmonary arteries and arterioles. Death results from acute right heart failure with low cardiac output and anoxæmia.

## CHRONIC PULMONARY HEART DISEASE

### EMPHYSEMA HEART DISEASE

**Ætiology.**—Chronic bronchitis is largely a disease of middle-aged men and hence heart disease due to chronic bronchitis and emphysema shows a similar sex and age incidence. The incidence of right heart disease in emphysema is difficult to assess, but it is probable that it occurs in between one-third and one-half of patients.

**Pathogenesis.**—*Pulmonary hypertension.*—Fixed structural changes in the pulmonary vascular bed, which increase its rigidity or reduce its cross-sectional area, have previously been considered to play the major part in the production of high pulmonary arterial pressure in emphysema. Recently, however, by means of cardiac catheterisation studies, the high resting pressures recorded during cardiac failure have been shown to be transitory and reversible. Permanent structural changes, therefore, cannot alone be responsible for the transient high pressure, although they almost certainly play some rôle in maintaining the moderate pulmonary hypertension seen at rest in patients not in congestive cardiac failure.

Functional factors must therefore be considered in the mechanism of production of pulmonary hypertension in chronic bronchitis and emphysema. It is probable that anoxia is an important factor causing pulmonary hypertension, since the arterial saturation with oxygen is decreased when patients are in congestive cardiac failure and have raised right ventricular pressures, but, with recovery from failure, the saturation returns to a higher level as the pressure falls. The blood volume in emphysema heart disease increases during congestive failure and decreases on recovery and it is possible that this may contribute to the production of transient pulmonary hypertension. Variations in the pulmonary blood flow in emphysema may also influence the height of the pulmonary vascular pressure. The pulmonary arterial pressure rises during exercise as the cardiac output increases, whereas in normal subjects, little alteration in pulmonary arterial pressure results from changes in blood flow. At rest, however, it is unlikely that levels of flow are high enough to be directly responsible for the production of pulmonary hypertension. The extent to which neurogenic activity influences circulation through the pulmonary vascular bed remains uncertain, but there is evidence suggesting that it could play an important rôle.

**Cardiac output.**—Normal or even increased cardiac output is present in heart failure secondary to lung disease and is one of the features distinguishing it from left ventricular failure (see p. 809). The arteriovenous difference usually remains normal and the cardiac output is therefore appropriate to the raised level of oxygen consumption present in these breathless patients.

**Symptoms.**—The clinical diagnosis of the onset of cardiac complications in chronic bronchitis and emphysema is a matter of considerable difficulty, since symptoms due to emphysema heart disease are gradually superimposed upon those of pulmonary emphysema.

Three major patterns of onset of pulmonary symptoms are met. There are those, who have been subject to repeated episodes of winter colds and "bronchitis" gradually increase in severity and begin to recur each year. Some date symptoms from a specific respiratory illness, usually described as "pneumonia".

give a long history of asthma with the gradual development of a persistent cough. Regardless of the type of onset, the symptoms become similar in all patients with increasing severity of their pulmonary disease and the gradual development of cardiac complications. They have a round-the-year cough, usually productive of sputum, and increasing dyspnoea on exertion. Their exercise tolerance varies considerably: cold weather, fog and minor respiratory infections all increase their dyspnoea; patients subject to asthma, however, may be most incapacitated in the summer. Owing to interference with the normal oxygenation of the blood, they gradually become cyanosed. As the disease progresses, recurrent acute exacerbations of bronchitis incapacitate them more, until each exacerbation is attended by an attack of severe anoxia and frank congestive cardiac failure. Many patients die within a year of the onset of failure.

Physical signs of pulmonary hypertension may be partly obscured by those of emphysema. Owing to the anatomical changes in the thoracic cage usually associated with emphysema, clinical estimation of the cardiac size is usually impossible. For the same reason heart sounds are faint over the præcordium and an accentuated pulmonary second sound is heard only rarely. Forceful pulsation in the epigastrium, suggesting right ventricular hypertrophy, is often present. By auscultation in the epigastrium it is sometimes easier to detect the triple rhythm of failure than over the præcordium. The presence of a palpable liver should not be considered a sign of venous congestion, since most of these patients have a low diaphragm.

The general clinical picture of patients with emphysema heart disease is well known. They have a dusky blue cyanosis and in some cases mild curvature of the finger nails is present. Obvious clubbing usually signifies more pulmonary pathology than mere chronic bronchitis, *e.g.* bronchiectasis or fibroid changes. Their conversation is often punctuated by laboured breathing. Their thoracic cage is barrel-shaped and its movements limited. On auscultation of the chest, there may be signs of bronchial obstruction with widespread râles and rhonchi, and expiration is always prolonged. In attacks of congestive cardiac failure, there is marked cyanosis, the neck veins are distended and there is often considerable œdema. In cases with severe anoxia there may be drowsiness and delirium. Papillœdema may sometimes be present, without localising signs of intracranial disease.

**Radiography.**—Radiography of the chest may show right ventricular and pulmonary artery enlargement in addition to bronchitis and emphysema, but are probably not helpful in the early diagnosis of cardiac complications in emphysema. Cardiac enlargement is frequently seen in the presence of congestive cardiac failure.

**Electrocardiogram.**—Similarly the development of cardiographic evidence of right ventricular hypertrophy is often a relatively late event in the clinical course of emphysema heart disease and is seldom of help in diagnosing the inception of the disease. Special points to be looked for are the development of an RSR' pattern in right chest leads accompanied by a deep S wave in left chest leads. In some cases tall spiked P waves are seen in standard lead II.

**Diagnosis.**—The diagnosis of emphysema heart disease rests on the recognition of right heart enlargement with or without cardiac failure in the presence of emphysema and bronchitis. The disease is usually difficult to diagnose with certainty until definite evidence of right-sided heart failure develops, since the symptoms of dyspnoea and cyanosis may be due to respiratory disease alone and since radiological and electrocardiographic evidence of right heart enlargement may be absent in the early stages of the disease. When frank congestive cardiac failure with a rise in jugular venous pressure, hepatomegaly, œdema and triple rhythm have developed, the diagnosis is clear. Other causes of right heart enlargement, in particular mitral stenosis, should be excluded.

**Prognosis.**—Once congestive cardiac failure supervenes, the prognosis is poor,

and, in spite of treatment, many patients die within a year. The outlook is, however, considerably improved by energetic treatment of attacks of respiratory infection and heart failure.

**Treatment.**—Although no treatment is available to avert the steadily progressive downhill course of emphysema heart disease, much can be done to help the patient in attacks of congestive heart failure. Except where exceptional facilities for complete bed rest and skilled nursing are available at home, admission to hospital is desirable. Episodic pulmonary hypertension in heart failure is often associated with acute exacerbations of bronchitis, and it is probable that acute or subacute respiratory infection plays an important rôle in the production of pulmonary hypertension. In the treatment of congestive heart failure, therefore, antibiotics, selected according to the flora in the sputum, should always be given. Treatment with bronchodilators (ephedrine or aminophylline) is also useful. Oxygen therapy is of great value in combating hypoxia, but is not without danger, since it may induce carbon dioxide narcosis and should therefore be given intermittently, especially if an oxygen tent is used.

The response to mercurial diuretics during episodes of congestive failure is often excellent. A low salt diet may be helpful. The value of digitalis in the treatment of emphysema heart disease is probably not as great as in other forms of heart failure, but there is evidence that it improves myocardial function and it should be tried in all patients.

**OTHER CAUSES OF CHRONIC PULMONARY HEART DISEASE.**—(a) *Fibroid lung.*—Widespread pulmonary tuberculosis, advanced pneumoconiosis, bronchiectasis, sarcoidosis and scleroderma may all give rise to fibrotic lesions in the lung, which if sufficiently widespread may cause chronic pulmonary heart disease.

(b) *Kyphoscoliosis.*—Severe kyphoscoliosis is associated in about 75 per cent. of cases with chronic pulmonary heart disease, due to concomitant pulmonary emphysema and fibrosis.

(c) *Disease of the pulmonary arteries.*—Disease of the pulmonary arteries and arterioles in the absence of disease of the lung parenchyma may sometimes be responsible for chronic pulmonary heart disease. Primary pulmonary arteriolar sclerosis is a rare disease giving rise to pulmonary hypertension and eventually to right heart failure. The pathological lesion is a severe widespread sclerosis of the arterioles. This should not be confused with secondary pulmonary arterial and arteriolar sclerosis, which forms part of the normal ageing process and is a common autopsy finding in patients over the age of 60. In other cases, the lesion is a widespread endarteritis obliterans affecting the pulmonary arterioles, which has been attributed by some to chronic repeated embolisation and by others to syphilis. In other cases, there is widespread mural thrombosis extending throughout the pulmonary arterial tree from the main pulmonary artery to the arterioles, which may have resulted from repeated embolisation or from local thrombosis in the pulmonary tree.

These patients often present with substernal pain and faintness on effort. They have signs of pulmonary hypertension, polycythæmia, cyanosis and later congestive heart failure. Unlike emphysema heart disease, where the history of bronchitis and heart failure is typically episodic, in primary pulmonary hypertension the course is usually steadily downhill. Khellin and hexamethonium have been given in an attempt to lower the pulmonary arterial pressure, but it is doubtful if they influence the course of the disease. Routine treatment should be given for congestive cardiac failure when this supervenes.

Carcinomatous lymphangitis or embolism, causing widespread occlusion of the smaller pulmonary arteries, is another rare cause of pulmonary heart disease. The primary neoplasm is commonly a scirrhus carcinoma of the stomach. This form of pulmonary heart disease running a course of a matter of weeks or months has been termed "subacute".

Schistosomiasis may also give rise to pulmonary heart disease by recurrent embolism, the schistosome ova becoming impacted in the pulmonary arterioles and giving rise to a granulomatous necrotising arteritis.

## SYPHILITIC HEART DISEASE

Syphilis indirectly affects the heart by causing inflammation of the aorta; it is responsible for about 5 per cent. of heart disease in Great Britain, but the incidence is considerably higher in some non-European populations. Syphilitic aortitis is a relatively late manifestation of syphilis but may occur within 5 years of primary infection; clinically it is rarely detected in under 10 years and often not until 30 years after infection. Aortitis occurs in a large proportion of patients with syphilis, treated or otherwise, and in 80 per cent. of patients with neurosyphilis. It is probably present for many years before there are clinical manifestations, and in many patients the disease is discovered for the first time at necropsy.

During recent decades there has been a decline in the incidence of cardio-vascular syphilis, which is probably due to a fall in the incidence of primary infection and more effective early treatment. There is a higher incidence of all forms of the disease in males; for uncomplicated aortitis the ratio of men to women is 3 : 1, but for aortic aneurysm the ratio is 10 : 1. This difference is probably related to physical effort and occupation; similar factors probably explain the higher incidence of complicated aortitis amongst heavy manual workers when compared with sedentary workers. Congenital syphilis rarely affects the cardio-vascular system.

**Pathology.**—Aortitis is the fundamental lesion in almost all cases of cardio-vascular syphilis; a true spirochætal myocarditis and syphilis of medium-sized vessels are both very rare and they are not considered further.

Syphilitic aortitis begins as an obliterating endarteritis and periarteritis of the vasa vasorum, especially in the ascending aorta; ischæmic changes follow and the media undergoes a slow necrosis with resulting loss of elastic tissue and replacement by fibrosis. The underlying intima is damaged and may ulcerate, but more often it becomes scarred in a characteristic linear fashion. Other areas of the intima undergo thickening from hyalinisation and the development of secondary atheroma with calcification is common. This process of chronic inflammation results in dilatation and irregularity of the aorta which, under the influence of arterial pressure, tends to bulge locally or generally with resultant aneurysm formation. Saccular aneurysms may occur in more than one place and they are often filled with layers of partially organised clot. Surrounding structures are frequently damaged by pressure and adjacent bone is eroded.

The ascending aorta suffers most and aortitis usually extends down to the level of the aortic valve ring, causing dilatation at the aortic base; this is the most important factor in the production of aortic incompetence. The valve cusps contribute to the incompetence through a valvulitis which is shown by a thickening of the free upper edges and by a bulbous intimal thickening of the commissures.

If the mouths of the coronary arteries are situated above or near the upper margin of the sinus of Valsalva, they tend to be taken up in the aortitis and partially closed. Ischæmic changes of the myocardium follow and histologically a widespread diffuse fibrosis is not uncommon; such changes have been confused with syphilitic myocarditis, which is extremely rare. Gummata in the heart are also very rare but localised lesions in the ventricular septum are occasionally the cause of heart block.

**Clinical Features.**—The clinical features of syphilitic aortitis are due to aneurysm formation, or to basal mesaortitis, which causes coronary ostial stenosis and aortic incompetence.



Uncomplicated syphilitic aortitis presents no diagnostic symptoms, but a dull aching substernal pain which is constant and localised has occasionally been described. In patients known to have latent syphilis a loud second sound over the aorta or an aortic systolic murmur in the absence of hypertension suggests the possibility of aortitis. Radiological examination should be carried out in all cases of late syphilis and widening or irregularity of the aorta may be discovered before the clinical features of aortitis have developed.

*Angina pectoris* commonly develops in syphilitic aortitis. It is due to stenosis at the origins of the coronary arteries and is mostly accompanied by incompetence of the aortic valves which are also damaged by the aortitis. Coronary ostial stenosis produces cardiac pain on effort which is indistinguishable from angina pectoris due to coronary atheroma. However, syphilitic cardiac pain tends to last longer and often comes on at rest, especially at night; it is not readily relieved by trinitrin and a dull, substernal ache tends to persist between the attacks. Coronary ostial stenosis occasionally causes acute coronary insufficiency, but massive cardiac infarction is rare. As in all conditions producing cardiac ischæmia, sudden death is not uncommon.

*Aortic incompetence* is due to dilatation of the valve ring, thickening of the cusp margins, and thickening of the commissures by fibrotic granulation tissue. It is more common in males than in females, in the ratio of 3 to 1. There are no symptoms until pathological dyspnoea indicates early heart failure or cardiac pain indicates involvement of the coronary ostia.

The physical signs are as in rheumatic aortic incompetence (see p. 874). A mid-systolic murmur is usually present in addition to the early diastolic murmur and both are heard best at the "aortic area" or in the left parasternal region. The systolic murmur, though similar to that found in aortic stenosis, is not loud enough to cause a thrill and does not indicate stenosis. The incompetence soon becomes well established with gross signs in the peripheral vessels and the murmur takes on a "to and fro" character. There are no accompanying signs of mitral valve disease, but when the leak is severe a functional presystolic murmur may develop (Austin Flint murmur); this is thought to be due to the large aortic regurgitant stream preventing complete opening of the anterior mitral valve cusp. The apex becomes heaving and characteristic of left ventricular hypertrophy.

Left ventricular failure, as shown by effort dyspnoea or cardiac asthma, appears early in the disease, and thereafter deterioration is relatively rapid, especially when cardiac pain indicating myocardial ischæmia is also present.

*Aneurysms of the aorta.*—Diffuse fusiform dilatation and localised saccular bulging of the aorta are common in syphilitic aortitis. Radiological examination is essential to the diagnosis of both conditions but a saccular aneurysm often produces characteristic symptoms and signs which depend on its anatomical site. Some aneurysms remain symptomless for many years, but others cause severe pressure pain, and rupture may occur after a relatively short period.

*Aneurysm of the ascending aorta.*—Aneurysm in this situation may present a local bulge in the anterior chest wall, usually to the right of the sternum. Those skilled in percussion may detect dullness to the right of the sternum before superficial bulging occurs. The second sound due to aortic valve closure is often sonorous and usually heard widely in the right chest and often in the right axilla. A dull sternal pain due to rib erosion is common, but many aneurysms are symptomless for a long time. Aortic incompetence and angina pectoris tend to develop with aneurysms in this situation. Sometimes the right bronchus is compressed with the development of partial atelectasis, and occasionally a medial extension of the aneurysm leads to deviation of the trachea. Death may be due to external rupture of the aneurysm, or more commonly to rupture into the pleura, pericardium or bronchus.

*Aneurysm of the arch* of the aorta produces symptoms and signs by pressure on adjacent structures in the superior mediastinum. The orifices of vessels arising from the aorta are frequently involved and cause differences in the pulse pressures in the two arms. Compression of the great veins leads to a pulseless distension of the veins of the neck and upper chest wall. The bloated facies of superior mediastinal obstruction are characteristic. Pressure on the trachea produces stridor and an unproductive cough, whilst damage to the recurrent laryngeal nerve causes changes in the voice and cough. Hæmoptysis may be due to congestion of the tracheal mucosa, or a leak from the aneurysm which not uncommonly ruptures into the trachea. A tracheal "tug" may be detected with each heart beat by placing the tip of a finger under the cricoid ring. Upward and backward extension of an aneurysm into the paravertebral sulcus may lead to severe brachial neuralgia and a Horner's syndrome from sympathetic paresis. The phrenic nerve is sometimes damaged with resulting paralysis of the diaphragm. Death from rupture of the aneurysm into trachea, pleura, mediastinum or pericardium is usual.

*Aneurysms of the descending aorta* may develop to a large size without producing symptoms. They almost never occur below the origin of the celiac vessels and rarely below the diaphragm. Erosion of vertebrae may cause a severe constant pain in the back and occasionally large aneurysms present in the posterior chest wall. Aneurysms in the abdominal aorta are usually symptomless but may be palpated in the epigastrium; they rarely cause pressure symptoms on the viscera.

Patients with syphilitic aortitis may have evidence of syphilis elsewhere; neurosyphilis is present in approximately 25 per cent., and evidence of past gummatosis and of leukoplakia of the tongue is not infrequent.

*Radiology of syphilitic aortitis.*—Radiological examination is most important. Uncomplicated aortitis may show a diffuse dilatation of the aorta which is often particularly prominent in the ascending portion and well shown in the left oblique view, where the anterior border of this part of the aorta may bulge beyond the level of the ventricle below it. The calibre of the arch of the aorta may be assessed in the right oblique position, and a barium swallow in this position outlines the posterior circumference. Irregularities in the calibre of the vessel are usual in aortitis and best detected by following the course of the aorta in the left oblique or left lateral views. Thin linear calcification in the wall is common in aortitis, and is very strong evidence of aortitis when seen in the ascending portion of the vessel.

Angiocardiography can show more clearly the calibre of the lumen and its irregularities, but it is doubtful whether this investigation is ever justified in uncomplicated aortitis. When there is aortic incompetence the aorta usually shows the signs of aortitis and becomes more pulsatile; the left ventricle becomes rounded and enlarged and is best assessed in the left oblique position.

Aneurysms show as large local bulges in the three main regions described above. Examination with a barium swallow shows deviation of the œsophagus around the aneurysm which often helps in the assessment of its anatomical location and size. Calcification is common in the wall and its recognition is of great value in diagnosis. Pulsation is often absent but may be clear and expansile, or transmitted from the adjacent aorta and heart. Erosion of bone is commonly seen. Angiocardiography is a valuable aid in doubtful cases; if not filled with clot, radio-opaque dye enters the cavity, confirming its aneurysmal nature. Retrograde aortography is unnecessary for diagnostic purposes; the simple method of injection by the venous route is satisfactory and in any case rarely indicated. Tomography and roentgenkymography help in the assessment of the anatomy and pulsations of the mass but are also rarely necessary. It is emphasised that these more elaborate radiological methods add little to, and are no substitute for, careful clinical assessment, and good X-ray films in the

postero-anterior and oblique views, together with radioscopy, should be carried out in all cases of late syphilis, treated or otherwise.

The *electrocardiogram* in syphilitic aortitis may be normal if the lesion is uncomplicated, or pathological when there is ischæmia from coronary ostial stenosis or ventricular hypertrophy from aortic incompetence. When cardiac pain indicates ischæmia the electrocardiogram usually shows varying degrees of S-T depression and inversion of T waves in lead I and left-sided chest leads. The changes are similar to those found in ischæmic heart disease due to coronary atheroma and emphasise the frequent occurrence and severity of ischæmia in syphilitic aortitis. Pathological Q waves from massive infarction do not occur.

*Serological tests* are positive in some 80 per cent. of patients with syphilitic aortitis (see p. 211). Past treatment often modifies these tests without having influenced the development of aortitis. In some cases blood reactions are negative whilst the cerebrospinal fluid may show a positive reaction. The *erythrocyte sedimentation rate* is frequently raised and is related to the degree of activity of syphilitic aortitis in some cases.

**Diagnosis.**—Isolated aortic incompetence in an adult over 30 years of age is possibly due to syphilis; if the leak is great and rapidly developing syphilis is a probability, and if it is associated with cardiac pain, it is almost a certainty. The association of aortic incompetence with signs of neurosyphilis or positive serological reactions confirm the diagnosis of syphilitic aortitis. Radiological examination is the most important aid to diagnosis, and should be carried out in all suspected cases; dilatation of the aorta, irregularity of its calibre and calcification in the wall of the ascending portion are diagnostic points, but should not be confused with the smooth aortic unfolding and tortuosity which occur with hypertension and with atherosclerosis in the elderly.

The *differential diagnosis of aortitis from cardiac pain due to coronary atheroma* is not difficult because in syphilis there is usually an associated aortic incompetence. The early diastolic murmur should be carefully sought. Rheumatic aortic incompetence presents difficulties in differential diagnosis when it occurs alone, but often there is associated aortic stenosis or mitral valve disease; rheumatic aortic incompetence is usually less severe and there is often a history of rheumatic fever, and on radiological examination the aorta is not dilated or calcified although the aortic valves are usually calcified when there is aortic stenosis.

The diagnosis of aortic aneurysm is essentially radiological unless the aneurysm presents as a pulsating superficial swelling. Aneurysm should be suspected when there are signs of superior mediastinal obstruction with cough, a pathological aortic second sound, differences in the pulses of the arms and other signs of syphilis. The differential diagnosis from mediastinal tumours and bronchial carcinoma is sometimes difficult; angiocardiology is confirmatory when simpler methods are inadequate.

Positive serological tests are strong evidence that the clinical findings in question are due to syphilis, but this is not always so; conversely, in aortitis, tests do not exclude syphilis, for in some 15 to 20 per cent. of cases they are negative.

**Prognosis.**—The history of patients with syphilitic aortitis is extremely variable. Some pursue a rapid, downhill course whilst others live long and die of another malady. Consequently prognosis is difficult. In aortic insufficiency there is often a long, asymptomatic period, and after the appearance of symptoms many patients live from 5 to 10 years, but few patients live more than 2 years after definite signs of heart failure have appeared. Cardiac pain indicating coronary ostial stenosis is an adverse factor in all cases and sudden death is not uncommon. The prognosis for cases of aortic aneurysm is also variable. Some appear to progress rapidly whilst in others the condition appears to be stationary, and many live for more than 10 years. Heavy physical work is an unfavourable factor and probably women do better

than men. Antisyphilitic treatment carried out in the asymptomatic stages appears considerably to improve the outlook, but it is doubtful whether treatment has much influence in the later stages of the disease.

**Treatment.**—The management and treatment of syphilitic heart disease consists of the treatment of syphilis and of the sequelæ of aortitis.

All untreated cases of syphilitic heart disease should receive a course of anti-luetic treatment after the cerebrospinal fluid has been examined. The course of advanced disease is probably not materially altered by this treatment, but the prognosis of uncomplicated and mild cases is improved since there is active syphilitic inflammation in all untreated cases.

The risks of treatment are slight, but an acute exudative reaction (Jarisch-Herxheimer reaction) accompanied by fever may occur within 24 to 48 hours. In patients with coronary ostial stenosis this may be serious and lead to acute coronary insufficiency. Rarely contracting scar tissue may result in the therapeutic paradox of increased aortic incompetence or increased cardiac pain. In general there is no element of urgency in treatment of the luetic condition, so that a course of bismuth or iodides, which diminish the risk of severe reactions from the more powerful anti-luetic drugs, should be given first. Various schedules of treatment are recommended and may be modified to suit individual cases (see also general article on syphilis, pp. 212, 221). The following method is satisfactory for most cases of syphilitic heart disease. A single weekly injection of metallic bismuth (0.3 g.) is given together with potassium iodide (gr. 10 t.d.s.) for 4 weeks, then a daily injection of procaine penicillin (600,000 units) is given for 12 days, making a total of 7.2 million units. Bed rest is advisable for the first week or so and again during treatment with penicillin. Six further weekly injections of bismuth (0.3 g.) complete the course. After 6 months the Wassermann reaction, sedimentation rate and the general condition of the patient should be reviewed; if there is any evidence of activity or deterioration a modified course of anti-luetic treatment should be repeated, and thereafter the situation should be reviewed at regular intervals.

*Cardiac pain* should be treated as described (see p. 840), but the nitrite drugs are not as effective as in angina pectoris due to coronary atheroma.

*Heart failure* in aortitis should be treated as in other cases of left ventricular failure (see p. 812). A prophylactic low salt régime is advisable as soon as effort dyspnoea is present.

**TREATMENT OF AORTIC ANEURYSM.**—Pain may necessitate the frequent use of analgesic drugs. Various operative procedures have been devised to treat aneurysms of the aorta, but none have had great success. Wires introduced into the aneurysm were thought to limit extension by causing clot formation. Cellophane wrapped around the aneurysm induces a fibrous tissue reaction which may limit further extension and strengthen the wall. Excision of the aneurysm has been performed but the pathological state of the remaining aorta is not conducive to effective reconstruction and grafting.

## CHRONIC VALVULAR DISEASE

### MITRAL VALVE DISEASE

Chronic mitral valvulitis is the commonest form of rheumatic heart disease. The valve may be narrow, thereby offering an obstruction to the circulation (mitral stenosis) or it may be incompetent. Dominant mitral stenosis with some lesser degree of incompetence is the commonest form of organic mitral valve disease, but all grades of the combination occur and either lesion may occur alone, pure mitral stenosis being much commoner than pure mitral incompetence.

**Ætiology.**—Mitral stenosis is almost always due to rheumatic heart disease

although only some 60 per cent. of adult patients give a history of rheumatic fever. In the majority of patients with acute rheumatic carditis the mitral valve is involved and it is affected in some 85 per cent. of cases of chronic rheumatic heart disease examined at necropsy. During the first attack of acute rheumatic carditis, mitral valvulitis causes incompetence but this is a transitory lesion and many patients ultimately develop stenosis. Mitral stenosis is more common in females in the ratio of 3 : 1. Pure organic mitral incompetence in adults is relatively rare and is probably due to rheumatism in most cases, but only 25 per cent. give a past history of rheumatic fever; mitral incompetence also differs from pure mitral stenosis in the sex incidence since men are affected rather more commonly than women.

Functional mitral incompetence is common; it develops when ventricular dilatation from any cause results in dilatation of the valve ring and stretching of the chordæ tendinæ and papillary muscles. Bacterial endocarditis may cause ulceration of mitral valve cusps or rupture of chordæ tendinæ producing acute mitral incompetence or an increase of pre-existing incompetence. Occasionally fracture of chordæ tendinæ may occur at the junction with papillary muscles as a result of cardiac infarction. Congenital lesions of the mitral valve are rare but a few cases of congenital mitral stenosis have been reported.

**Pathology.**—In chronic rheumatic mitral valvulitis the valve cusps are thickened and deformed to varying degrees. The chordæ are also shortened and thickened by fibrosis. In stenosis the orifice of the valve is narrowed by fusion of the cusp margins whilst rigidity and thickening of the cusps and chordæ holds the valve in a relatively fixed position so that a narrow slit is formed. The whole ring, cusps and chordæ may be fused into a narrow rigid funnel. Incompetence results from deformity of the cusps, and from shortening and sclerosis of the chordæ. In pure incompetence the valve ring is thickened and immobile and the chordæ are shortened, but there is no fusion of the commissures. Calcification in the valve ring and adjacent cusps is not uncommon. Microscopic examination shows vascularisation of the cusps and thickening from fibrosis.

The left auricle is dilated and its walls are thickened in mitral stenosis and incompetence. The mural endocardium is often scarred and a thickened patch is especially likely to occur above and adjacent to the valve ring when there is incompetence. The lumen of the auricular appendage is sometimes obliterated by clot and layers of partially organised clot may line the auricular chamber. In mitral stenosis the left ventricle tends to be small (except when there are aortic valve lesions or systemic hypertension), whereas in mitral incompetence the left ventricle is dilated and moderately hypertrophied. In mitral stenosis the right ventricle is hypertrophied and dilated to varying degrees. The lungs are especially damaged in mitral stenosis, they become brownish, indurated and inelastic; the small branches of the pulmonary artery are thickened and project from the cut surface of the lung. Pulmonary infarcts of varying size are common. On microscopic examination the alveolar walls are thickened, the capillaries dilated and the alveolar cavities tend to contain cellular debris and large "heart failure" cells containing iron pigment.

#### MITRAL INCOMPETENCE

In mitral incompetence the left auricle receives a regurgitant stream of blood during ventricular systole, in addition to the inflow from the pulmonary veins. The auricular pressure rises with ventricular systole, but the absence of obstruction at the mitral orifice prevents the development of diastolic hypertension in the auricle. The left ventricle is overfilled in diastole by the augmented volume, and an effective output into the aorta is maintained by rapid ejection. The increased stroke volume is expelled at relatively normal pressures and compensation is thus maintained by the left ventricle at the expense of only a slight increase in cardiac work.

Pressures do not rise greatly above normal in the left heart except for a systolic peak in the auricle, so that pulmonary congestion and pulmonary hypertension are not prominent features. The hypervolæmic state of the left heart is well tolerated if the muscle is good; hypertrophy is not great, and heart failure tends to develop late in the disease.

**Symptoms.**—There are no symptoms peculiar to mitral incompetence. The pure lesion is well tolerated and many patients remain in active employment to the sixth or seventh decade. Palpitation due to extrasystoles is common. Some patients complain of fatigue and weakness rather than breathlessness, which tends to appear late. Many die of an intercurrent disease. Patients with severe mitral incompetence develop heart failure which does not respond well to treatment and when rupture of the chordæ causes acute mitral incompetence, severe heart failure tends to occur.

**Signs.**—The pulse is normal or full and rapidly rising—almost waterhammer in some patients. In cases where regurgitation is considerable, ventricular overfilling may be appreciated at the apex which is hyperdynamic; after the lift of systole, which is never as forceful as in left ventricular hypertension, a small diastolic filling wave may be seen or palpated. Many patients have minor degrees of incompetence which do not alter the pulse or apex beat, and a systolic murmur is then the only sign.

Auscultation provides the most significant signs of mitral regurgitation. The first sound is normal and it is immediately followed by a systolic murmur which is loudest at the apex and radiates towards the axilla; very loud murmurs may be palpated as an apical systolic thrill and are widely heard in proportion to their loudness. The murmur is pansystolic and tends to be crescendo in late systole; occasionally the murmur appears to be confined to late systole but phonocardiograms show that vibrations start early in systole. The second sound is often inaudible at the apex, being buried in the murmur. A third heart sound, related to augmented ventricular filling is frequently present. In pure cases the first heart sound is not loud, there is no opening snap and no mid-diastolic murmur, and usually no signs of pulmonary hypertension. Extrasystoles are common, and auricular fibrillation may occur late in the disease.

**Radiology.**—Radioscopy shows a varying degree of left auricular enlargement, but the most important change is in the dynamics of the auricle which may be seen to expand during ventricular systole. In the anterior view the left auricle expands laterally in systole, appearing as a momentary bulge high up on the left border and as a less obvious bulge in the upper part of the right border. In the oblique view the barium-filled œsophagus is moved backwards by the left auricle during ventricular systole. Systolic expansion indicates a considerable degree of mitral regurgitation and the absence of this sign does not mean that there is no regurgitation. Slight to moderate enlargement of the left ventricle is also seen.

The *electrocardiogram* may show the presence of arrhythmia. The standard leads tend to show normal or left axis deviation. Left-sided chest leads may show the signs of slight to moderate left ventricular hypertrophy.

**Complications.**—Bacterial endocarditis may occur on the scarred valve in mitral incompetence, and it is not an uncommon complication in mild cases when a mitral systolic murmur is the only evidence of abnormality.

**Diagnosis.**—Mitral incompetence should not be diagnosed lightly on the finding of a systolic murmur. A pansystolic murmur which is loudest at the apex and engulfs the second sound there is highly suggestive of organic mitral incompetence in the absence of any cause for cardiac dilatation. A hyperdynamic apex beat is further evidence. Expansion of the left auricle in ventricular systole seen on radioscopy is confirmatory. The diagnosis of mitral incompetence in dominant mitral stenosis is suggested by the presence of an apical pansystolic murmur in addition to the signs of mitral stenosis. Furthermore, mitral incompetence in this combination is frequently

associated with calcification of the mitral valve seen on screening. The sudden appearance of a pansystolic murmur at the apex during the course of cardiac infarction or bacterial endocarditis suggests acute mitral incompetence due to the fracture of chordæ tendineæ.

The murmur of ventricular septal defect is also pansystolic (a separate mid-systolic murmur may be heard over the pulmonary artery) and may be heard easily at the mitral area, but is loudest near the sternum. A functional mid-diastolic murmur may be present in ventricular septal defect and adds to the difficulty of differentiation from mitral valve disease, but on radiography there is pulmonary plethora without left auricular enlargement.

Other conditions causing a systolic murmur at the apex must be differentiated. Innocent murmurs are soft and most are parasternal or over the pulmonary artery. At the apex a very short late systolic murmur may be innocent, but such a murmur is readily confused with the late systolic crescendo murmurs of mitral disease. However, it should be fully understood that when such a murmur is the only indication of mitral disease (*i.e.* when there is no cardiac enlargement) the prognosis is good, the patient should live a normal life and be reassured, and the only added risk is the remote possibility of bacterial endocarditis.

Mid-systolic murmurs arise from ejection and flow into the great vessels. The murmur of aortic stenosis may be loud at the mitral area, but the second sound is audible and the murmur is also heard at the aortic area, and the pulse is characteristic. Anæmia, thyrotoxicosis, pregnancy, kyphoscoliosis and sternal depression may also produce mid-systolic murmurs, but these are usually soft, loudest in the parasternal region and the cause is usually obvious.

**Prognosis.**—The prognosis of functional mitral incompetence depends on the cause of cardiac dilatation. In acute rheumatic carditis mitral incompetence is a product of valvulitis and cardiac dilatation; immediate prognosis depends on the severity of the rheumatic process and the remote prognosis is variable; a few recover completely, many develop mitral stenosis and a few are left with organic incompetence only. In established organic mitral incompetence the prognosis is excellent in mild cases and a normal life span can be expected. In moderate cases with enlargement, heart failure may supervene after middle life, and this tends to be fairly rapidly progressive. Heart failure responds indifferently to the usual treatment and death occurs in a year or so of the onset of failure. Bacterial endocarditis may occur in any patient with mitral incompetence, whether the lesion is mild or severe. Early treatment may cure, but further deterioration is likely if treatment is delayed or ineffective; fracture of chordæ tendineæ causing a greater degree of mitral incompetence is common. Embolism and auricular fibrillation are much less common in mitral incompetence than in mitral stenosis.

**Treatment.**—The great majority of patients with organic mitral incompetence have only slight symptoms or none at all; they require no treatment and they should be reassured. However, it is advisable to give these patients a prophylactic injection of penicillin before undergoing dental extraction or other operation in a septic field. Heart failure is treated by routine methods.

In patients with severe organic mitral incompetence causing heart failure, surgical repair of the valve has been attempted; various methods are under investigation but none is yet satisfactory.

#### MITRAL STENOSIS

The essential feature of mitral stenosis is obstruction to blood flow through the valve orifice during diastole. Symptoms are not produced until the area of the orifice is reduced from normal (8.5 sq. cm.) to approximately 2.5 sq. cm., although the signs are present with lesser degree of stenosis. Increasing hæmodynamic disorder

and a resulting increase in severity of symptoms occurs with greater degrees of stenosis, and most patients are bed-ridden when the valve orifice is less than 1 sq. cm.

In significant mitral stenosis the blood flow to the left ventricle is diminished and the pressure and volume of blood in the left auricle rises. The high auricular pressure and increased contraction of the auricle, which shows compensatory hypertrophy, result in an increased pressure gradient across the valve which partially compensates for the obstruction. The increased left auricular pressure is transmitted to pulmonary veins, pulmonary capillaries and the pulmonary artery. Some degree of pulmonary hypertension develops in the majority of patients with severe mitral stenosis, and in some the pressure rises to very high levels from a greatly increased pulmonary vascular resistance, which appears to be due to arteriolar spasm and secondary changes in the vessel walls. Pulmonary hypertension causes right ventricular hypertension and compensatory hypertrophy.

Compensation occurs at the expense of muscular hypertrophy and increased work of the left auricle and right ventricle. Decompensation may occur in the left auricle for its walls are relatively thin; it is also affected by rheumatism and auricular fibrillation is common; this produces the syndrome of left heart failure. Decompensation of the right ventricle produces the features of right heart failure. The raised tension and congestion throughout the pulmonary circulation causes severe secondary changes in the lungs.

**Clinical Features.**—Patients with mild mitral stenosis are asymptomatic and may remain so throughout a long life, but this is unusual. Sooner or later most patients with mitral stenosis develop symptoms of left heart failure, and ultimately congestive heart failure.

**Dyspnoea.**—Breathlessness on effort tends to occur during early adult life in most cases of mitral stenosis. Effort tolerance steadily diminishes unless episodes of pulmonary infarction, pulmonary oedema, auricular fibrillation or bronchitis cause relatively rapid phases of deterioration. Sudden paroxysmal attacks of cardiac asthma are not uncommon and may even appear in apparently mild cases before effort dyspnoea is noticed; cardiac asthma may occur during the day, but is more common at night and often occurs for the first time during pregnancy; some attacks are more severe and reach the stage of pulmonary oedema. Pulmonary oedema tends to occur in those patients with slight or only moderate pulmonary hypertension rather than in those with very high levels of pressure; it is characterised by extreme respiratory distress, expectoration of pink frothy sputum, cyanosis, hypotension and peripheral vasoconstriction. The various forms of dyspnoea due to left auricular failure tend to subside when right heart failure develops.

**Right heart failure.**—The signs of congestive cardiac failure may develop slowly or appear rapidly after a variable period during which dyspnoea has been the dominant symptom. Oedema appears at the ankles, the jugular venous pressure is raised, and the liver becomes palpable and tender. In some patients this phase brings relief from the symptoms of pulmonary congestion, but in many it does not. During the early stages of right heart failure, discomfort and even pain in the right hypochondrium and epigastrium may accompany effort and are due to hepatic congestion. Right heart failure steadily increases, but with treatment improvement occurs and many episodes may recur before a chronic unresponsive stage is reached, which is characterised by a low fixed cardiac output. Activity is then severely restricted by dyspnoea and fatigue, appetite is poor and weight loss is evident, tricuspid incompetence is often gross but saves the patient from paroxysmal dyspnoea, the liver becomes large, firm and pulsatile, and recurrent ascites may be a serious problem. Slight icterus from cardiac cirrhosis is usually present.

**Hæmoptysis** is a common symptom at various stages of the natural history of mitral stenosis. There are three main types: pink staining of the sputum with relatively small quantities of blood due to pulmonary congestion, occasional massive



hæmoptysis, and blood-stained sputum associated with pleural pain which indicates the presence of pulmonary infarction. Hæmoptysis may be repeated many times over a span of years.

*Pain* in the chest in mitral stenosis is not a prominent feature, but there are three types: a submammary discomfort which is probably psychogenic and reflects anxiety about the heart condition; a dull præcordial discomfort when there is great cardiac enlargement, and true ischæmic cardiac pain which is due to failure of the coronary circulation when there is a low cardiac output, pulmonary hypertension and anoxæmia. Most patients, however, do not complain of pain.

Dysphagia, a dry persistent cough, or hoarseness of the voice may occur from pressure on adjacent mediastinal structures by an enlarged left auricle. Very rarely aneurysmal enlargement of the left auricle appears to be the cause of erosion of the vertebral bodies giving rise to severe pain between the scapulae.

*Signs.*—Mitral stenosis presents a pattern of characteristic signs, some of which are directly related to the valve lesion and others to the secondary hæmodynamic disturbance. *The most constant and important one is the apical diastolic murmur set up during the passage of blood through the obstruction.*

There is often a slight bulging in the left præcordium, the cardiac impulse may be seen in the parasternal intercostal spaces (right ventricle) and the apex beat (left ventricle) is seen as a separate pulsation farther to the left. On palpation the apex beat is localised and it has a sharp, tapping quality, largely due to vibrations of the loud first heart sound. An apical diastolic or presystolic thrill is common and its presence depends on the loudness of the characteristic murmur. Over the parasternal region there may be a strong pulsation due to right ventricular hypertrophy, indicating pulmonary hypertension, which is also suggested by a palpable second sound over the pulmonary artery.

On auscultation the first sound is mostly sharp and loud; it can be heard over the whole præcordium but is loudest at the apex. A soft systolic murmur is common at the apex but in pure mitral stenosis systole may be significantly silent. The second heart sound is loud at the pulmonary area and its second component due to pulmonary valve closure is especially loud when there is pulmonary hypertension. An additional sound, the "opening snap", occurs shortly after the second heart sound, which it resembles in pitch and brevity, but it is loudest just internal to the apex. The "opening snap" is audible in most cases of mitral stenosis but, like the first heart sound, it is soft when there is gross calcification of the mitral valve. The opening snap is distinguished from the second component of a widely split second sound by timing and by the area where they are best heard: the third heart sound is distinguished by its low-pitched quality, but this sound does not occur in dominant mitral stenosis. The "opening snap" appears to be essentially related to the pathological state of the valve itself.

A low-pitched, rumbling, mid-diastolic murmur follows the opening snap. This murmur is best heard through a bell stethoscope placed lightly on the apex, with the patient reclining and slightly tilted to the left side. The mid-diastolic murmur may be short in mild cases, but it is mostly long and continues throughout diastole. When the rhythm is normal, the diastolic murmur merges into a sharp, crescendo murmur—the presystolic or auricular systolic murmur, which is most readily heard after brief exercise. When there is severe pulmonary hypertension, auricular fibrillation and a very low cardiac output, there may be no murmurs and the opening snap may be the only sign to indicate the diagnosis.

The arterial pulse tends to be small in mitral stenosis and the blood pressure is often low, but in some patients mitral stenosis is associated with systemic hypertension. The venous pulse may show prominent "a" waves when there is pulmonary hypertension and the rhythm has remained regular. A general rise in the level of venous pressure occurs when there is right heart failure.

*Auricular fibrillation* occurs in the great majority of patients with mitral stenosis. Its onset marks a definite stage of deterioration and it is responsible for further diminution of cardiac reserve. A phase of changeable rhythm, when auricular ectopic beats are frequent or short periods of auricular fibrillation alternate with normal rhythm, often precedes the establishment of permanent auricular fibrillation. The change to abnormal rhythm may be associated with symptoms of palpitation, increased dyspnoea and fatigue, and sometimes congestive cardiac failure first appears at this time. Auricular fibrillation is usually responsible for tachycardia, but when the heart is very large there is often a high degree of block, causing a slow heart rate.

**MITRAL STENOSIS AND INCOMPETENCE.**—The signs of the common combined lesion depend on the relative dominance of regurgitation or obstruction. The signs of mitral stenosis are modified by additional incompetence, as follows. The apex tends to be less localised, the tapping quality is less obvious and it tends to become more hyperdynamic and left ventricular in character. The signs of pulmonary hypertension may or may not be present. The first sound and the opening snap are softer when there is calcification of the mitral valve, which is commonly associated with a mixed lesion. A pansystolic murmur is usually present—the absence of an apical systolic murmur means there is no significant incompetence. When mitral incompetence is great, the opening snap is replaced by a third heart sound.

*Radiology.*—Asymptomatic patients with mild mitral stenosis show no abnormalities apart from slight backward bulging of the left auricle in the right oblique view. In all of the more severe degrees of mitral stenosis the enlarged left auricle may be seen as a hump below the pulmonary arc and as a bulge below the right hilum, and when penetrating films are taken the contour of the whole auricle may be seen through the heart shadow. The barium-filled œsophagus is deviated backwards in a characteristic curve, usually best seen in the right oblique view, but in some patients the œsophagus is deviated to the left, and left oblique views then show the large left auricle surmounting a small left ventricle. The left auricle may be "aneurysmal" and seen bulging across the right hemithorax almost to its lateral wall. In advanced cases the right auricle is also large. The aorta tends to be small and the pulmonary artery tends to be large. The heart shadow develops a rather triangular shape.

The lungs show varying degrees of congestion. The hilar shadows are large and the clear outlines of vessels are often blurred. The peripheral lung fields lose normal translucency, show a fine reticulation and occasionally large miliary shadows due to hæmosiderosis are seen. Wedge shadows of pulmonary infarcts are common, and small effusions frequent. The lung parenchyma in the costophrenic angle shows horizontal thread-like lines in cases of long-standing congestion.

*The electrocardiogram.*—P waves are characteristically widened and notched, especially in lead II and left-sided chest leads. The second peak of the notch is due to delayed left auricular activation. The P waves may be single and tall when there is severe right heart hypertension. The QRS complex shows varying degrees of right axis deviation in cases with pulmonary hypertension. The chest leads show increased positivity on the right side depending on the degree of right ventricular hypertrophy.

**Complications.**—Hæmoptysis, cardiac asthma, pulmonary œdema and pulmonary infarction are sufficiently common to be considered a part of the natural history of the disease. The most important complications are due to peripheral emboli arising from clot in the left auricle. Embolisation may occur in patients with mild mitral stenosis and normal rhythm, but patients having auricular fibrillation are more commonly affected. Emboli are of varying size. Medium-sized cerebral and limb vessels are frequently occluded; aphasia with hemiplegia is a common sequel to middle cerebral arterial embolism and may be transient or permanent. Renal infarction, splenic infarction and mesenteric infarction sometimes occur. Many patients have repeated attacks of arterial occlusion. A massive clot may even occlude the aorta at its bifurcation with resulting severe pain in the legs, buttocks and abdomen,

and peripheral signs of arterial insufficiency. Occasionally massive clot in the left auricle may become free and occlude the narrow mitral orifice causing sudden death. Rarely recurrent attacks of syncope, characteristically relieved by a change of position, are due to intermittent occlusion of the mitral orifice by a ball valve thrombus. Bacterial endocarditis is a very rare complication of pure mitral stenosis.

**Diagnosis.**—The diagnosis of stenosis of the mitral valve depends on the findings on auscultation and radiology. A loud and sharp first heart sound, usually palpable, is strongly suggestive, but a low-pitched mid-diastolic murmur at or near the apex is the essential evidence of mitral stenosis; the opening snap is further evidence when there is doubt about the presence of a mid-diastolic murmur. Rarely, when the flow through the valve is greatly reduced, the mid-diastolic murmur may become inaudible and then the opening snap and sharp first heart sound are the only auscultatory signs. Left auricular enlargement determined by radioscopy confirms the clinical diagnosis and in conditions where a mid-diastolic murmur may be functional (as in ventricular septal defect), the presence or absence of left auricular enlargement is decisive.

The diagnosis of mitral stenosis is incomplete without an assessment of the functional state of the circulation. Particular attention should be paid to effort intolerance, paroxysmal dyspnoea, hæmoptysis, embolisation, rhythm, the signs of pulmonary and systemic congestion, and the presence and approximate level of pulmonary hypertension which is recognised by the degree of right ventricular hypertrophy and the loudness of the pulmonary second sound. Difficulties in the assessment of the state of the pulmonary circulation are likely to arise in some patients when mitral stenosis is combined with mitral incompetence or with pulmonary disease; in such cases the pulmonary artery pressure, pulmonary capillary pressure and the pulse pressure tracings should be obtained by cardiac catheterisation. Diagnosis in mitral stenosis must include an assessment of the state of other valves which are often affected.

Differential diagnosis of the signs: on casual auscultation a normal split first heart sound may be mistaken for a presystolic murmur, but in mitral stenosis the mid-diastolic murmur, loud first sound and opening snap, as well as the radiological signs are present. In pure aortic incompetence a presystolic murmur (Austin Flint) may be present, but the other signs of mitral stenosis are absent and the aortic lesion is always severe. Functional diastolic murmurs also occur in auricular septal defect and ventricular septal defect, but in these conditions also attention to the detailed findings of auscultation show that the other signs of mitral stenosis are absent, whilst the signs of a left to right shunt are present on clinical examination and on radiography.

Differential diagnosis of symptoms: hæmoptysis and dyspnoea may suggest pulmonary disease, paroxysmal dyspnoea may suggest left ventricular disease or bronchial asthma and embolisation may cause symptoms referable to any organ, but when the physical signs of the mitral valve lesion are recognised the aetiology of these symptoms is usually clear.

**Course and Prognosis.**—A minority of patients live a normal life span and a minority deteriorate progressively from attacks of rheumatic fever in childhood and adolescence. Most die of the disease between the ages of 30 and 50, the average age at death being 35; most of these have had a symptom-free period in early adult life, followed by the development of increasing effort dyspnoea and then congestive heart failure. The prognosis in an individual case depends on a full assessment of many factors; the presence of recurrent rheumatic activity, severe pulmonary hypertension and right heart failure are serious adverse factors. Patients with auricular fibrillation may live for several years but many die within 3 years of its onset and peripheral embolism is, at any time, an additional hazard. Pregnancy is tolerated moderately well, but it is noticeable that many patients have their first symptoms or a first attack of heart failure at this time. Favourable factors in prognosis are a continued absence

of symptoms in the third decade, absence of rheumatism, a small heart with no signs of pulmonary hypertension on clinical examination and the absence of right ventricular preponderance on the electrocardiogram. A short and soft mid-diastolic murmur with a normal pulse volume, together with the factors mentioned, suggests that the valve has an area greater than 2 sq. cm. and that the obstruction is slight and prognosis correspondingly good. Successful mitral valvotomy reverses much of the symptomatology, diminishes pulmonary hypertension and may restore some patients to a relatively normal life, but sufficient time has not passed to appraise the long-term results of this operation.

**Treatment.**—Asymptomatic patients with mild mitral stenosis having no evidence of pulmonary congestion or pulmonary hypertension do not require treatment. All other patients with dominant mitral stenosis must be considered as possible subjects for mitral valve surgery unless the severity of the disease and great enlargement of the heart are obvious contraindications. Surgery offers the only cure of the disease.

**General.**—Exercise in patients without heart failure should not be unduly restricted but it should be kept within the limits imposed by symptoms. Occupation, though largely dictated by economic and social factors, should be regular and not of the manual variety. In pregnancy there should be regular frequent medical supervision and regular hours of extra daily rest. A period of 2 weeks' partial bed rest is advisable before delivery, which is best conducted in hospital or similar institution. Mitral valvotomy should be performed during pregnancy if symptoms are severe and increasing in severity.

The symptoms of mitral stenosis are largely due to heart failure, which should be treated by routine methods (see p. 812 *et seq.*). Digitalis may be given at any stage, whether rhythm is regular or not, preferably early rather than late in the natural history of the disease. Sodium restriction is advisable in co-operative patients and may prevent attacks of pulmonary oedema; mercurial diuretics are necessary at the stage of dropsy. Hæmoptysis rarely requires special treatment but if it is severe, bed rest is necessary. Bacterial endocarditis requires treatment with appropriate antibiotics (see p. 888). The treatment of embolic episodes depends on the site of embolism and severity of ensuing ischæmia. Embolectomy is almost never necessary in the arm, but is occasionally advisable if the site of embolism can be accurately located in the femoral or popliteal vessels. A saddle embolism at the aortic bifurcation should be removed if the peripheral effects indicate great obstruction. Auricular fibrillation marks a definite stage in the deterioration of patients with mitral stenosis and little is gained by attempts to restore the rhythm with quinidine unless mitral valvotomy has been performed.

#### MITRAL VALVOTOMY

**SELECTION OF CASES.**—Mitral valvotomy is indicated in all patients in whom serious obstruction to the flow of blood through the stenosed mitral valve is the dominant functional disorder. The selection of patients can usually be made by clinical examination alone, aided by electrocardiography and radiographic screening, and only rarely is it necessary to perform cardiac catheterisation in their pre-operative assessment. Contraindications to operation are of two types. The stenosis may not be of sufficient degree to warrant operation, or mitral stenosis may be complicated by other factors and hence is no longer the dominant functional disorder.

Patients with a minor degree of mitral stenosis are not troubled with dyspnoea and hence the history is of great importance in assessing the severity of the lesion. In those with serious mitral valve obstruction, symptoms are always present, the commonest being exertional dyspnoea, paroxysmal nocturnal dyspnoea or recurrent hæmoptyses. An attempt should be made to assess the degree of exertional dyspnoea for this is often a rough guide to the degree of stenosis. The patient's ability to

perform ordinary daily routine tasks is a useful yardstick. In doubtful cases in which functional overlay is suspected in the patient's symptoms, a simple exercise test on stairs will often help to evaluate the disability.

Age is an important factor in the selection of patients. The older patients in whom a greater degree of coronary and cerebral atherosclerosis may be expected do not respond as well to valvotomy as those in the younger age groups. On the whole 50 years should be considered the upper age limit, although no hard-and-fast dividing line should be drawn, and a patient's cardio-vascular age as well as his chronological age should be taken into account. In view of the greater likelihood of recurrent attacks of rheumatic fever in patients under the age of 20 years, it is probably undesirable to operate in this age group. If, however, mechanical obstruction at the mitral valve is sufficient to cause congestive cardiac failure or pulmonary oedema, mitral valvotomy should be performed even in this age group.

Chronic congestive cardiac failure of several years' duration, not responding to medical treatment, is usually associated with considerable cardiac dilatation and myocardial failure. In such cases relief of the mechanical obstruction of the mitral valve does little to relieve heart failure. Great enlargement of the left auricle to giant or aneurysmal proportions is another contraindication to valvotomy. These large auricles are often lined with mural thrombus and the danger of detaching a small piece at operation and hence risking a cerebral embolus is considerable. In addition, in "giant left auricle" mitral regurgitation rather than stenosis is usually the dominant lesion. A small degree of aortic incompetence complicating dominant mitral stenosis is no contraindication to mitral valvotomy, but where such a lesion has given rise to left ventricular enlargement, operation is contraindicated. In the presence of aortic stenosis sufficient to cause left ventricular enlargement, mitral valvotomy should not be considered, except in conjunction with aortic valvotomy. Functional pulmonary incompetence secondary to pulmonary hypertension is no contraindication to mitral valvotomy. Likewise tricuspid stenosis, or regurgitation of minor degree, is no bar to the operation. Where mitral regurgitation complicates mitral stenosis the decision as to whether valvotomy will help the patient depends on which lesion predominates functionally. A minor degree of mitral regurgitation associated with severe stenosis is compatible with excellent results after mitral valvotomy.

Auricular fibrillation should not influence the decision as to whether the patient should have a valvotomy, although better results are usually obtained in patients with sinus rhythm. Calcification of the mitral valve, although often causing the actual valvotomy to be technically more difficult, does not prevent an excellent result from the operation.

Pulmonary hypertension of varying degree is present in most cases suitable for valvotomy, but a normal pulmonary artery pressure at rest may coexist with severe mitral stenosis. The absence of pulmonary hypertension therefore does not indicate that the case is unsuitable for surgery, and indeed it is especially in the group of patients with tight stenosis and only moderate pulmonary hypertension that fatal pulmonary oedema is prone to occur if surgery is delayed.

**PRE-OPERATIVE CARE.**—In the absence of congestive cardiac failure, little special pre-operative treatment is required. Pre-operative digitalisation, in patients in sinus rhythm and not already digitalised, is usually employed as a prophylactic measure against the sudden onset of rapid auricular fibrillation, during or immediately after the operation. Routine treatment of congestive cardiac failure is indicated with digitalis, Neptal and low salt diet as required. In patients confined to bed with congestive failure, calf vein thrombosis and pulmonary emboli may occur and these will call for anti-coagulant treatment. In bronchitic patients, in addition to routine pre-operative breathing exercises, antibiotics and antispasmodic drugs should be given.

**The operation.**—The usual route of entry into the left auricle at operation is through

the left auricular appendage. Where this is too small or filled with organised clot, entry may be made through the wall of the left auricle using a tourniquet, or through a pulmonary vein. The valvotomy can usually be satisfactorily performed by splitting the adherent commissures with the finger. Only in cases in which dense fusion has occurred is the use of a valvotome necessary. The degree of mitral stenosis, and the degree of associated regurgitation, if any, can be assessed by the surgeon's palpating finger.

An intravenous procaine drip is often given in an attempt to damp cardiac irritability and thus avoid serious cardiac arrhythmias. Ventricular fibrillation and ventricular arrest are rare but serious complications during the operation itself. Cardiac massage and in some cases an electrical defibrillator are indicated.

**POST-OPERATIVE COMPLICATIONS.**—Auricular fibrillation may occur for the first time in the immediate post-operative period and is commonest during the first 14 days. Reversion to sinus rhythm may be attempted with quinidine; in some cases this reversion occurs spontaneously.

A traumatic pericardial effusion sometimes develops and this may give rise to subacute pericardial tamponade during the first or second post-operative week. Pericardial effusions are less frequent, if local intrapericardial procaine is avoided at operation and adequate dependant drainage into the pleural cavity allowed for, when the pericardium is sutured. Post-operative mitral regurgitation, where none was present pre-operatively, is rarely produced when the finger alone splits the commissures of the valve at their line of fusion. After the use of a valvotome, post-operative regurgitation has been reported more frequently, although it is seldom of any serious functional significance.

Cerebral emboli or emboli elsewhere, originating from particles of clot detached from the intra-auricular thrombus or from calcified masses on the valve itself, may occur at the operation or in the immediate post-operative period.

**RESULTS.**—In most reported series of patients treated by mitral valvotomy results are classed as excellent in about a quarter of cases; in about a half they are good, while in the remaining quarter improvement, if any, is poor. The mortality rate is about 5 per cent. An excellent result indicates that the patient is able to return to full work again and even to enjoy sports such as swimming and cricket.

It is too soon yet to assess the long-term prognosis, but in a few instances the valve cusps have become adherent again within the first 3 years of the original operation, and a second valvotomy has been necessary. Fortunately such cases have so far proved rare.

#### AORTIC STENOSIS

Narrowing of the aortic orifice to one-quarter or less of its normal size causes symptoms and signs from the decreased cardiac output, decreased coronary flow, and left ventricular hypertrophy which eventually results in failure of the myocardium to overcome the obstruction.

**Ætiology.**—The ætiology in most cases is rheumatic and the aortic stenosis is frequently combined with aortic incompetence and mitral stenosis. In many cases of pure or predominant aortic stenosis a murmur has been heard at a very early age, and a congenital origin has been suggested for this; this is further supported by the rarity of a history of rheumatism in such cases and by a striking predominance of males (about 3 to 1) compared with the female dominance in mitral stenosis. With the development of more accurate criteria for diagnosis, aortic valve stenosis has been found to be common. Congenital subaortic stenosis is excessively rare and cannot be distinguished clinically from the valvular variety. Syphilis is never a cause of narrowing of the aortic valve.

**Pathology.**—The aortic cusps are thickened and deformed and often joined

together. In severe cases the identity of the cusps is lost and only a narrow crescentic or triangular orifice is left. Extensive calcification is almost invariable in the older age groups. Beyond the obstruction the aorta often shows a local area of dilatation: the aorta and the coronary arteries are strikingly free of atheroma. There is usually considerable hypertrophy of the left ventricle and the heart may weigh between 500 and 700 g. Dilatation of the ventricle is usual, though late, and some interstitial fibrosis of the myocardium occurs.

**Symptoms and Signs.**—Slight or moderate aortic stenosis causes no symptoms. Severe aortic stenosis causes striking and characteristic symptoms which tend to appear in middle life, and late in the course of the disease. Shortness of breath on exertion is usually the first symptom and gradually progresses until left ventricular failure causes paroxysmal nocturnal dyspnoea (see Left Ventricular Failure, p. 809). Cardiac ischæmic pain on effort is caused by the diminished coronary flow and is indistinguishable from angina pectoris due to coronary disease. The reduced cardiac output is responsible for attacks of dizziness, "blackout", or even syncope which is characteristically provoked by effort, but these symptoms may occur as a result of changes in posture, or peripheral vasodilatation. Sometimes no provoking cause can be discovered, and syncopal attacks may be severe and frequent.

Characteristic abnormalities are found on examination of the pulse, on palpation of the heart and on auscultation. All these abnormalities are required for the firm diagnosis of aortic stenosis. The pulse is small and rises slowly, and pulse tracings frequently show a notch on the ascending limb (anacrotic pulse). The blood pressure is normal or low. The venous pulse is normal in form and in pressure. On palpation the apex beat may be displaced to the left, but, far more important, its character changes to an obvious and sustained heave, indicating hypertrophy of the left ventricle. On auscultation there is an obvious systolic murmur in the aortic area which may be loud enough to produce a thrill and is well transmitted to the neck. The same murmur is transmitted to the apex where it may be as loud as in the aortic area, and occasionally the murmur is loudest at the apex. In many cases the systolic murmur is no more than moderately loud, and does not produce a thrill. The murmur is due to the flow of blood through the narrow, distorted valve. It starts at the moment of ejection, rises to a crescendo in mid-systole and diminishes as the flow diminishes, ceasing before the second sound. This mid-systolic pattern, which can be detected with the stethoscope, is common to all systolic murmurs produced during ejection through the aortic (or pulmonary) valve and does not mean stenosis unless accompanied by the abnormal pulse and hypertrophy of the left ventricle. The aortic component of the second sound may be soft or absent, but it is frequently normal and can be clearly heard at the apex where the pulmonary component of the second sound is not normally transmitted. Physiological splitting of the second sound in the pulmonary area, due to inspiratory delay of the pulmonary component, is seldom heard in aortic stenosis. This may be due to prolongation of left ventricular systole making the two sounds coincide, or to reversal of the normal order of valve closure making the earlier pulmonary component difficult to detect in the systolic murmur. A faint aortic diastolic murmur indicating a minor degree of aortic incompetence is not uncommon.

The *electrocardiogram* is useful in assessing the degree of left ventricular hypertrophy and therefore the severity of the aortic obstruction. Deep S-T depression and T wave inversion are a feature in chest leads taken over the left ventricle, and this pattern with a tall R wave is frequently transmitted to both the left arm and left leg, making all three standard limb leads of a similar pattern. There may be left bundle branch block. The rhythm is usually normal, but prolonged auriculo-ventricular conduction and dissociation are not uncommon. On *radiography* the left ventricle may be enlarged but evidence of hypertrophy is usually found earlier by *electrocardiography* and by palpation. The ascending aorta can usually be seen to

be dilated immediately distal to the valve. Calcification of the aortic valve can be detected by fluoroscopy in a very high proportion of the older patients.

**Complications.**—Bacterial endocarditis may occur at any time in the course of the disease, even in the early stages when the only physical sign is a mid-systolic murmur (see p. 886). Sudden death is not infrequent once symptoms have developed.

**Course and Prognosis.**—The course of patients with aortic stenosis is long and benign. A systolic murmur may have been heard in childhood and passed as innocent, and the stenotic pulse and left ventricular hypertrophy may not develop until middle age. Once symptoms of cardiac failure have been noticed, the course is usually downhill. Shortness of breath on exertion is succeeded by paroxysmal nocturnal dyspnoea from left ventricular failure; pulmonary congestion and congestive heart failure ensue. In some cases raised jugular venous pressure and œdema may appear without preceding symptoms of left ventricular failure (Bernheim's syndrome) and this is probably due to interference with the capacity of the right ventricle owing to encroachment by the massive hypertrophy of the left ventricle. Angina pectoris and syncope on effort adversely affect prognosis and sudden death is not uncommon.

**Diagnosis.**—A diagnosis of aortic stenosis is made by finding a slow rising pulse, an aortic systolic murmur and evidence of left ventricular hypertrophy. In hypertension with aortic dilatation there may be left ventricular hypertrophy and a soft aortic systolic murmur but no stenotic pulse. In dilatation of the aorta from atheroma alone there may be a soft aortic systolic murmur but no abnormal pulse or left ventricular hypertrophy.

In active rheumatism with aortic valvulitis without stenosis there is a soft or moderately loud aortic systolic murmur but no abnormal pulse or evidence of left ventricular hypertrophy. In aortic incompetence there is usually an aortic systolic murmur, and when associated with aortic dilatation as in syphilis, there may be a loud systolic murmur and even a thrill, but the pulse is waterhammer and the left ventricle feels hyperdynamic as well as hypertrophied. Differentiation from mitral incompetence can be difficult since in both conditions there may be a loud apical systolic murmur. The systolic murmur in mitral incompetence is always pansystolic often with a crescendo in late systole obliterating the second sound at the apex, though this sound is clear enough elsewhere. The mitral systolic murmur is not loud in the aortic area and is frequently better conducted to the axilla and back. In mitral incompetence the pulse is not anacrotic unless there is associated aortic valve disease.

**Treatment.**—No treatment is necessary for cases of mild or moderate aortic stenosis except to avoid hard physical effort, especially competitive games. Reassurance and encouragement can benefit many of these patients. In severe aortic stenosis with ischaemic pain, or syncopal attacks, exertion sufficient to produce symptoms must be strictly avoided, and this is usually compatible with a sedentary occupation. Left ventricular failure is treated with digitalis, a low sodium diet and mercurial diuretics (see p. 812). Some patients have been successfully treated by aortic valvotomy but the value of this operation cannot yet be assessed.

#### AORTIC INCOMPETENCE

Damage to the aortic cusps, a dilated valve ring or a combination of these circumstances leads to aortic incompetence. The magnitude of the backflow varies from a small fraction to half of the stroke output when the cusps are totally deficient; this regurgitated blood increases the residual left ventricular volume and stretches the myocardium, causing a more vigorous contraction of the left ventricle and a steep rise of intraventricular pressure resulting in early ejection of an increased volume of blood. This steep rise of pressure imparts a "hyperdynamic feel" to the apex beat, which is transmitted to the carotid arteries where it is known as Corrigan's sign, to



the peripheral arteries causing a waterhammer pulse, and to the capillaries where the increased pulsation may be seen. The increased left ventricular volume causes dilatation, and the increased work causes hypertrophy of the left ventricle which may reach an enormous size.

**Ætiology and Pathology.**—Rheumatic valvulitis is by far the commonest cause of aortic incompetence in Great Britain, and in most cases there is additional involvement of the mitral valve. Syphilitic aortic incompetence is now less commonly seen (see p. 859); here the main damage is in the aorta, causing dilatation of the aortic ring, and severe involvement of the cusps is much less common. Syphilitic aortitis also results in aneurysm formation, coronary ostial stenosis leading to cardiac ischaemia and, rarely, cardiac infarction. In severe hypertension stretching of the aortic ring may cause a minor degree of incompetence. Damage to the aorta from a dissecting aneurysm occasionally causes aortic incompetence. Bacterial endocarditis is rarely the primary cause, although it may increase pre-existing damage and is the commonest cause of a ruptured aortic cusp. Congenital bicuspid aortic valves, or rarely, quadricuspid valves, tend to be incompetent when associated with hypertension or atheroma. A minor degree of incompetence from a bicuspid valve is frequently found in patients with coarctation of the aorta. Congenital abnormalities of the aortic valve causing incompetence are occasionally associated with large ventricular septal defects or other more serious forms of congenital heart disease.

**Symptoms and Signs.**—A slight or moderate degree of aortic incompetence usually produces no symptoms for many years, especially if it is of the rheumatic variety. Shortness of breath on exertion is the first significant symptom and, as with aortic stenosis, left ventricular failure tends to progress rapidly with paroxysmal nocturnal dyspnoea and cardiac asthma. Ischaemic pain is not uncommon, especially in the syphilitic group with coronary ostial stenosis, and the pain tends to occur during an attack of paroxysmal nocturnal dyspnoea.

The pulse of aortic incompetence rises steeply in systole and gives a characteristic tap to the palpating finger which is described as simulating a waterhammer. The rapid fall of pressure is described as collapsing. These signs are best appreciated by palpating the radial and brachial arteries with the flat of the fingers when the arm is elevated. The same pulsation can be seen in the carotid arteries as described by Corrigan, and in the capillaries especially of the nail bed. The compensatory rise in systolic pressure and low diastolic pressure from the aortic backflow and peripheral vasodilatation produces a wide pulse pressure, and a blood pressure of about 180/50 is not uncommon. There may be difficulty in estimating the diastolic pressure, and persistence of the diastolic sound down to zero does not indicate a diastolic pressure at this level. The apex is heaving from left ventricular hypertrophy and the sudden steep lift in systole combined with a second small wave in diastole gives the apex a hyperdynamic quality. The apex is displaced downwards and to the left. On auscultation there is an early diastolic murmur commencing immediately after the aortic component of the second sound. This murmur is high pitched and best heard with the diaphragm type of stethoscope. It is usually maximal to the left of the sternum in the third and fourth left spaces over the aortic valve, but when the ascending aorta is dilated, especially in syphilitic aortitis, the murmur is often loudest to the right of the sternum. Early diastolic murmurs may be very difficult to hear, but they are usually more easily heard on expiration, in the sitting position, and when the heart is slowing after exertion. An aortic systolic murmur is usually heard, and is of the same quality as in aortic stenosis but is not so loud. Occasionally the systolic murmur may be loud, and even associated with a thrill when the first part of the aorta is greatly dilated from syphilitic aortitis. Wide splitting of the first heart sound is not unusual, and is due to the addition of an extra ejection sound in early systole from dilatation of the aorta. In some patients with isolated free aortic incompetence a rumbling mid-diastolic murmur, with or without a presystolic murmur,

pulsation of the right auricle in tricuspid incompetence, but more often the auricle is so large that the regurgitant stream produces little movement; however, appropriate auricular or ventricular pulse waves may be seen in the superior vena caval shadow. The lungs are frequently clear in spite of the degree of heart disease.

**Diagnosis.**—Careful observation of the venous pulse is the key to diagnosis in tricuspid valve disease. Tricuspid incompetence is frequently overlooked because of the dominant signs of associated organic heart disease. Tricuspid stenosis is relatively rare: it should be considered in chronic rheumatic heart disease when there are signs of right heart failure, recurrent ascites and hepatomegaly: if the heart rhythm is regular, large auricular waves in the neck veins and presystolic hepatic pulsation are diagnostic signs.

**Prognosis.**—The prognosis in functional tricuspid incompetence is essentially that of the causal disease. In organic tricuspid disease prognosis also largely depends on the degree of associated chronic mitral valvulitis and its effect on the whole heart.

**Treatment.**—The treatment of functional or organic tricuspid incompetence is the treatment of heart failure. The rare cases of pure or dominant tricuspid stenosis should be treated by tricuspid valvotomy.

## DISEASES OF THE PERICARDIUM

### PERICARDITIS

Inflammation of the pericardium may be acute or chronic and occurs as a primary infection or as part of a general disease. The acute form may be dry (fibrinous) or accompanied by effusion (serous). Chronic pericarditis occurs as constrictive pericarditis, adhesive mediastino-pericarditis and rarely as a chronic effusion. The important considerations in all forms are the nature of associated disease, and the presence of circulatory embarrassment through interference with diastolic filling and ventricular systole.

#### ACUTE PERICARDITIS

**Ætiology.**—The age and sex incidence in acute pericarditis depends on the nature of the cause. It is frequently due to acute rheumatic fever, and sometimes to pyogenic bacterial infections and tuberculosis. Idiopathic or acute benign pericarditis is probably due to a virus infection. Other causes are uræmia, trauma and invasion by neoplasm. Acute pericarditis frequently results from cardiac infarction.

**Pathology.**—The morbid anatomical findings largely depend on the ætiology of the pericarditis. The acute fibrinous forms may be local or general in distribution. In the early stages the pericardium loses its smooth, shiny appearance because of a surface exudate of lymph, fibrin and inflammatory cells. This exudate may become thick and irregular, resulting in a ragged, honeycombed appearance—the so-called “bread-and-butter pericardium”. In many cases the superficial layers of the myocardium also show an inflammatory reaction. Organisation takes place, leaving varying degrees of slight pericardial thickening, often with adhesions. In other forms the fibrinous reaction may be associated with a large effusion of serous or sero-sanguinous or sero-purulent fluid, and occasionally the sac may be full of pus.

**Clinical Features.**—1. *Acute fibrinous pericarditis (i.e. without effusion).*—In many cases there are no symptoms; in others the symptoms are submerged in those of associated disease, i.e. rheumatic carditis and cardiac infarction, whilst in others distinctive features are present.

Pain varies in intensity and is situated across the front of the chest, sometimes radiating to the neck, shoulders and arms; it may occasionally be confined to the epigastrium. Pericardial pain may be indistinguishable from the pain of cardiac

infarction, but sometimes it is made worse by moving the chest, especially into the hyperextended position, and on deep breathing. It is generally agreed that the visceral pericardium is insensitive and the pain of pericarditis appears to arise from the parietal pericardium and its area of continuity with the diaphragm and pleura. Some degree of dyspnoea is usual, but this is not a prominent feature unless there is pericardial effusion.

There is often moderate fever, sweating and a leucocytosis, depending on the ætiology of the pericarditis. The characteristic physical sign is a friction rub which occurs in systole and diastole, giving it a "to and fro" character, which sometimes resembles the murmur of aortic stenosis and incompetence. Friction rubs are best heard towards the base. They have a superficial scratching quality and vary in intensity with pressure of the stethoscope; they are often transient and generally disappear when an effusion develops.

2. *Pericarditis with effusion.*—The clinical picture varies with the amount of fluid and the rate at which it accumulates. If the amount is small there may be no symptoms. If, on the other hand, it is large and the accumulation is rapid, pain is usual and the patient is often anxious, restless and pale. The pain may be severe, but there is more often a sense of dull sternal oppression. Dyspnoea and orthopnoea develop in proportion to the size of the effusion and appear to be due to a direct compression of adjacent lung and diminution of vital capacity. An irritating cough occurs with large effusions. Cardiac asthma sometimes occurs, but is probably due to underlying myocardial disease.

A friction rub is sometimes heard towards the base of the heart. The apex beat becomes weak and may disappear, and the heart sounds are soft at the apex. The extent of cardiac dullness increases and is said to vary with the posture of the patient. In large effusions dullness to percussion and bronchial breathing occur posteriorly over the left lower lobe, due to partial or complete atelectasis.

The interference with cardiac function known as *cardiac tamponade* which occurs in many cases is related to the size of the effusion and its rate of development. The clinical features of tamponade are due to restriction of diastolic filling and consequent reduction in cardiac output, a rise in right auricular pressure above the pericardial pressure, and peripheral vasoconstriction which maintains blood pressure in the presence of a falling cardiac output. Tamponade is recognised by a rising jugular venous pressure and this should be carefully assessed in all cases of suspected pericardial effusion. The systemic blood pressure tends to fall and the radial pulse may become very small—occasionally it fades during inspiration (pulsus paradoxus). A paradoxical rise of venous pressure with inspiration may be observed in the jugular veins. Tachycardia is usual. Rapidly developing tamponade may lead to shock, whilst a slowly increasing pericardial effusion may produce widespread venous congestion resembling congestive heart failure.

*The radiology of acute pericarditis.*—Radiological changes in acute pericarditis occur when an effusion collects in the sac. The important signs are (1) an enlargement of the heart shadow and a decrease in size with recovery shown by serial films; (2) a rounding of the heart shadow, becoming almost globular in some cases, with obliteration of the normal angulation along the left border, sharpening of the pericardiophrenic angles and a bulging into the retrocardiac space best seen in the right oblique view; (3) diminution of cardiac pulsation seen on radioscopy—in extreme cases the shadow appears quite still; (4) on cardiac catheterisation there is a space between the catheter tip lying against the right auricular endocardium and the outer border of the heart. This increase in thickness of the wall due to fluid may be clearly demonstrated by angiocardiology—a small quantity of dye introduced through a catheter is sufficient for diagnostic purposes.

*The electrocardiogram in acute pericarditis* tends to show pathological changes in all leads due to the widespread nature of the injury. The time relations of various

complexes remain normal. P waves are unaffected. The QRS complex remains normal in form but the voltage is frequently diminished in all leads in pericardial effusion. The important pathological changes in pericarditis are due to epicardial injury, and are found in the S-T segment and T waves. The S-T segment is slightly elevated in all leads, showing more in some leads than in others. Usually the S-T is concave upwards, in others it is straighter and occasionally covered with a convexity upwards, as is found in myocardial infarction. These changes fluctuate, tend to be transient and rarely last for more than 10 days. The T waves tend to become flattened and inverted. A small inversion of T waves in all standard leads and chest leads is sometimes seen—the widespread nature of such a change is strong evidence of pericarditis. Occasionally the T wave is tall and sharp at the termination of a raised concave S-T segment.

The electrocardiogram of cardiac infarction is partly due to epicardial disease so that differentiation from pericarditis is sometimes difficult. The changes in pericarditis are more diffuse and are never associated with Q waves. An isolated steep inversion of T waves occurring in only one or two leads is not due to pericarditis.

*Paracentesis of the pericardium* is indicated when diagnosis remains in doubt, when examination of the fluid is required for diagnosis of the cause, and as an urgent therapeutic measure when cardiac tamponade is great or increasing rapidly.

The skin and underlying tissues should be anaesthetised down to the pericardium. The needle should be inserted just beyond the apex beat, or high in the angle between the ensiform cartilage and the left margin of the sternum and then passed upwards, backwards and slightly to the right; the needle should be withdrawn a little when pulsation of the heart is felt on reaching the epicardium. Sufficient fluid is withdrawn for diagnostic purposes or to relieve symptoms. This procedure is not indicated unless there is evidence of a considerable quantity of fluid or severe tamponade.

**SPECIAL TYPES OF PERICARDITIS.**—1. *Acute benign pericarditis* (idiopathic pericarditis, non-specific pericarditis or virus pericarditis).

This condition is of considerable importance because it is readily mistaken for cardiac infarction. Adults of either sex are affected, the aetiology is unknown but an upper respiratory tract infection or pneumonitis frequently precedes the pericarditis. A moderate-sized effusion may develop, friction may appear and fever may last a few days. The condition lasts for days or weeks, but relapse is not uncommon; however, recovery is invariable and apparently complete.

2. *Tuberculous pericarditis.*—This is a relatively rare clinical condition. It usually appears to be the primary manifestation of tuberculosis, but in most cases it is secondary to an obscure lesion elsewhere. The onset is often insidious, with general symptoms rather than local ones due to pericarditis. Chest pain usually develops, but may be transitory, cough is common and fever is high and irregular, but may be completely absent in elderly patients. Signs of tamponade develop and cardiac arrhythmias are common. The tuberculous aetiology may be confirmed by examination of aspirated pericardial fluid. The prognosis is bad without treatment; mortality rate in the first year after the onset of symptoms being approximately 50 per cent. Surviving patients, whether treated or untreated, may develop constrictive pericarditis later.

**Treatment.**—Prolonged bed rest similar to sanatorium régime is necessary. The prognosis is greatly improved by the concurrent administration of 1 g. of streptomycin intramuscularly and 12 g. of sodium aminosalicylate (P.A.S.) daily for 120 days. Streptomycin can also be combined with isoniazid. When pericardial aspiration is possible and indicated by the size of the effusion, 1 g. of streptomycin in saline should be injected into the sac. This procedure may be repeated at weekly intervals and good results have been obtained. The treatment of tuberculous pericarditis is still largely experimental and various combinations of chemotherapeutic drugs merit a trial. There is some evidence that early surgical drainage after treat-

ment with streptomycin may be beneficial. The progress of treatment is assessed from the degree of fever, improvement in general symptoms, the erythrocyte sedimentation rate, radiological heart size and the electrocardiogram.

3. *Rheumatic pericarditis*.—Some degree of transient fibrinous pericarditis probably occurs in a majority of cases of rheumatic carditis and its significance is subordinate to the whole disease. In some cases, however, usually the more serious ones, an effusion develops and this adversely affects the course of the disease.

4. *Purulent pericarditis* is fortunately rare now that the pyogenic conditions which cause it are treated with antibiotic agents or chemotherapy. Surgical drainage together with the appropriate chemotherapy is indicated.

**Diagnosis.**—Chest pain, a friction rub, fever and widespread S-T elevation and T wave changes in the electrocardiogram are the diagnostic features of acute fibrinous pericarditis, but these features do not always occur together. Pain is often absent, friction rubs are often fleeting, fever may be absent or due to associated disease and the electrocardiogram may be pathological only for a brief period. When pain, friction or electrocardiographic changes occur in the course of a disease known to be complicated by pericarditis, such as rheumatic fever, septicæmia, chest neoplasm and uræmia, the diagnosis is readily made.

The accumulation of pericardial fluid is recognised by radiographic change in heart shape, softening of the heart sounds, electrocardiographic changes and the signs of developing tamponade. The withdrawal of pericardial fluid by paracentesis is diagnostic and helps in the investigation of its ætiology. Repeated physical examinations, serial electrocardiograms and chest films are of great importance, not only for observing the progress of the disease, but for diagnostic purposes.

The important differential diagnosis of acute virus pericarditis is cardiac infarction (see above). Congestive cardiac failure must be differentiated from pericardial effusion causing tamponade. Here a knowledge of the underlying ætiology, the radiographic features, serial electrocardiograms and special investigations mentioned above for pericardial effusions are of diagnostic importance. The prognosis and treatment of acute pericarditis depend on the underlying cause.

#### CHRONIC CONSTRICTIVE PERICARDITIS

**Synonym.**—Pick's Disease.

This condition is essentially one of great thickening of the pericardium, which imposes a restrictive action on the heart so that diastolic filling is impeded, systolic ejection is diminished and venous congestion develops. It was known long before a series of cases were described by Pick in 1896. There are descriptions by Lower and by Lancisi over a century before, and Chevers discussed the pathophysiology of the condition in 1842.

**Ætiology.**—Constrictive pericarditis occurs in men more often than in women and mostly between 15 and 40 years of age.

It is not surprising that the ætiology is difficult to find since it is not until healing and organisation of previous inflammation have taken place that the condition comes into existence. Probably many cases are due to tuberculosis, but a definite history of previous pericarditis is rare and tuberculosis can only be demonstrated in some 16 to 20 per cent. of biopsy or necropsy specimens by histological and bacteriological methods. Rarely inflammation with pyogenic organisms may produce constrictive pericarditis, and it may also occur as a result of organisation of hæmopericardium.

**Pathology.**—The heart is encased in pericardium which is thickened from 2 to 10 mm. This scar tissue shows varying degrees of hardness from an heterogeneous fibro-caseous mass to hard homogeneous hyalinised tissue or dense fibrosis with extensive calcification. This compression scar usually encases most of the heart and

sometimes extends up to the great vessels, but occasionally it is more localised. The heart is essentially normal, but the superficial myocardium is frequently involved in the overlying pericarditis so that a line of cleavage cannot be found.

The serous cavities usually contain effusions and the peritoneum is often thickened, sometimes to the extent of producing a so-called "sugar-icing" appearance. The liver shows the results of long-standing venous congestion; it may be large or normal sized with a nutmeg appearance, or shrunken and fibrotic. It appears that the cirrhotic process continues after surgical relief of the constrictive pericarditis, if it has developed sufficiently to produce its own effects.

**Clinical Features.**—The clinical features are the result of restricted diastolic filling, especially of the right heart, which causes a reduction in cardiac output; this leads to sodium and water retention. The resulting hypervolaemia means an increased venous return which, however, cannot be accommodated by the constricted ventricles so that extreme venous congestion results.

Constrictive pericarditis develops quietly and symptoms are not usually prominent until the signs are well developed. The patient may first complain of dyspnoea on effort or swelling of the abdomen. Sometimes cough is a prominent feature and occasionally faintness on bending down or coughing may be troublesome.

The most important physical sign is congestion of the cervical veins—this may be so great that the top level of venous pulsation is well above the ears and cannot be seen (20 to 30 cm. above the right auricle is usual). The venous pulse wave form appears continuously high with sharp descents in early diastole and a paradoxical rise in venous pressure with inspiration is usually present. Constrictive pericarditis does not occur without venous hypertension. The arterial pulse tends to be small and often shows a diminution with inspiration (pulsus paradoxus). The blood pressure is usually low; peripheral arterial constriction shown by peripheral cyanosis and coldness of the extremities is sometimes present. Auricular fibrillation is not uncommon.

The apex beat is small or absent. The heart sounds tend to be soft but a cadence of three sounds is usually heard. The additional sound occurs in early diastole and is rather shorter, higher pitched and earlier than the physiological third sound. It is related to the high pressure of ventricular filling.

Ascites is usually present and is a prominent feature of the disease. Its extent is in contrast to the smaller amount of peripheral oedema. Ascites is persistent and peritoneal tapping is followed by recurrence. The liver may be small or moderately enlarged; it is hard but cannot always be felt through the ascites. Pleural effusions of varying extent are often present. The disease runs a long chronic course with gradually increasing venous congestion, diminishing cardiac output and hepatic failure.

**Radiology.**—The heart is not enlarged and on radioscopy the pulsations are seen to be diminished and the angulations of the left border are smoothed out. The most conspicuous finding in many cases is extensive calcification of the pericardium. This is often best seen in oblique views and sometimes appears completely to encase the heart excepting the origin of the great vessels. Small pleural effusions are common. The lungs do not usually appear congested.

**The electrocardiogram.**—The P waves may show abnormal forms or they are absent when there is auricular fibrillation. The QRS complex tends to be of low voltage, but is otherwise normal. The S-T segment is isoelectric but T waves are usually flattened or inverted in several leads. Occasionally the electrocardiogram is surprisingly normal and there is some evidence that the pericarditis has not involved the underlying myocardium in such cases.

Other investigations are not usually indicated. Liver biopsy shows the degree of cirrhotic changes. Catheterisation of the right heart shows the high level of the right auricular venous pressure and the right ventricle shows a characteristic pressure

curve. Diastolic filling causes a very rapid rise of pressure which then reaches a plateau presumably when the restrictive forces prevent further change.

**Diagnosis.**—The diagnostic features of constrictive pericarditis are jugular venous congestion, ascites and a quiet small heart with an additional heart sound in early diastole. The radiological features are important and calcification of the pericardium is diagnostic in the presence of venous hypertension; however, there may be calcified plaques in the pericardium without pericardial constriction. The electrocardiogram provides important additional evidence, but the diagnosis is essentially based on the clinical findings.

Congestive heart failure is differentiated from constrictive pericarditis by the presence of extensive œdema, lower levels of jugular venous pressure, cardiac enlargement and the recognition of a cause for the heart failure. Other causes of ascites are not usually difficult to differentiate because of the absence of severe venous congestion.

The greatest problem in differential diagnosis is provided by obscure conditions which primarily involve or infiltrate the myocardium and endocardium, *e.g.* myocarditis, amyloidosis and endocardial fibrosis (see p. 889). The hæmodynamics are somewhat similar, for diastolic filling may be restricted and the heart pulsations diminished, but calcification does not occur and the QRS complex of the electrocardiogram usually shows evidence of myocardial involvement. An inspection of the pericardium at operation may in the last resort be the diagnostic method of choice so that pericardectomy can be performed if constriction is present.

**Prognosis.**—Untreated patients with constrictive pericarditis steadily deteriorate, become bedridden and die of the long-term effects of low cardiac output and hepatic failure. Surgical treatment entirely alters the outlook and patients are now living reasonably active lives several years after operation.

**Treatment.**—Decompression of the heart by surgical removal of the pericardium is indicated. It is advisable to reduce ascites before operation, and pre-operative treatment with streptomycin or other appropriate antibiotics is indicated if there is any evidence of activity of the infection. Thickened pericardium is gradually removed from the left ventricle, and increased movement of the underlying heart or herniation through the area of removal indicates that decompression is being effective. It is often necessary to carry the decortication process over the right heart and the right auricle. Hæmorrhage and infection are dangers, but in expert hands and with the use of antibiotics the mortality rate is less than 10 per cent. An indifferent result from pericardectomy may mean that resection has not been sufficiently extensive. The results of operation are extremely satisfactory and it should be advised in all cases of constrictive pericarditis.

#### CHRONIC ADHESIVE PERICARDITIS

In this condition there are fibrous adhesions between the parietal layer of the pericardium and adjacent mediastinal structures, the chest wall, the pleura or the diaphragm. Various symptoms and signs have been attributed to this condition, but none is reliable and most are due to other changes such as chronic valve disease, cardiac enlargement or even true constrictive pericarditis. Although much has been written on this condition in the past, there is no evidence that it has any adverse effect on the function of the heart. No treatment is indicated.

#### PNEUMOPERICARDIUM

Air in the pericardial sac is a rare condition and occurs as a result of chest wounds and erosion by malignant growths from the bronchus or œsophagus. It is invariably associated with serous or purulent effusion. The symptoms and signs depend on

called the "flea-bitten kidney" (deriving from the days when flea bites were "physiological" and did not cause a brisk surrounding allergic response); (3) a diffuse glomerulo-nephritis is not uncommon and has been found in patients dying after penicillin treatment has cured the active endocarditis. Heart failure is not a prominent feature until late in the disease.

**Clinical Features.**—The symptoms and signs are due to toxæmia, septicæmia, emboli in various organs and cardiac failure. The onset is gradual so that it is rarely possible to determine accurately when the disease began, but occasionally the onset is sudden, with high fever and rigors. The initial symptoms are general weakness and anorexia, with frequent sweats. Fever is usual and variable, there may be brief apyrexial periods, but it is mostly continuous and rarely rises above 102° F. Rigors are not uncommon and occur especially when there are crops of petechial hæmorrhages. Headache and pain in the joints and limbs are common. Anæmia develops from the start and tends to be progressive; splenomegaly appears early in the disease.

**The heart.**—In the great majority of cases there are definite signs of heart disease at the onset. Often the signs are slight at first; a pansystolic murmur at the apex with no cardiac enlargement indicating a minimal mitral valve lesion is common. On the other hand, there may be obvious signs of extensive aortic valve disease or the signs of a congenital defect. As the disease progresses it is common to find evidence of spread to other valves, especially the aortic valve when the mitral valve was originally involved. Undue importance has been attached to changes in the character of murmurs from day to day. The sudden appearance of a loud rasping or a musical murmur in systole or diastole may be due to the rupture of a cusp or fracture of one of the chordæ tendinæ. Auricular fibrillation is most unusual in the early stages of the disease, but it occasionally develops later.

**Embolic phenomena.**—Arterial emboli cause important signs of the disease. Lesions range from multiple microscopic ones to single large ones and may affect any organ of the body. The skin shows a variety of lesions. Petechiæ are commonest, there may be no more than two or three or there may be vast numbers; they are commonly seen under the nails as splinter hæmorrhages, at the base of the neck, in the conjunctiva of the lower lid, and in the fundus oculi and the buccal mucosa. Petechiæ may recur in showers, but in the early stages a diligent search is often required to find one. Larger areas of ecchymosis are not uncommon and may be tender. Osler's nodes are small, tender, swollen areas, usually a few millimetres in diameter, occurring commonly on the pulp of the fingers or toes; they are usually discoloured and transient, the patient complains of a sudden tender spot and often the examiner finds no signs a few days later. Osler's nodes appear to be almost specific for the disease.

The spleen enlarges early in the disease and is generally rather soft. Episodes of sudden severe left hypochondriac pain suggest splenic infarction; the spleen is then tender and a friction rub due to perisplenitis may be heard. Sudden loin pain may indicate renal infarction which sometimes causes macroscopic hæmaturia. Microscopic hæmaturia is common and is the result of focal embolic nephritis. Renal failure is a late manifestation of the disease.

Cerebral embolic episodes with resulting hemiplegia are not uncommon. Rarely diffuse cerebral damage may produce a meningitic or encephalitic picture. Central retinal arterial embolism occasionally occurs and causes sudden blindness, and optic atrophy may cause a more insidious loss of vision. The mesenteric vessels and those of the limbs are frequently involved. Mycotic aneurysm may develop, leading to fatal hæmorrhage or gangrene. Sudden pain in a joint is probably due to endarterial embolism; repeated attacks of joint pain may cause confusion with rheumatic fever. Coronary embolism may cause cardiac infarction, resulting in heart failure or sudden death.

When bacterial endocarditis complicates a congenital lesion with left to right shunt, e.g. patent ductus arteriosus and ventricular septal defect, there may be few,



if any, manifestations of systemic embolisation; the clinical features are then largely pulmonary; the lungs may show repeated infarction and rarely abscess formations.

Cachexia with a *café au lait* complexion, gross finger clubbing, severe anaemia, hæmorrhagic lesions, heart failure and renal failure are late features of the disease. The clinical picture and natural history of bacterial endocarditis have been changed by antibiotic drugs and chemotherapy. In early cases the disease may be completely cured; however, this is by no means invariably the case. When treatment is started late in the disease infection may be eradicated, but extensive valve lesions may lead to progressive heart failure. In some cases progressive renal failure from diffuse nephritis continues after sterilisation of the infection.

*Investigations.*—The blood shows a progressive anaemia averaging between 8 and 12 g. of hæmoglobin per 100 ml.; the red cells rarely fall below three million per c.mm. The white cell count is variable, most cases show a slight to moderate leucocytosis but leucopenia sometimes occurs. Large monocytes are usually increased. The sedimentation rate is usually raised but this is not invariable.

Blood cultures are positive in some 75 per cent. of cases. Several samples of 10 to 20 ml. of blood should be examined, and several days must elapse before culture can be accepted as negative. When cultures are attempted after penicillin therapy has started they are likely to be negative unless treated with penicillinase.

Radiological and electrocardiographic examinations aid the assessment of the cardiac condition but are not specifically altered by bacterial endocarditis.

*Diagnosis.*—Early diagnosis is imperative if antibiotic therapy is to prevent further irreparable damage to the heart. Any patient with an organic heart murmur who has vague ill health or prolonged fever should at once be considered as a possible case of bacterial endocarditis and appropriate investigations undertaken. The main features which lead to clinical diagnosis are (1) heart disease, (2) fever, (3) embolic features, particularly petechiæ and Osler's nodes, (4) splenomegaly, (5) anaemia and (6) hæmaturia. Positive blood cultures confirm the diagnosis but in some 10 to 15 per cent. of cases the blood culture remains negative. The diagnosis is rarely tenable when the hæmoglobin concentration and the sedimentation rate are normal. *Differential diagnosis.* If bacterial endocarditis is kept in mind when considering patients with an organic heart murmur, confusion with other conditions rarely arises. However, bacterial endocarditis which is characterised by prolonged fever and the involvement of many organs must obviously be distinguished from many other conditions.

Fever, endocarditis and anaemia due to active rheumatism in adolescents and young adults may resemble bacterial endocarditis, and in any case these conditions may coexist. The presence of Osler's nodes, petechiæ, clubbing, splenomegaly and positive blood cultures do not therefore exclude rheumatic fever but indicate the existence of bacterial infection. Other causes of fever such as malignant reticulosis, tuberculosis and the enteric fevers should be considered but are readily excluded by the absence of signs of endocarditis described above. Malignant reticulosis with fever, splenomegaly and anaemia may cause difficulty but investigations usually reveal the true nature of the condition and signs of endocarditis are absent. Tuberculosis and the enteric fevers causing pyrexia and wasting are usually excluded on clinical grounds, but in cases of doubt the blood culture, Widal reaction, Mantoux test and a search for tubercle bacilli are decisive. Disseminated lupus erythematosus and other collagen diseases, if associated with a heart murmur may resemble bacterial endocarditis, but clubbing, Osler's nodes and positive blood cultures are absent, and in disseminated lupus erythematosus the presence of L.E. cells can be demonstrated in the blood (see p. 933). If the presenting feature of bacterial endocarditis is due to embolism, such as hemiplegia, hæmaturia, pulmonary infarction, the nature of the underlying disease may not be immediately apparent but continued fever and other features soon reveal the presence of infection and endocarditis.

Infected ventricular septal defect causing repeated episodes of pulmonary infection and infarction may be confusing, but if the possibility of superadded endocarditis is always kept in mind when dealing with patients with an organic murmur the diagnosis is readily made.

**Prognosis.**—Prognosis without treatment is hopeless. Antibiotic therapy has completely changed the outlook which is now good, provided that treatment is applied early in the disease. Relapse may occur and when this happens it usually does so within one month of the cessation of treatment. Resistant strains of organisms may develop, but by increasing dosage and with the wide range of antibiotics now available this problem can be overcome. In spite of sterilisation of the infection some cases continue to deteriorate from heart failure, renal failure, or as the result of infarction of vital organs. Heart failure is the commonest cause of death, and tends to occur during treatment or within 6 months after treatment. Other adverse prognostic factors are increasing age, severe primary valve lesions and poor nutrition of the patient; the most important factor in prognosis is the duration of infection prior to the start of treatment.

**Treatment.**—**PROPHYLACTIC.**—Any patient with rheumatic heart disease (especially organic mitral incompetence, or lone aortic valve disease) or with congenital heart disease should receive penicillin before undergoing any operative procedure, particularly dental extraction, tonsillectomy or any sort of endoscopy; 500,000 units of soluble penicillin should be given 1 hour before operation, and the blood level maintained for 48 hours thereafter by a 12-hourly injection of 250,000 units procaine penicillin. Larger doses for a longer period before or after operation are indicated if this is for a known septic lesion.

**CURATIVE.**—Bed rest, a good diet and added iron are indicated, but the essential part of treatment is the early and adequate administration of penicillin. The sooner it is started the better is the outlook, and a delay of 24 hours may determine the existence of a serious embolic episode. If the clinical diagnosis is reasonably certain, penicillin therapy should be started after several samples of blood have been withdrawn for culture during the first 24 to 48 hours; there is no justification for awaiting a positive culture which may take several days, and indeed negative culture does not invalidate a sound clinical diagnosis. The positive blood culture provides confirmation of the diagnosis, and the infecting organism should be tested for sensitivity to penicillin and other antibiotics. Penicillin should be given in a minimum daily dose of 2,000,000 units for 6 weeks. It should be divided into a 4-hourly intramuscular injection or given by continuous intravenous drip. It is probable that 12-hourly injections of 1,000,000 units of procaine penicillin are adequate for 90 per cent. of cases; however, the intermittent intramuscular route of soluble penicillin is recommended at least until the results of bacteriological investigation are available. A larger daily dose should be given if the resistance of the infecting organism is four or more times that of the Oxford staphylococcus, or if clinical improvement is not apparent in the first week. On such grounds it may be necessary to give 6,000,000 units or occasionally 10,000,000 units daily. In other cases, depending on the bacteriology and clinical response, it may be advisable to combine penicillin with streptomycin or other antibiotic drugs.

The effectiveness of treatment is shown by remission of fever, improved appetite and well being, and a gain in weight; anaemia improves and the sedimentation rate falls. It should be noted that petechiae may continue to appear for some time after the temperature is normal. Failures of treatment are due to delay in starting treatment through delay in diagnosis, inadequate dosage and the development of resistant organisms.

**SURGICAL TREATMENT.**—In cases of patent ductus arteriosus it is advisable to ligate the ductus when treatment and convalescence are completed. Occasionally ligation should be advised whilst infection is still present if this is resistant to anti-

biotic therapy. Mycotic aneurysms require removal and grafting of the affected vessel where this is possible.

Ninety per cent. of patients with bacterial endocarditis may be cured if treated within 6 weeks of the onset of the disease, but if treatment is delayed until after the third month, only 50 per cent. are cured.

#### ACUTE BACTERIAL ENDOCARDITIS

There is much overlap with subacute bacterial endocarditis and now that serious septic conditions are treated effectively with antibiotic drugs, the differentiation of these conditions is of doubtful value.

Acute bacterial endocarditis is now rare. It is mostly due to one of the pyogenic organisms, and is incidental to the course of an acute pyogenic illness. The primary lesion is generally obvious, such as suppurative pneumonia, puerperal fever, osteomyelitis, a carbuncle or gonorrhœa. An undamaged heart may rarely be affected. Vegetations develop on the valvular and mural endocardium, and there is a greater tendency to ulceration and destruction than in subacute bacterial endocarditis.

**Clinical Features.**—The onset is rapid, but it cannot always be detected against the background of the severe septic primary disease. The symptoms are largely septicæmic; swinging fever, rigors and sweats are usual; pain and swelling of joints together with cutaneous ecchymoses are common. Finger clubbing is rare, but petechial hæmorrhages and a soft enlargement of the spleen are usual. Embolic phenomena occur as in the subacute variety, but tend to produce metastatic abscesses. Meningitis, pericarditis, pleurisy and peritonitis are possible complications.

**Prognosis.**—This disease was invariably fatal in a few days or weeks, but treatment of the ætiological condition with antibiotic drugs is preventative, and curative if the endocarditis has not progressed too far (see Subacute Bacterial Endocarditis).

**Treatment.**—Treatment is essentially that of the primary condition and otherwise the same as for subacute bacterial endocarditis (see p. 885).

#### RHEUMATIC ENDOCARDITIS (ACUTE AND SUBACUTE)

Endocarditis involving the valves (valvulitis) is present in the majority of cases of rheumatic fever and is always present as the principal manifestation of rheumatic carditis (see pp. 48, 862). The valves are inflamed and their surfaces become roughened from exudates and adherent platelets; small beady vegetations develop, the valve becomes vascular and infiltrated with cells and Aschoff bodies. Mitral and aortic cusps are mainly affected. The earliest signs of mitral valvulitis are the development of a pansystolic murmur at the apex with or without a short mid-diastolic murmur (Carey Coombs). Aortic valvulitis is shown by the development of a basal systolic murmur which ends before the second heart sound and it is confirmed by the development of an early diastolic murmur. These valve murmurs are variable in the acute stages and may disappear with recovery (see Rheumatic Fever, p. 49).

#### OTHER FORMS OF ENDOCARDITIS

**Endocardial fibrosis** (fibro-elastosis, endocardial fibroplasia).—This condition is rare in Great Britain, but it is being recognised with increasing frequency in infancy and early childhood, and it may be of congenital origin. A similar condition occurs amongst negroes in central and South Africa and appears to be due to nutritional deficiency. The symptoms are those of an intractable and insidious heart failure.

**Acute disseminated lupus erythematosus** (Libman-Sacks disease, atypical verrucous

endocarditis).—Endocardial vegetations are sometimes found in this rare condition. The valves are not affected so that heart murmurs are not a prominent feature. The vegetations are large and fleshy but do not appear to fragment, for embolism is uncommon (see p. 933).

*Tuberculosis* of the endocardium is extremely rare. *Granulomatous verrucæ* and ulcers due to tubercle have been described. *Non-bacterial mural thromboses* are not uncommonly found at necropsy after prolonged cachectic illnesses such as nephritis, carcinomatosis and chronic pulmonary suppuration. These lesions develop in the terminal stage of these illnesses and are non-specific platelet agglutinations on the mural endocardium.

## DISEASES OF THE MYOCARDIUM

All forms of heart disease eventually affect the heart muscle and in some, such as coronary disease and rheumatic fever, the myocardium is directly damaged from the onset by ischæmia or inflammation. This section deals with those relatively rare conditions in which the myocardium seems to be affected primarily by inflammation, infiltration and metabolic disturbances.

### MYOCARDITIS

In the past this term has been misused. It should be applied only to conditions in which the myocardium is affected by inflammatory processes. Classification is unsatisfactory because the ætiology of myocarditis is obscure. Diagnosis is often difficult because signs and symptoms are sometimes slight or absent, and circulatory impairment may be due to vasomotor disturbances resulting from a primary disease rather than from myocarditis.

*Ætiology and Pathology.*—Rheumatic fever is the most important cause of myocarditis in Great Britain. The lesions are essentially interstitial and consist of either widespread or focal accumulation of cells and œdema; it is part of a total carditis (see below and Rheumatic Fever, p. 48). Bacterial endocarditis (see p. 885) also causes myocarditis which may be responsible for heart failure; the lesions are both parenchymal and interstitial with small focal accumulations of cells which may form a suppurative myocarditis in the pyogenic varieties. Some degree of myocarditis probably occurs in many specific bacterial, viral and rickettsial diseases, but it is not usually recognised and rarely causes significant deterioration apart from the fact that myocarditis occurs in the more serious cases of the particular infection. Diphtheria is an exception; its faucial, laryngeal or cutaneous forms frequently produce serious parenchymatous myocarditis which is not necessarily related to the severity of infection at the primary site (see below). The cause or causes of isolated interstitial myocarditis are unknown (see below, p. 891).

*Clinical Features.*—The clinical picture depends on the severity of the myocardial lesion and on its cause. Myocarditis leads to a diminished cardiac reserve and to dilatation of the heart with congestive cardiac failure when muscle damage is extensive and severe. Fever, malaise and other general symptoms depend largely on the ætiology. A dull præcordial ache is common but may be absent, or variable—it is more often present in interstitial myocarditis than in the toxic parenchymal lesions which do not usually involve the pericardium. Dyspnoea is usual but often not a prominent feature and it may be impossible to distinguish cardiac dyspnoea from that due to an associated pneumonitis, e.g. in pneumonia, typhoid and rickettsial disease. It is a most significant symptom in diphtheria.

Examination usually shows a tachycardia which is greater than expected from

the fever. The pulse tends to be soft and thready, and the blood pressure is normal or low with a tendency to low pulse pressures. *Pulsus alternans* may be present, extrasystoles are common and the more serious arrhythmias sometimes develop. The apex beat is diminished in force and may be shifted to the left from cardiac enlargement. The heart sounds tend to become soft and triple rhythm is usually present due to a third heart sound. Murmurs are often conspicuously absent but with increasing dilatation and the development of heart failure, mitral and tricuspid systolic murmurs tend to develop.

All degrees of heart failure may result from myocarditis, but acute left heart failure is rare. Congestive heart failure, shown by a rise in jugular venous pressure, may occur early in the disease and may be progressive or transient, depending on aetiology. In diphtheria the great veins may be collapsed when shock is associated with heart failure; this is usually a fatal combination.

**Radiology.**—Radiographic examination reveals the extent of cardiac enlargement and shows the presence of pulmonary congestion which, however, is not usually a prominent feature of myocarditis. In diphtheritic carditis and other acute cases with evidence of heart failure, examination should not be carried out except by means of portable apparatus at the bedside.

**The electrocardiogram** provides important evidence of myocardial disease and is pathological in almost all cases of myocarditis. Changes in the QRS complex are variable; the voltage may be diminished with notching of complexes and even intraventricular delay shown by widening of the QRS. The S-T segment and T waves are most frequently affected. The S-T tends to be depressed and T waves are flat or inverted in several leads. As in pericarditis the emphasis is on the widespread nature of relatively slight changes compared with the more localised and severe changes which are found in cardiac infarction. Arrhythmias and conduction defects are not uncommon.

**TYPES OF MYOCARDITIS.**—1. *Diphtheritic myocarditis.*—Some degree of myocarditis probably occurs in the majority of patients with diphtheria. The muscle fibres are diffusely damaged and histological examination may show little in contrast to the findings in interstitial myocarditis. In some it produces serious clinical features and may be fatal. Where recovery occurs it is usually complete, but occasionally there are permanent electrocardiographic changes. The first clinical signs tend to appear in 7 to 10 days. Arrhythmias occur early and heart block is common. Other signs of myocarditis may develop and are followed by those of congestive heart failure in severe cases. The haemodynamic state may be complicated by toxic depression of the vasomotor system so that the shock state is associated with central failure.

**Prognosis.**—The outlook for diphtheritic carditis which is causing symptoms and signs is poor, but if there is recovery from the acute illness, it is usually complete.

**Treatment.**—Prophylaxis is essential and consists of the early diagnosis and treatment of diphtheria with adequate antitoxin and bed rest for 1 month. There is no active curative treatment for carditis when this has developed. Patients should be kept at complete rest for at least 6 weeks. If there is congestive heart failure a mercurial diuretic should be given but digitalis is contraindicated.

2. *Rheumatic myocarditis* cannot be separated from the whole picture of rheumatic carditis which generally is dominated by endocarditis. The myocarditis is interstitial with Aschoff bodies in various stages of development scattered throughout the muscle, and particularly in the regions of the auriculo-ventricular junctions. Myocarditis is always severe and probably responsible for the outcome in cases dying during the acute and subacute phases of the disease.

3. *Isolated myocarditis* (Fiedler's myocarditis, primary myocarditis, idiopathic myocarditis).

These unsatisfactory terms indicate that the cause of the disease is unknown and it may not be a single disease but rather a similar myocardial reaction to various

causes. However, the pathological and clinical findings are fairly constant in the cases which have been described. At necropsy the heart is dilated and soft; the pericardium and endocardium are normal. Histological examination of the myocardium shows a diffuse interstitial cellular reaction which is mainly monocytic but various other cells are found. There is a variable degree of damage to the muscle cells and usually some degree of healing by interstitial fibrosis.

The symptoms are slight at first with a dull sternal aching and fatigue. Soon congestive heart failure develops and deterioration continues in spite of treatment until death occurs in a few weeks from the onset. Thrombo-embolic episodes are often a feature and there are phases of fever, but much of the course may be afebrile. The signs are as in other cases of myocarditis and congestive heart failure. The electrocardiogram shows pathological changes suggesting myocarditis, as described above. No specific tests for this disease are known. Isolated myocarditis must be differentiated from all causes of congestive heart failure, and the diagnosis is largely made by exclusion of other disease and the positive signs described above; a rapidly deteriorating febrile course is strongly suggestive but confirmation comes only with necropsy. The treatment for congestive heart failure is indicated but lack of response is characteristic of the disease.

**NON-INFLAMMATORY DISEASE OF THE MYOCARDIUM.—*Amyloidosis of the heart.***—Primary amyloidosis of the myocardium is an uncommon condition but has been recognised many times during recent years. In this form of amyloidosis there is no associated chronic suppuration and the heart is mainly affected, but amyloid may be found elsewhere, e.g. in vessels of the tongue and gums. At necropsy the heart is dilated and the muscle feels firm, but histological examination shows extensive replacement of the muscle cells by amyloid material. There are no symptoms or signs apart from those due to progressive heart failure and cardiac enlargement. The disease runs a long course, often with signs of heart disease for 3 to 5 years. The electrocardiogram shows signs of extensive myocardial damage. Bundle branch block or pathological Q waves in several leads may occur. The electrocardiogram may be indistinguishable from the pattern of myocardial infarction, but the changes tend to be more widespread in amyloidosis. Radiological examination shows cardiac enlargement. Histological examination from biopsy may show deposits of amyloid material in the walls of small vessels. There is no specific remedy but heart failure requires the usual treatment.

***Idiopathic hypertrophy of the heart.***—The conditions to which this descriptive term applies do not form a single ætiological group. The essential feature is the absence of any known cause of hypertrophy. Massive hearts are occasionally responsible for heart failure in infants and children; the condition has been called congenital idiopathic hypertrophy, but there is little evidence that it is a congenital abnormality.

***Familial cardiomegaly*** mostly affects young adults. There is great cardiac enlargement and the electrocardiogram often shows bundle branch block. Death is often sudden, or may follow progressive heart failure. Cardiomegaly together with myocardial infiltration and degeneration occurs in Friedreich's disease and in myotonia atrophica. Arrhythmias and various degrees of heart block are not uncommon in these neurological conditions, and occasional cases have led to heart failure or sudden death.

The myocardium may be affected in *scleroderma* by a similar process to that which is found in the skin. Cardio-vascular symptoms and electrocardiographic changes occur. Sarcoid infiltration of the heart may occur in generalised *sarcoidosis*; it is extremely rare.

***Von Gierke's Disease.***—This condition is due to a congenital error of metabolism resulting in abnormal glycogen storage. Both sexes are affected and the condition may be familial. Abnormal glycogen storage occurs in various organs including the

liver, kidneys and the heart. Involvement of the heart causes cardiomegaly and sudden death may occur. Diagnosis is suggested by the combination of unexplained cardiomegaly and hepatomegaly. No treatment is known.

W. W. BRIGDEN

## CONGENITAL HEART DISEASE

About three children in each thousand are born with congenital heart disease, but those with the more serious forms do not live long, and by 10 years of age the proportion is reduced to about one in each thousand. In about 2 per cent. of all patients with organic heart disease, the condition is congenital.

**Ætiology.**—The cause is nearly always a failure of development. In the past some types have been attributed to fetal endocarditis but this is almost certainly incorrect. Rubella during the second month of the mother's pregnancy is an uncommon cause and some other virus infections may act in the same way.

It seems, however, that heredity is the main cause. Rarely, but more often than would be expected by chance, parent and child or two sibs both have congenital heart disease. Generally the subject is the only known sufferer in the immediate family but statistics show that sibs and relatives are affected more often than the general population. Most other congenital abnormalities are found from time to time in association.

Lesions of the aortic valve and coarctation of the aorta are found more often in boys; patent ductus arteriosus and atrial septal defect are more common in girls.

**Diagnosis and Classification.**—Diagnosis has become more important with the progress of surgical treatment. Several forms of congenital heart disease, including those of most practical importance, can be diagnosed by simple clinical methods alone; others may be difficult and may require cardiac catheterisation or angiocardigraphy.

Increased understanding of some underlying principles has made classification more rational and comprehensible. The division into those with and those without central cyanosis is most important and if the cyanosis is only occasional or doubtful the patient must be kept under observation until it is decided.

Central cyanosis is best recognised in the tongue and mucous membrane of the mouth, in the conjunctivæ and in the nails *when the hands are warm*. The arterial oxygen may be as low as 50 to 60 per cent., and is generally under 90 per cent. when central cyanosis is obvious. Peripheral cyanosis may be very striking in the hands, cheeks, ears and lips, and is seen in Raynaud's syndrome, in many open-air workers, and in any thin child after exposure on a cold day. The arterial oxygen saturation is normal and it has little significance for diagnosis. It may be due to peripheral stasis only or more rarely to a general slowing of the circulation.

*Central cyanosis nearly always indicates a right-to-left (veno-arterial) shunt* and therefore gives a partial diagnosis at once. There must be an opening between the right and left sides of the heart and there must be something else raising the pressure on the right side so that the shunt is from right to left.

A second division is into those where the blood flow to the lungs is increased (pleonæmic) and those where it is diminished (oligæmic). This is of great practical importance, especially for cyanotic cases, since it can now be increased by operation. The distinction is made mainly by the appearances of the radiogram and by radioscopy, but a loud or widely split pulmonary second sound will suggest pulmonary hypertension or an increased pulmonary flow.

Oligæmic lungs are shown by light vascular markings in the lung fields. They are most common in the cyanotic group. Pleonæmic lungs are shown by large pulmonary arteries and increased vascular markings, often with pulsation that can be easily seen in the pulmonary branches.

*Pleoneæmic lungs indicate a left-to-right (arterio-venous) shunt* and so give part of the diagnosis at once. Atrial septal defect, ventricular septal defect and patent ductus arteriosus (all acyanotic) and transposition (cyanotic) are the main examples, and all these may give a somewhat similar radiological picture. If the amount passing through the shunt is small the changes in the lung fields may not be apparent.

Congenital heart disease can, therefore, be divided into the four following groups: i. Acyanotic. With no communication between the two sides of the heart. ii. Acyanotic. With a potential communication between the two sides (*i.e.* a foramen ovale that is not sealed). iii. Acyanotic. With a left-to-right (arterio-venous) shunt and pleoneæmic lungs. iv. Cyanotic. With a right-to-left (veno-arterial) shunt: most of these have oligæmic lungs but some have pleoneæmic lungs because there is also a left-to-right shunt.

**General Principles of Treatment.**—Even if an exact diagnosis is uncertain, most patients can be given reasonable advice about the degree of activity that is best for them and about the prognosis. Symptoms are generally more important than physical signs in judging this, although there may be a large heart with relatively few symptoms. A patient with striking physical signs may have little disability.

The best plan is to find what the child can do by gradually increasing its activity and then to keep the daily level somewhat below this and to insist on adequate rest and a long night in bed. This principle applies in the same way to the cyanotic children, even if they can do very little. In other respects they should be treated as far as possible as normal children. Some patients are still limited in their activity more than they should be because a systolic murmur has been heard; and improvement may simply mean that a child has broken free from unnecessary restrictions and is doing as much as he can without distress.

The child should be carefully treated when transient infections occur and sulphonamides and antibiotics should be used readily to minimise the risks of bacterial endocarditis, as nearly all forms except atrial septal defect are specially liable to this infection.

#### (1) ACYANOTIC. WITH NO COMMUNICATION BETWEEN THE LEFT AND RIGHT SIDES OF THE HEART.

*Ectopia cordis.*—The heart is situated outside the thoracic cavity and the patient is not likely to survive for long. Simpler defects of the pericardial sac are also found.

*Dextrocardia.*—When the heart is on the right side of the chest with complete transposition of all the viscera they form a mirror image of the normal. This has no clinical significance except that there is sometimes bronchiectasis. It must be distinguished from a heart displaced to the right by intrathoracic disease. It is inherited as a Mendelian recessive character and so is more common in the offspring of first-cousin marriages.

Less commonly the heart is on the right without the abdominal and other viscera being transposed, or the heart is on the left with the abdominal viscera transposed. It is then difficult for the circulation to function, for blood from the venæ cavæ will tend to enter the wrong atrium. There are nearly always other congenital abnormalities of the heart, large septal defects and perhaps pulmonary stenosis and transposition of the aorta and pulmonary trunk, and the patient is generally cyanotic.

*Congenital heart block.*—This is not very uncommon. Although the block is nearly always complete, the rate is faster than in most other forms, about 50 a minute or more after exertion. Stokes-Adams attacks are rare, and generally the prognosis is good. It is often associated with a small ventricular septal defect.

*Bicuspid aortic valves.*—These are not uncommon but generally cannot be recognised as they do not cause aortic regurgitation unless they become deformed by disease. Atheroma may occur early, and they are specially prone to bacterial endocarditis, so that the diagnosis may be suspected when this occurs on the aortic valves only in a patient without a rheumatic history.



*Aortic stenosis.*—Generally this is valvular but sometimes it is sub-valvular and due to a failure of development of the bulbus cordis. If there is a rough systolic murmur and thrill maximal in the aortic area in a child with few symptoms and a heart that is normal in size, the stenosis is more likely to be congenital than rheumatic, as the latter generally occurs with a seriously damaged heart. The slow-rising pulse and small pulse pressure are later signs of more severe stenosis. Many patients do well, and in the absence of cardiac enlargement, electrocardiographic signs of left ventricular strain, or other special features, it should call for little, if any, limitation of activity. Later, however, perhaps in the fourth decade, increasing fibrosis and calcification of the valve are likely to make the stenosis worse.

*Coarctation of the aorta.*—The aorta is narrowed so that the pressure on the proximal side is raised to overcome the obstruction. The narrowing varies in degree, and in severe cases there may be an hour-glass stenosis. The site of the coarctation is not just above the valve but farther round the arch at the isthmus where the ductus arteriosus joins the aorta, so that the left subclavian is above the constriction. A much lower pressure in the left than in the right arm would indicate obstruction above the origin of the left subclavian artery.

The auscultatory signs are similar to those of aortic stenosis, but may be slight. Sometimes the systolic murmur may be widespread and heard also over the back as it may be produced over dilated collateral arteries. The essential diagnostic feature is the high pressure in the upper part of the body with a low pressure and a delayed or absent pulse in the arteries of the legs; and if it is made an invariable rule to feel for the femoral pulse in all patients with a high brachial blood pressure, with unexplained aortic incompetence, or with abnormal pulsation in the neck, the diagnosis should not be missed. Dilated collateral vessels may be found over the chest or back, especially round the scapula, and these are often made more obvious if the patient bends forward with his arms hanging by his side. Notching of the lower border of the ribs on radiographs may be further confirmation, but the diagnosis should be made without this.

The prognosis is good in patients without symptoms where the lesion is found by chance after the age of 20, and not so good in those where symptoms develop in childhood, though slight dyspnoea or aching of the legs are hardly significant. The blood pressure does not rise progressively through life, though it may not reach its maximum till 15 or 20 years of age. A patient with a pressure of 180 mm. may show only slight left ventricular enlargement and may be able to lead an active life for many years.

*Aortic incompetence* is common and may be due to dilatation of the aorta or to changes in the aortic valves and may cause some of the symptoms. Congenital cerebral aneurysms are often present and may lead to fatal subarachnoid hæmorrhage, and though the risk of this is minimised by reduction of the blood pressure it is not entirely removed.

The condition can now be cured by operation but it is difficult to decide when it is indicated, as the prognosis is often good. Operation should be performed only by those with special experience, and even in such hands, the mortality is about 10 per cent., though this may continue to drop. If the patient has serious symptoms in childhood or if the blood pressure continues to rise much after 15 years of age, operation should be advised. After 20, the risks are greater and the anastomosis may be difficult or impossible, so that a greater degree of disability is needed to justify the risk.

(2) **ACYANOTIC. WITH A POTENTIAL COMMUNICATION BETWEEN THE TWO SIDES OF THE HEART (Cyanose tardive).**

*Pulmonary valvular stenosis* is often found with a closed ventricular septum as well as with Fallot's tetralogy (see p. 897). The stenosis may not be severe in spite of striking physical signs—a rough systolic murmur and thrill, maximal in the pulmonary area and sometimes a diminished and single second sound at this

This diagnosis can be made when cyanosis has been present from birth or from the first 18 months of life; when there is a systolic murmur of moderate intensity, often with a thrill, in the pulmonary area and a diminished or normal pulmonary second sound; when there is no diastolic murmur; when the heart is not much enlarged; when there is no prominence of the pulmonary arc or pulmonary arteries (though less than half of them show a real sabot-shaped heart, the remainder having a relatively straight left border or even slight prominence of the pulmonary arc due to dilatation of the infundibulum beyond the stenosis); and, most important of all, when the density of the lungs on radiology is lighter than usual. It is curious that four-fifths of the patients with Fallot's tetralogy should have the habit of squatting, though it is seen also in other forms of cyanotic heart disease, even in Eisenmenger's complex where there is no pulmonary stenosis.

These criteria should enable the diagnosis of Fallot's tetralogy to be made with confidence, and it is here and in simple pulmonary stenosis that surgical treatment is most successful.

*Pulmonary atresia.*—Cases with pulmonary atresia as well as those with pulmonary stenosis have been included as Fallot's tetralogy but the former must now be differentiated because the small and thin-walled pulmonary artery that is generally present beyond the atresia makes subclavian-pulmonary anastomosis more difficult but not always impossible. This diagnosis must be considered when there is the general picture of Fallot's tetralogy but no systolic murmur and a rather loud second sound in the pulmonary area, the aorta being more over to the left than usual. There may also be a continuous murmur, because the circulation to the lungs is helped either by a patent ductus arteriosus or by a bronchial artery that is large enough to produce such a murmur.

The only operative treatment is subclavian-pulmonary anastomosis, because the atresia generally involves too broad a section of the pulmonary valve region for a direct operation to be practicable.

*Tricuspid atresia.*—When there is the general picture of Fallot's tetralogy but a rather larger heart with hypertrophy of the *left* ventricle, and *left* ventricular preponderance in the electrocardiogram, the diagnosis is generally tricuspid atresia with a small or non-functioning right ventricle; there must be a defect of the atrial septum so that blood from the right atrium can re-enter the circulation. The aorta and pulmonary trunk may both arise from the left ventricle, in which case the lungs will not be oligæmic and the patient cannot be helped by operation. More often there is pulmonary stenosis, or the pulmonary trunk arises from a diminutive right ventricle reached through a ventricular septal defect.

This last group can be helped by subclavian-pulmonary anastomosis because they are suffering from a reduced pulmonary blood flow; but the improvement to be expected is less than and may not last as long as in Fallot's tetralogy. In both groups the prognosis is worse than in Fallot's tetralogy.

*Pulmonary valvular stenosis with a right-to-left inter-atrial shunt.*—This is the most common condition after Fallot's tetralogy in the oligæmic group. The physical signs are the same as in the acyanotic cases (see p. 895), but as the condition *worsens* the murmur and thrill may become much less evident. The electrocardiogram often shows the pattern of right ventricular strain, with deep inversion of T in leads II and III, and in the chest leads from V1 to V4.

The diagnosis should be suspected when cyanosis has developed later, sometimes not until early adult life. When this happens the patient generally becomes progressively worse, sometimes rather quickly, and operation should be considered at once. This must be pulmonary valvotomy, as subclavian-pulmonary anastomosis is liable to be followed by congestive heart failure.

**SURGICAL TREATMENT OF CYANOTIC CASES WITH PULMONARY OLIGÆMIA.**—The outlook of many of these children has been completely changed by the introduction

of subclavian-pulmonary anastomosis (Blalock-Taussig operation), and by Brock's operation for direct relief of the stenosis: here the stenosed valve is divided (valvotomy), or infundibular resection is performed, or both procedures may be needed. All these operations increase the blood flow to the lungs, and this brings more oxygen to the circulation and so the disability and cyanosis are both greatly relieved.

Whenever the disability calls for it, operation should be advised. Any indication that such a child is losing ground and is unable to walk as far as before is a sign of serious significance, and if anything is to be done it must be done quickly, as such deterioration is generally progressive until the child dies. This, unfortunately, applies only to children over the age of 3. However bad the outlook in young children, and this is often because of frequent attacks of increased cyanosis with unconsciousness, operation should be deferred, as in infants it is more dangerous and the improvement is often less lasting, because the anastomosis is too small as the child grows larger. For this reason operation should rarely be performed until the age of 3, or, if possible, 5 years of age. From then until 10 is perhaps the ideal age, though the results seem nearly as good in older children, and it is only in those over 20 that the risks seem much greater and the degree of improvement less.

The operation is a serious one with a mortality of about 5 per cent. in Fallot's tetralogy and much more in pulmonary atresia and the more complex conditions. The results are excellent in about three-quarters of these patients so that they may be able to walk a mile or more instead of 100 yards or so, and get about all day almost normally. The polycythæmia quickly diminishes or disappears and the clubbing of the fingers improves more slowly. The arm to which the subclavian has been divided gives no trouble.

It is important for the parents to realise that the heart condition has not been cured and that although the outlook is much improved it is still uncertain for how long this will last. The diminished blood flow to the lungs has been relieved by operation but the ventricular septal defect remains and the right ventricle is still working against the systemic pressure, whether the operation is an anastomosis or a direct one. One cannot, therefore, expect that the patient will be able to lead a more active life without some increase in the work of the heart. The heart increases in size in the first few months but generally not greatly, and so far, follow-up studies show that for 4 or 5 years the increase is not generally progressive or serious. Until however the ventricular septal defect can also be closed, the patient still has a limited outlook, and cardiac enlargement and increasing right ventricular strain will follow some day, but fortunately in most cases, not for several years.

(4B) CYANOTIC CASES WHERE THE PULMONARY BLOOD FLOW IS NORMAL OR INCREASED.—The diagnosis is best made by radioscopy, but physical examination may help, as large hearts and pulmonary diastolic murmurs are much more common in this group. If the pulmonary second sound is much increased and booming, or widely split, or if it is palpable, the patient probably has a raised pulmonary arterial pressure and an adequate blood supply to the lungs, so cannot be helped by operation.

In this group, accurate diagnosis is at present less important. Transposition and Eisenmenger's complex are the commonest lesions, the latter being the more likely diagnosis in adults.

*Transposition of the aorta and pulmonary trunk.*—In small children this is one of the commonest forms of morbus cœruleus but the mortality is heavy in the first years of life and relatively few survive. When both main vessels are completely transposed life would, of course, be impossible without some communication between the two sides. This may be through an atrial septal defect and a patent ductus arteriosus, when the outlook is very bad; or through a large ventricular septal defect when many patients who survive the first 2 or 3 years of life continue to carry on surprisingly well. The circulation is sometimes made easier by one of the main arteries being only partly transposed, i.e. overriding a ventricular septal defect.

Several forms of surgical treatment have been tried but at present the results are not good enough to justify the procedure.

*Eisenmenger's complex*.—This consists of the combination of ventricular septal defect, right ventricular hypertrophy, and overriding aorta. Patients with this condition have generally started as simple ventricular septal defects (see p. 896), for the relative pressure in the two ventricles will decide whether there is a right-to-left shunt and cyanosis much more than the degree to which the aorta is overriding, as nearly all ventricular septal defects are high up in the septum just below the aortic valve. Sometimes the pressure on the right side has been high from infancy and they have always been cyanotic and then they may be difficult to distinguish from cases of Fallot's tetralogy.

More often they become cyanotic later in life, perhaps when about 20. When this cyanotic stage is reached the pulmonary second sound is generally much increased, the pulsation of the pulmonary artery is easily palpable and as pulmonary hypertension develops, the pulmonary blood flow diminishes. The patient becomes seriously limited but may be able to carry on quietly for some years. Restriction of activity and symptomatic treatment are the only useful measure, that can be taken.

MAURICE CAMPBELL.

## THE HEART IN MISCELLANEOUS CONDITIONS

### HYPERTHYROIDISM

Elevated basal metabolism is responsible for functional changes in the circulation in hyperthyroidism, but the high incidence of auricular fibrillation in thyrotoxicosis suggests that the heart may be directly affected by toxæmia. Increased tissue demands for oxygen are met by an increased cardiac output, which is characteristic of thyrotoxicosis. Circulating blood volume is increased, and peripheral vasodilatation, amounting to extensive arterio-venous shunting, leads to an increased venous return. The increased cardiac output is achieved largely by an increase in heart rate, although there is some evidence that stroke volume is also elevated. The circulation becomes hyperdynamic and there is a greatly diminished circulation time. Tachycardia, hyper-volaemia and increased circulation velocity are well tolerated by the heart in young subjects with thyrotoxicosis, although the metabolism of the myocardium is presumably pathological. The manifestations of thyrotoxic heart disease are auricular fibrillation and cardiac failure; these occur almost exclusively in the older age groups, suggesting that degenerative changes in the heart are the cause of breakdown in the circulatory compensations for hyperthyroidism. The clinical features of congestive cardiac failure develop in spite of the high cardiac output. This apparent paradox is characteristic of thyrotoxic heart failure. Although the cardiac output is often higher than normal, it is inadequate for the demands of the thyrotoxic state.

*Symptoms*.—Palpitation, weakness and dyspnoea are common symptoms in thyrotoxicosis but these do not indicate heart disease. Palpitation may be continuous and regular and without apparent cause, or it may be paroxysmal or continuous and irregular when due to multiple ectopic beats or auricular fibrillation. Palpitation may occur in young patients, but it is more common in older patients with toxic adenoma. Dyspnoea and weakness are present in uncomplicated thyrotoxicosis, but true cardiac dyspnoea develops only with the onset of cardiac failure, which is confined to the older age groups. Ischaemic cardiac pain may also occur in patients after middle life, and is probably due to latent coronary disease which is revealed by the increased cardiac work.

In thyrotoxic heart disease the general signs and symptoms of thyrotoxicosis may be obvious or they may be slight and easily overlooked. In particular the thyroid gland may not be visibly enlarged and only careful examination may reveal a small adenoma, or radiography may show an intrathoracic gland.

The signs of a hyperdynamic circulation are present; there is tachycardia, an increased pulse pressure with a moderately elevated systolic pressure and palpable digital arteries. The apex beat is increased in force and rate and the whole præcordium may pulsate with the heart beat. The first heart sound is loud, and it is usually followed by a systolic murmur which is best heard over the pulmonary artery and is in mid-systole. The second heart sound is not remarkable, and there are no murmurs in diastole unless there is associated valvular disease.

Auricular fibrillation is common in patients over the age of 45. It may be paroxysmal or permanent and is characteristically associated with chaotic high ventricular rates in untreated patients. Paroxysmal tachycardia and auricular flutter occur occasionally in hyperthyroidism. Congestive cardiac failure occurs when there is auricular fibrillation and severe thyrotoxicosis in the older age groups; it is shown by jugular venous congestion, pulmonary congestion and œdema, but there is often the distinctive paradox that the circulation remains hyperdynamic in spite of cardiac failure. Other forms of organic heart disease, especially hypertension, coronary disease or chronic valvular disease, are sometimes associated with thyrotoxicosis.

**Radiology.**—Cardiac enlargement is not present unless there is cardiac failure or associated heart disease. Thyrotoxic heart failure causes moderate generalised cardiac enlargement. An intrathoracic extension of the thyroid gland may be shown.

The electrocardiogram is not characteristic. Arrhythmia is confirmed when present. Changes associated with ventricular hypertrophy or ischæmia, such as T wave flattening or S-T depression, are present if there is additional organic heart disease.

**Diagnosis.**—Thyrotoxic heart disease is recognised in the presence of obvious hyperthyroidism by auricular fibrillation or the signs of congestive heart failure. However, many patients with thyrotoxic heart disease do not have obvious general signs of hyperthyroidism and the condition is therefore easily missed. Persistent tachycardia, unexplained auricular fibrillation, or unexplained heart failure, even in the presence of organic heart disease, indicate the possibility of hyperthyroidism, which may be further suggested by a history of weight loss, increased appetite, nervousness and other symptoms of Graves' disease. The diagnosis may be confirmed by radio-active iodine studies and tests of basal metabolism, which, however, are difficult to evaluate in the presence of heart failure. The differential diagnosis of the thyrotoxic state is considered elsewhere (see p. 494).

**Prognosis.**—The degree of damage to the heart in thyrotoxicosis depends on the age of the subject and the duration of the malady rather than on the type of goitre or the severity of the symptoms of hyperthyroidism. It is more serious with advancing age. The prognosis depends greatly on the successful treatment of the hyperthyroidism; congestive cardiac failure responds well and auricular fibrillation may cease spontaneously after treatment. The prognosis is poor if the hyperthyroidism is unrecognised and untreated, for the usual remedies of cardiac failure and auricular fibrillation are largely ineffective.

**Treatment.**—The primary object of treatment is the correction of hyperthyroidism (see p. 494). Although partial thyroidectomy is highly successful, the mortality is greater in patients with thyrotoxic heart disease than in those with uncomplicated Graves' disease. Surgical treatment will probably be replaced by medical methods in all patients with thyrotoxic heart disease. After correction of hyperthyroidism, congestive heart failure subsides and auricular fibrillation tends to be replaced by sinus rhythm. If the arrhythmia persists, quinidine should be used (see p. 828).

## HYPOTHYROIDISM

The heart is affected in the majority of cases of advanced myxœdema. Basal metabolism is reduced and there is a corresponding reduction in cardiac output and peripheral blood flow. The circulating blood volume is low and venous return is diminished. At necropsy the heart is dilated and there is usually a large pericardial effusion. Coronary atheroma is common. Histological examination shows non-specific degenerative changes in the muscle fibres, and patchy fibrosis which is indistinguishable from that due to ischæmia.

**Clinical Features.**—Angina pectoris occurs but other symptoms of heart disease are rare because physical activity is greatly reduced by the disease. Obvious congestive cardiac failure is unusual. The pulse is small and slow (50 to 60 a minute) and the venous pulse is not remarkable. The apex beat is not usually palpable and the heart sounds are soft. On radiography there is cardiac enlargement and diminished pulsation; the stencilled outline and globular shape of the heart is partly due to pericardial effusion, but in advanced cases there is also some dilatation of the heart. The pathogenesis of the effusion and cardiac dilatation is obscure.

The *electrocardiogram* shows bradycardia and low voltage of all complexes in all leads, but the T waves are especially affected and may be isoelectric or inverted in leads showing left ventricular complexes, *i.e.* in standard leads I and II and chest leads 4 to 7. These pathological changes become normal during treatment with thyroid. The electrocardiographic changes in myxœdema may be partially due to pericardial effusion. Diagnosis and treatment are described on pp. 497–498.

## ADDISON'S DISEASE

Cardiac disorder is not an outstanding feature of either diminished or increased function of the adrenal glands. In Addison's disease there are no cardiac symptoms, but the heart is reduced in size and pulsation is diminished as shown by radiographic screening. The *electrocardiogram* shows varying changes which depend on the degree of electrolyte disturbance; the level of serum potassium appears to be the most important factor. All complexes tend to be of low voltage and the T waves may be isoelectric or inverted. Treatment with cortical hormones may at first cause further pathological changes in the *electrocardiogram*, but if general recovery occurs, the *electrocardiogram* tends to become normal.

cardiogram may show profound ischaemic changes with S-T depression and T wave inversion in leads I, II and V5-V7. Recovery is usual but permanent muscle damage may occur.

#### BERIBERI HEART DISEASE

Wet beriberi is often associated with congestive cardiac failure. The condition occurs in Great Britain in mental patients, alcoholics and in other conditions associated with malnutrition. The symptoms are those of heart failure, the onset of which may be gradual or occasionally very acute. The heart is dilated; murmurs are not conspicuous but there is tachycardia and commonly a summation gallop rhythm. The clinical features of congestive heart failure appear, although the peripheral pulses and skin temperature suggest that the cardiac output is elevated above normal. The diagnosis should be considered in any patient with unexplained heart failure, especially if there is evidence of avitaminosis or nutritional disorder (see also p. 469).

#### TRAUMATIC HEART DISEASE

The heart may be injured by direct penetrating wounds or by non-penetrating blows to the praecordium. *Penetrating wounds* are mostly caused by stabbing, gunshot or shell fragments, and rarely by fracture of adjacent sternum or ribs, the passage of a foreign body from the oesophagus, or paracentesis of the pericardium. Most deep, penetrating injuries are rapidly fatal, but recovery occurs in a considerable proportion when the injury is relatively superficial, especially when due to stabbing. Any part of the heart may be damaged. Penetration of the myocardium results in haemopericardium and cardiac tamponade (see p. 879). Wounds adjacent to the heart or grazing the pericardium tend to cause a serous pericarditis which is recurrent if a foreign body remains imbedded in adjacent tissues. The symptoms and sign are those of pericarditis, with or without an effusion (see p. 878).

**Treatment.**—The possibility of injury to the heart should be considered in all cases of penetrating chest injury. Haemopericardium with tamponade requires urgent paracentesis followed by surgical evacuation of clot and repair of the wound as soon as possible. Deep, penetrating wounds may damage any structure of the heart and death is the usual result.

*Non-penetrating injuries* of the heart sometimes present difficult medico-legal problems. A history of trauma to the chest followed by cardiac symptoms, which may be due to neurosis or natural heart disease, should be interpreted with the greatest caution. Blunt injuries to the anterior chest wall by heavy blows or crushing may injure the heart by causing sudden arrhythmia, contusion of the pericardium, myocardium or coronary arteries, and rarely by causing rupture of one of the valves, one of the cardiac chambers or the aorta. A previously diseased heart is more likely to be damaged by blunt trauma than a normal heart which, however, is not immune.

**Arrhythmia:** Palpitation and tachycardia is common after injury and is due to emotional disturbance, not infrequently associated with the possibilities of compensation. However, serious arrhythmia may be precipitated by blows of varying severity and by sudden immersion in cold water. Arrhythmia is probably induced by reflex action in most cases, but when the trauma is over the praecordium, contusion of the myocardium may be the cause. Transient auricular fibrillation is the commonest disturbance; sometimes it occurs in young subjects with a normal heart. Ventricular tachycardia and sudden death from ventricular fibrillation have been recorded after relatively trivial injury. Elderly subjects and those with coronary artery disease are probably the most vulnerable. Transient heart block may follow indirect trauma; the cause is presumably contusion of the conducting tissues but reflex inhibitions cannot be excluded.

**Contusion :** Bruising of the pericardium and epicardium may result in transient pericarditis, pericardial effusion or hæmopericardium. Spontaneous recovery is usual. Contusion of the myocardium causes varying degrees of muscle damage with or without damage to the coronary vessels; the right auricle, right ventricle, septum or left ventricle may be involved. The clinical features and electrocardiographic changes may be similar to those of cardiac infarction; cardiac pain of all degrees from a dull præcordial ache to severe widespread pain associated with fever and leucocytosis may result. Angina pectoris occasionally follows blunt injury which has involved the coronary vessels.

The *electrocardiogram* shows various changes in the ventricular complex, ranging from transient T wave flattening or inversion, and S-T elevation or depression, to the development of pathological Q waves when there is extensive muscle necrosis. These changes are best seen in præcordial leads, but occasionally injury to the præcordium results in electrocardiographic changes indicating isolated damage to the septum or posterior wall of the ventricle.

**Valve rupture** may follow blunt injury or excessive effort in subjects with pre-existing heart disease. The aortic valve is most likely to be damaged in patients with syphilitic aortitis. The resulting acute aortic incompetence causes severe chest pain and left ventricular failure. Rupture of the mitral valve chordæ with resulting acute mitral incompetence has been recorded but it is also extremely rare.

**TREATMENT OF DISORDERS FOLLOWING NON-PENETRATING INJURY.**—Arrhythmia is usually of brief duration but if prolonged the appropriate anti-arrhythmic drugs should be used (see p. 828). Patients with cardiac contusion require bed rest for 3 to 6 weeks, depending on the severity of the damage. In rare cases where there is cardiac tamponade, paracentesis is indicated.

#### PSYCHONEUROSIS AND THE HEART

**Synonyms.**—Cardiac Neurosis, Neurocirculatory Asthenia, Effort Syndrome, Da Costa's Syndrome.

The common symptoms of palpitation, flushing, sweating and hyperventilation associated with transient anxiety are well known to all. These physiological symptoms of alarm merge imperceptibly into the pathological when they become persistent and present without reasonable provocation. The somatic symptoms of increased cardiac activity induce further anxiety in susceptible individuals; the pressor reaction is reinforced and the mechanism becomes self-perpetuating. In some individuals alarm produces a depressor response in the vascular system as shown by a tendency to fainting; but there is much overlap between these interacting cardiovascular responses which are the manifestations of instability of the autonomic nervous system resulting from psychoneurosis.

The common psychological disturbance associated with cardiac symptoms is excessive anxiety with or without depression. In some patients the disorder is relatively superficial and is a transient reaction to external stress in a relatively sound personality, but in others the disorder is severe, endogenous and permanent. Functional cardio-vascular symptoms occur in susceptible subjects when there is an excessive emotional reaction to real heart disease, when there is fear of sudden death or of a particular form of imagined heart disease, and it is in its most complete form in effort syndrome, which is essentially psychoneurosis with cardiac symptoms and signs of severe autonomic disturbance.

**Clinical Features.**—Most patients have several symptoms, but any of the following symptoms and signs may occur alone, in combination or in any degree of relative severity.

**Pain.**—Psychogenic "heart" pain is variable and contrasts at all points with true cardiac pain. It is rarely the central theme of a clinical history as in ischæmic



heart disease, and many patients wander off the subject into other troubles, or may be readily deviated into a discussion of other symptoms real or imaginary. Psychogenic pain is usually present for long periods; it may be made worse by effort but never brings the patient to a halt; it is usually in the left infra-mammary region and rarely radiates elsewhere, although some patients complain of discomfort in the left arm. It is described as stabbing, pricking, a dull ache or sometimes in bizarre terms which cannot be applied to pain at all, but it is never crushing or constricting as in angina pectoris. The mechanism of functional pain is obscure; often its severity and significance to the patient appears to diminish under interrogation. The important differential diagnosis is with angina pectoris, and musculo-skeletal lesions should be kept in mind.

*Dyspnoea.*—Breathlessness without effort or after slight effort is common. Respiration is often shallow, irregular and interrupted by deep sighs. It is never like the distressing dyspnoea of heart failure but a sense of suffocation is common. Occasionally functional hyperventilation may be prolonged to the point of tetany, but this symptom is unusual in effort syndrome, occurring mostly in monosymptomatic psychoneurotic females.

*Palpitation* from tachycardia and cardiac overaction is probably the commonest functional symptom of "cardiac neurosis". Palpitation is particularly responsible for the perpetuation of the vicious circle of anxiety and cardio-vascular symptoms. Exhaustion and weakness are also common complaints and transient giddiness, sweating and headaches are other common manifestations of vasomotor disturbance.

*Signs.*—The heart is usually normal but where functional symptoms are associated with heart disease the apparent severity of symptoms is incompatible with the physical findings. The general appearance of dejection, anxiety and tension often suggests the underlying psychogenic nature of the symptoms. Peripheral vasomotor disturbances are common: sweating is usually confined to the axillæ and palms of the hands; desquamation and eczematization of the palmar skin is common. Tachycardia, a hyperdynamic apex beat and high normal systolic level of blood pressure are the main cardio-vascular signs.

*Diagnosis.*—The diagnosis is made on a detailed analysis of the symptoms; their psychogenic nature is usually obvious. The signs of anxiety, autonomic disturbance and the absence of heart disease are confirmatory. When functional disorder and organic heart disease coexist, the symptomatology and severity of the organic lesion are incompatible. Effort syndrome must be distinguished from organic heart disease, hyperthyroidism and chronic disease causing loss of weight, weakness and tachycardia, such as pulmonary tuberculosis and reticulosis.

*Prognosis.*—Prognosis is concerned with the persistence of symptoms and ability to perform useful work, and this depends on the severity of the underlying psychiatric disorder. When symptoms are an acute reaction to external stress and there is no past history of psychopathology the prognosis is relatively good after the precipitating factors have been removed. When symptoms are insidious, unrelated to immediate external stress, and when there is a long history of psychoneurotic traits the outlook is correspondingly poor.

*Treatment.*—The first step in treatment is to give an explanation of the psychogenic nature of the symptoms, reinforced by an assurance that there is no organic heart disease. When the disorder is acute and in a relatively sound personality symptoms are normally cured by explanation and removal of the source of immediate stress. Rest is not generally indicated but sound sleep should be secured by sedation. In patients with long-standing psychoneurotic ill health the treatment is psychological, and reassurance about the heart is of little help and often tends to result in the appearance of other symptoms.

WALLACE BRIGDEN.

## DISEASES OF THE BLOOD VESSELS

Diseases of the blood vessels are closely related to diseases of the heart, and combined cardio-vascular disorders now form the largest group of fatal diseases. Arterial degeneration, mainly by its effects on the heart and brain, is the commonest underlying factor. With advancing years there is a steadily rising incidence of ischæmic heart disease and cerebral vascular disorders, of the same order as the incidence of cancer. Examination of the Registrar General's returns over the past 20 years does not indicate any increase in deaths due to arterial disease apart from the greater incidence in the later decades due to longer survival, largely resulting from more effective treatment of infectious disease.

The mechanisms involved in the production of arterial degeneration are obscure, but advancing age, diabetes and high blood pressure are the chief contributory causes. High blood pressure is the result of increase in arteriolar tone. This may be secondary to renal disease or more rarely to endocrine dysfunction; but in the great majority of cases of arterial hypertension no organic cause for the increase in arteriolar resistance can be demonstrated. High blood pressure, whatever its origin, is a major factor in determining the age of onset and severity of atheroma, and coronary atheroma is the commonest cause of heart disease. Hypertension therefore not only increases the work which the heart must perform to overcome the increased peripheral resistance, but also leads to steady deterioration in the blood supply to the myocardium owing to coronary artery degeneration. Since atheroma is a generalised disorder, peripheral vascular disease, by which is usually meant occlusive arterial disease of the limbs, will frequently be associated with ischæmic heart disease and with the effects of arterial degeneration in other organs.

Maintenance of circulatory function involves the peripheral vessels no less than the heart. For example, after severe hæmorrhage or fluid loss, the blood pressure is maintained by peripheral vasoconstriction. Failure of this compensatory vasoconstriction leads to a fall in blood pressure and is a major factor in the production of shock.

**CLASSIFICATION OF ARTERIAL DISEASE.**—Pathological processes in the arteries can be classified as follows:

(1) *Congenital.*—This group of arterial diseases is relatively small. It includes a number of developmental defects such as congenital aneurysm of the cerebral arteries, coarctation of the aorta and vascular tumours such as cirroid aneurysm.

(2) *Traumatic.*—Injuries to the peripheral vessels by penetrating wounds, particularly in the lower limbs, may lead to arterial obliteration or to formation of an arterio-venous aneurysm.

(3) *Inflammation.*—The arteries are particularly resistant to specific bacterial infections. Syphilis is exceptional in producing inflammation of the media of the aorta (mesaortitis) with destruction of elastic tissue; it also involves the cerebral vessels, producing endarteritis and thrombosis. Tuberculosis is also a cause of endarteritis. Arteritis may result from obstruction by infected emboli in bacterial endocarditis and weakening of the wall leads to mycotic aneurysm. Non-specific arteritis is a feature of a large and diverse group of disorders which are classified as allergic or collagen diseases. Sensitisation to some bacterial or chemical antigen is probably the common ætiological factor, and histologically, necrotic changes in the capillaries, arterioles or arteries are associated with a degeneration of collagen which leads to widespread changes throughout the body. Rheumatic fever, rheumatoid arthritis, periarteritis nodosa, disseminated lupus erythematosus, scleroderma and dermatomyositis are all diseases of this type.

*Necrotising arteriolitis and endarteritis* are also the characteristic lesions of malignant hypertension. Although morphologically there is a close similarity with the vascular lesions of the collagen diseases, the mechanism of their production in hypertensive states is quite different, being most probably related to excessive intra-vascular pressure which leads to acute ischaemia of the vessel wall.

(4) *Degeneration*.—By far the commonest and most important arterial degeneration is atheroma. This is a primary degeneration of the intima. Arterial stress or "wear and tear" is the chief predisposing factor, so that the maximum incidence is seen in old age and chronic hypertension. Disordered cholesterol metabolism may also play a part, and patients with diabetes, myxœdema and hypercholesteræmia are particularly prone to develop atheroma. Medial degeneration is less common. It is a disorder of old age and is usually associated with atheroma.

(5) *Neoplasm*.—True neoplasms of the arteries are rare. Angiomata affect the capillaries and are commonly found in the skin. Larger tumours, so-called cavernous angiomata, occur in the liver. Capillary angioma (hæmangioblastoma) occurs in the cerebellum in association with similar lesions elsewhere.

(6) *Local disorders of vascular tone*.—Excessive vasoconstrictor response to cold or mechanical stimuli produce digital asphyxia (Raynaud's phenomenon). Arterial spasm may also complicate arteriosclerosis. Other disorders of peripheral tone are erythromelalgia and erythrocyanosis. Disturbances of vascular tone may occur as premonitory symptoms in the collagen disorders.

## SYSTEMIC ARTERIAL HYPERTENSION

**THE NORMAL BLOOD PRESSURE.**—There is a wide range of blood pressure in healthy subjects varying usually from 100 to 145 mm. Hg. systolic and 60 to 90 diastolic. The average normal is about 125/75 and a figure of 140/90 in an otherwise healthy adult may be taken as the upper limit of normal. A slight increase tends to occur with age. In the same individual, transient variations in blood pressure are common; nervousness, excitement, exertion, fatigue, cold and smoking may raise the normal level 20 or 30 points or more, but in these conditions the systolic pressure is affected more than the diastolic.

The systolic blood pressure is chiefly determined by the force of contraction of the left ventricle. The diastolic pressure is regulated by the arteriolar resistance, which converts the intermittent output of the heart into a continuous capillary blood flow. During systole the large musculo-elastic arteries are distended and during diastole their elastic recoil helps to maintain the arterial pressure.

**SYSTOLIC HYPERTENSION.**—A raised systolic pressure may be associated with a low, normal or high diastolic pressure. Increased emptying of the arterial system during diastole, either centrally as in aortic incompetence or peripherally due to vasodilatation as in thyrotoxicosis or severe anaemia, tends to lower the diastolic pressure and this is compensated by increase in systolic pressure. In such conditions, therefore, the pulse pressure is greatly increased. If the diastolic pressure falls considerably the pulse has a large volume and may be "water hammer" in type. A high systolic pressure with a normal diastolic pressure is seen in elderly patients in whom arteriosclerosis has impaired the elastic properties of the large arteries. Maintenance of the diastolic pressure then requires the production of a higher systolic pressure by the heart.

**DIASTOLIC HYPERTENSION.**—Apart from the various disorders enumerated above, systolic hypertension is always associated with elevation of the diastolic pressure, the primary dysfunction being increased arteriolar resistance. The common forms are essential hypertension and renal hypertension; less frequently diastolic hypertension results from endocrine disease.

(1) *Essential hypertension*.—This is by far the commonest type of high blood pressure. The term essential hypertension is used to indicate the absence of any discoverable extravascular cause such as renal or endocrine disease. In benign essential hypertension (Hyperpiesia of Allbutt) clinical evidence of renal involvement is nearly always lacking. In malignant essential hypertension secondary arterial damage leads to rapidly progressive renal destruction; hypertensive encephalopathy and retinopathy develop as a result of vascular disturbance in the brain and retinae.

(2) *Renal Hypertension*.—The great majority of patients with renal disease develop high blood pressure. The usual cause is acute or chronic glomerulo-nephritis. Hypertension may be encountered in chronic pyelonephritis, congenital cystic kidney, tumours of the kidney, hydronephrosis and amyloid disease. Unilateral renal disease may also produce high blood pressure, the underlying lesion usually being pyelonephritis with congenital deformity of the kidney or more rarely tuberculosis, hydronephrosis, obstruction to a main renal artery or renal tumour.

(3) *Endocrine hypertension*.—High blood pressure is a feature of adrenal cortical hyperfunction (Cushing's syndrome). This syndrome may be due to a tumour or simple hyperplasia of the adrenal cortex, or to cortical hyperfunction, without discoverable organic lesion. In severe progressive cases malignant hypertension may develop. Administration of cortisone or corticotrophin sometimes causes a sharp rise in blood pressure. Phæochromocytoma of the adrenal medulla or of ectopic medullary tissue may lead to attacks of paroxysmal hypertension. Eventually in this condition the hypertension becomes fixed at a high level and may pass into the malignant phase. The blood pressure may be raised in hyperthyroidism; usually the systolic pressure alone is raised, but there may be an associated benign essential hypertension. High blood pressure is a frequent complication of diabetes and in this disease renal arterial and glomerular sclerosis may be an important contributory factor.

(4) *Other causes of diastolic hypertension*.—In coarctation of the aorta the blood pressure may be considerably raised in the arms. In the lower limbs the systolic pressure is low but there is commonly slight diastolic hypertension which is probably due to renal ischæmia.

Organic disease of the brain may give rise to acute elevation of blood pressure. This is particularly encountered with rapidly expanding lesions, e.g. hæmorrhage into cerebral tumours, and with sudden increase in intracranial pressure such as occurs after subarachnoid hæmorrhage. Hypertension in renal disease is discussed on p. 1111. Further reference to endocrine disorders which produce hypertension will be found on pp. 516-518.

## ESSENTIAL HYPERTENSION

The nomenclature of this condition is somewhat confused owing to the common use of the term essential hypertension in different senses. Thus it is sometimes applied to benign hypertension or it may be used to cover all forms of non-renal hypertension. This confusion will be avoided if the term essential hypertension is restricted to those patients in whom no primary cause for the hypertension can be discovered. Such a definition would exclude primary renal and endocrine causes of all kinds. It would, however, include the malignant as well as the benign phase of the disease.

*Ætiology*.—The cause of essential hypertension is unknown. There is no evidence that it is referable to organic disease of the renal arteries or arterioles. There are, however, certain facts concerning the development and incidence of essential hypertension which are important. There is a clearly recognised hereditary factor or more probably a combination of factors. The incidence is highest in the sixth decade and the disease is slightly more common in women, but more severe in its

course and complications in men. There is some racial variation, hypertension being rare in Chinese and in negroes in their native countries, although under western civilisation hypertension may be more common and more severe in negroes than in whites. In the benign phase hypertension is often labile and large variations may be produced by nervousness, emotion or activity. Later in the disease the level of blood pressure tends to become fixed even at rest, fluctuations diminishing in size and finally disappearing. There is evidence to suggest that transient hypertension occurring in times of stress may later become persistent; nevertheless, no consistent psychogenic factor can be demonstrated in patients with high blood pressure particularly when this is of the more severe type. The fact that sympathectomy may bring the blood pressure back to normal is not evidence of a neurogenic origin. Similar lowering of the blood pressure is often observed after non-specific operations and the blood pressure frequently returns to a high level after sympathectomy. Obesity is undoubtedly an aggravating factor in essential hypertension and the blood pressure is usually observed to fall with weight reduction.

## BENIGN HYPERTENSION

**Synonyms.**—Hyperpiesia; Benign Nephrosclerosis.

**Pathology.**—The only morbid anatomical changes found in essential hypertension are secondary to the high blood pressure. They are of two main types; cardio-vascular hypertrophy, which is a direct response to the increased strain imposed on the heart and blood vessels, and arterial degeneration. In benign hypertension the degenerative process takes the form of fatty hyaline change in the arterioles with homogeneous swelling of the wall, but without necrosis. This is characteristically seen in the afferent arterioles to the renal glomeruli. In larger arteries a combination of medial hypertrophy and intimal thickening is seen, the latter being characterised by proliferation of elastic and fibrous connective tissue. In medium and large arteries atheromatous degeneration occurs in the intima and the atheromatous plaques may ulcerate or calcify and may be the site of arterial thrombosis. Occlusion of the lumen may lead to infarction, or embolism may occur from an arterial thrombus and lead to obstruction of more peripheral vessels. The cerebral, coronary, mesenteric and the peripheral arteries of the limbs are the sites of election for atheromatous degeneration and its sequelæ. Progressive narrowing of arteries may lead to slow ischæmia of tissues such as the myocardium, brain and kidney; obliteration of small arteries may lead to repeated focal parenchymal lesions as in cerebral arteriosclerosis and arteriosclerotic retinopathy. The pathological changes in malignant hypertension are described later.

**Symptoms.**—Benign hypertension may be symptomless for many years, particularly if the patient is unaware of its existence. The various clinical syndromes of the disease are in fact related to the degenerative changes in the organs resulting from arterial degeneration. Before manifestations of organic vascular disease appear, however, it is not uncommon for symptoms such as headaches, giddiness, nervousness and palpitations to arise. These may, on the one hand, be due to awareness of the high blood pressure and a fear of its consequences, particularly where there is a family history of vascular catastrophes. Or again these symptoms may be part of a general anxiety state, particularly in women at the menopause, for hypertension is likely to be discovered when menopausal symptoms first lead the patient to seek medical advice. Apart from these circumstances there is no doubt that some patients with benign hypertension develop headaches which are often severe, intractable and apparently related to the high blood pressure. They are often present when the patient awakens in the morning and may last for the greater part of the day. They may be associated with morning nausea or even vomiting. Not infrequently they

are migrainous in type and in such patients there may be a long history of migraine. There is no evidence that these headaches are due to organic cerebral vascular disease. The condition is not severe enough to warrant the diagnosis at this stage of hypertensive encephalopathy which is so common in malignant hypertension. If the level of the blood pressure is reduced by administration of sympatholytic drugs or by sympathectomy, dramatic relief of these headaches is usually obtained.

The majority of patients with benign essential hypertension will have no premonitory symptoms before the onset of organic complications. Breathlessness on exertion or, in more severe cases, paroxysmal nocturnal dyspnoea, indicates the development of myocardial insufficiency. Blurring of vision or sudden blindness in one eye may be due to hæmorrhage or thrombosis in one of the main cerebral veins or arteries. Hemiplegia results from cerebral thrombosis or from hæmorrhage, commonly into the internal capsule due to rupture of the lenticulo-striate branch of the middle cerebral artery; or subarachnoid hæmorrhage may result from escape of blood into the ventricular system. Focal paralyses occasionally occur, giving rise to diplopia, facial palsy or aphasia. Repeated attacks of paresis in one or more limbs may occur as the disease advances, and in older patients, progressive cerebral arteriosclerosis may lead to focal or generalised convulsions and steady deterioration of intellectual power, ending in progressive dementia. Hæmorrhagic manifestations outside the brain are not common, but occasionally isolated attacks of hæmoptysis, hæmatemesis or hæmaturia are attributable to benign hypertension.

There are few physical signs until the advent of complications. The appearance may be plethoric and obese, or thin and pale. The radial and brachial arteries are usually thickened due to medial hypertrophy, and may be tortuous. The heart is often enlarged on clinical examination, the apex beat being forcible, the first sound at the apex loud or duplicated and the second aortic sound accentuated. Yet many patients, particularly women, continue with a high level of blood pressure for decades without appreciable evidence, clinical or radiological, of cardio-vascular hypertrophy.

*The fundi.*—Hypertensive retinopathy is a general term which covers a variety of retinal changes encountered in different types of hypertension. The retinopathy of benign essential hypertension represents the basic picture found in all forms of chronic hypertension and on this may be superimposed more severe lesions, for example, in malignant hypertension or diabetes. The most constant feature is tortuosity of the arteries and nicking of the veins at the arteriovenous crossings. Very rarely the arteries are narrowed and threadlike but more often there is an obvious irregularity in calibre. The so-called "silver-wire" appearance of the retinal arteries is very inconstant and has no real diagnostic value. The veins usually appear congested. Superficial flame-shaped or small discrete deep hæmorrhages may be seen in any part of the fundus, but are most frequent in the macular region; there are often associated but scanty grey or creamy exudates. Massive hæmorrhages may result from retinal vein thrombosis or the retina may be pale due to thrombosis in the central artery. Resolution of these lesions leads to sclerosis of obstructed vessels and neighbouring parts of the retina; pigment usually remains at the site of old hæmorrhages. When hæmorrhages or exudates occur near the optic disk some swelling of the disk margin may be observed. This is usually distinguishable from the papilloedema of malignant hypertension, as it is almost invariably unilateral.

As Allbutt pointed out, clinical evidence of renal involvement is rare, but nocturnal polyuria occasionally develops in severe benign hypertension. The presence of albumin in the urine is again rare and is usually attributable to advanced renal arteriosclerosis, renal congestion due to heart failure, renal infarction or coincident diabetes. In elderly patients with longstanding benign hypertension and severe arteriosclerosis a slight to moderate degree of renal impairment may lead to reduction in tubular concentrating power and moderate elevation of the blood urea.

**Course and Prognosis.**—Benign essential hypertension is compatible with a

long life and freedom from symptoms; nevertheless in most patients complications occur which shorten the expectation of life. Whilst the height of the blood pressure, particularly the diastolic pressure, is an obvious pointer to the severity of the disease, there is *no method of forecasting if or when complications will occur*. At any time, either for no obvious reason or during periods of severe mental or physical strain or in pregnancy, the blood pressure may rise to serious levels; periodic exacerbations may lead to repeated or progressive vascular damage in the heart, brain, retinae or kidneys. Coronary thrombosis or a cerebral vascular accident may considerably lower the level of blood pressure and may so alter the patient's habits of life that the menace of the hypertension is greatly diminished. The prognosis is then that of the residual vascular complication.

**Treatment.**—In any individual it is impossible to prognosticate the course of the disorder or to prescribe a mode of life which will prevent complications. The introduction of active treatment by sympathectomy and hypotensive drugs has therefore aggravated rather than simplified the problem of treatment. To submit a patient to the trauma and risks of bilateral sympathectomy, or to commit him to a life of hexamethonium administration with its attendant side effects, are heavy premiums to pay for a doubtful insurance against uncertain hazards. On the other hand, when the complications have arisen these forms of therapy are even more hazardous and may be of doubtful or temporary benefit. In deciding on treatment various aspects of prognosis discussed above must be borne in mind. Hypertension is likely to run a more severe course, with cardiac and cerebral complications, in men than in women. The malignant change is rare, probably affecting less than 1 per cent. of patients, but a progressively rising diastolic pressure, exceeding 130 mm., is a warning sign. An occupation or mode of life involving excessive physical or mental stress is likely to have an unfavourable effect on prognosis. It is also axiomatic that the possibility of any primary cause for the hypertension must be excluded before active treatment is started.

In asymptomatic benign hypertension, *i.e.* when the high blood pressure is discovered accidentally on routine medical examination, the fact should not be disclosed to the patient if it can be avoided, or if this is not practicable he should be advised that the condition is benign. Obesity should be treated by dietary restriction. In the present status of therapy there is no justification in attempting to lower the blood pressure by drugs or operation in the absence of symptoms. An exception may be made in young subjects, especially men, with a high fixed level of blood pressure (*e.g.* diastolic exceeding 130). In such cases it may be felt that complications are likely to occur sooner rather than later and for this reason some reduction of the pressure with hypotensive drugs is justifiable. The level may be regarded as fixed when considerable residual hypertension persists after 7 days' complete rest in bed with adequate sedation.

The second grade of severity includes those patients with symptoms which are not referable to organic vascular disorders. This is a miscellaneous group and for the most part the symptoms will be anxiety, headaches, dizziness, palpitations, various aches and pains, spots before the eyes and even breathlessness. As already explained, many of these patients will be women at the menopause and appropriate hormone therapy will often relieve the symptoms; otherwise reassurance, weight reduction and a placebo are indicated. In a minority of this group severe headaches occur, especially on waking and may be associated with nausea. Such headaches will often respond to aspirin or codeine, but failing these, benefit is sometimes obtained from ergotamine tartrate 1 mg. at half-hourly intervals until the headache passes off, but not exceeding three or four doses. If in spite of this treatment headache is incapacitating, associated with a high relatively fixed pressure and unaccompanied by other anxiety symptoms, administration of hypotensive drugs may be considered justifiable.

are migrainous in type and in such patients there may be a long history of migraine. There is no evidence that these headaches are due to organic cerebral vascular disease. The condition is not severe enough to warrant the diagnosis at this stage of hypertensive encephalopathy which is so common in malignant hypertension. If the level of the blood pressure is reduced by administration of sympatholytic drugs or by sympathectomy, dramatic relief of these headaches is usually obtained.

The majority of patients with benign essential hypertension will have no premonitory symptoms before the onset of organic complications. Breathlessness on exertion or, in more severe cases, paroxysmal nocturnal dyspnoea, indicates the development of myocardial insufficiency. Blurring of vision or sudden blindness in one eye may be due to hæmorrhage or thrombosis in one of the main cerebral veins or arteries. Hemiplegia results from cerebral thrombosis or from hæmorrhage, commonly into the internal capsule due to rupture of the lenticulo-striate branch of the middle cerebral artery; or subarachnoid hæmorrhage may result from escape of blood into the ventricular system. Focal paralyses occasionally occur, giving rise to diplopia, facial palsy or aphasia. Repeated attacks of paresis in one or more limbs may occur as the disease advances, and in older patients, progressive cerebral arteriosclerosis may lead to focal or generalised convulsions and steady deterioration of intellectual power, ending in progressive dementia. Hæmorrhagic manifestations outside the brain are not common, but occasionally isolated attacks of hæmoptysis, hæmatemesis or hæmaturia are attributable to benign hypertension.

There are few physical signs until the advent of complications. The appearance may be plethoric and obese, or thin and pale. The radial and brachial arteries are usually thickened due to medial hypertrophy, and may be tortuous. The heart is often enlarged on clinical examination, the apex beat being forcible, the first sound at the apex loud or duplicated and the second aortic sound accentuated. Yet many patients, particularly women, continue with a high level of blood pressure for decades without appreciable evidence, clinical or radiological, of cardio-vascular hypertrophy.

*The fundi.*—Hypertensive retinopathy is a general term which covers a variety of retinal changes encountered in different types of hypertension. The retinopathy of benign essential hypertension represents the basic picture found in all forms of chronic hypertension and on this may be superimposed more severe lesions, for example, in malignant hypertension or diabetes. The most constant feature is tortuosity of the arteries and nicking of the veins at the arteriovenous crossings. Very rarely the arteries are narrowed and threadlike but more often there is an obvious irregularity in calibre. The so-called "silver-wire" appearance of the retinal arteries is very inconstant and has no real diagnostic value. The veins usually appear congested. Superficial flame-shaped or small discrete deep hæmorrhages may be seen in any part of the fundus, but are most frequent in the macular region; there are often associated but scanty grey or creamy exudates. Massive hæmorrhages may result from retinal vein thrombosis or the retina may be pale due to thrombosis in the central artery. Resolution of these lesions leads to sclerosis of obstructed vessels and neighbouring parts of the retina; pigment usually remains at the site of old hæmorrhages. When hæmorrhages or exudates occur near the optic disk some swelling of the disk margin may be observed. This is usually distinguishable from the papilloedema of malignant hypertension, as it is almost invariably unilateral.

As Allbutt pointed out, clinical evidence of renal involvement is rare, but nocturnal polyuria occasionally develops in severe benign hypertension. The presence of albumin in the urine is again rare and is usually attributable to advanced renal arteriosclerosis, renal congestion due to heart failure, renal infarction or coincident diabetes. In elderly patients with longstanding benign hypertension and severe arteriosclerosis a slight to moderate degree of renal impairment may lead to reduction in tubular concentrating power and moderate elevation of the blood urea.

**Course and Prognosis.**—Benign essential hypertension is compatible with a



long life and freedom from symptoms; nevertheless in most patients complications occur which shorten the expectation of life. Whilst the height of the blood pressure, particularly the diastolic pressure, is an obvious pointer to the severity of the disease, there is no method of forecasting if or when complications will occur. At any time, either for no obvious reason or during periods of severe mental or physical strain or in pregnancy, the blood pressure may rise to serious levels; periodic exacerbations may lead to repeated or progressive vascular damage in the heart, brain, retinae or kidneys. Coronary thrombosis or a cerebral vascular accident may considerably lower the level of blood pressure and may so alter the patient's habits of life that the menace of the hypertension is greatly diminished. The prognosis is then that of the residual vascular complication.

**Treatment.**—In any individual it is impossible to prognosticate the course of the disorder or to prescribe a mode of life which will prevent complications. The introduction of active treatment by sympathectomy and hypotensive drugs has therefore aggravated rather than simplified the problem of treatment. To submit a patient to the trauma and risks of bilateral sympathectomy, or to commit him to a life of hexamethonium administration with its attendant side effects, are heavy premiums to pay for a doubtful insurance against uncertain hazards. On the other hand, when the complications have arisen these forms of therapy are even more hazardous and may be of doubtful or temporary benefit. In deciding on treatment various aspects of prognosis discussed above must be borne in mind. Hypertension is likely to run a more severe course, with cardiac and cerebral complications, in men than in women. The malignant change is rare, probably affecting less than 1 per cent. of patients, but a progressively rising diastolic pressure, exceeding 130 mm., is a warning sign. An occupation or mode of life involving excessive physical or mental stress is likely to have an unfavourable effect on prognosis. It is also axiomatic that the possibility of any primary cause for the hypertension must be excluded before active treatment is started.

In asymptomatic benign hypertension, *i.e.* when the high blood pressure is discovered accidentally on routine medical examination, the fact should not be disclosed to the patient if it can be avoided, or if this is not practicable he should be advised that the condition is benign. Obesity should be treated by dietary restriction. In the present status of therapy there is no justification in attempting to lower the blood pressure by drugs or operation in the absence of symptoms. An exception may be made in young subjects, especially men, with a high fixed level of blood pressure (*e.g.* diastolic exceeding 130). In such cases it may be felt that complications are likely to occur sooner rather than later and for this reason some reduction of the pressure with hypotensive drugs is justifiable. The level may be regarded as fixed when considerable residual hypertension persists after 7 days' complete rest in bed with adequate sedation.

The second grade of severity includes those patients with symptoms which are not referable to organic vascular disorders. This is a miscellaneous group and for the most part the symptoms will be anxiety, headaches, dizziness, palpitations, various aches and pains, spots before the eyes and even breathlessness. As already explained, many of these patients will be women at the menopause and appropriate hormone therapy will often relieve the symptoms; otherwise reassurance, weight reduction and a placebo are indicated. In a minority of this group severe headaches occur, especially on waking and may be associated with nausea. Such headaches will often respond to aspirin or codeine, but failing these, benefit is sometimes obtained from ergotamine tartrate 1 mg. at half-hourly intervals until the headache passes off, but not exceeding three or four doses. If in spite of this treatment headache is incapacitating, associated with a high relatively fixed pressure and unaccompanied by other anxiety symptoms, administration of hypotensive drugs may be considered justifiable.

The third therapeutic group consists of those patients with benign hypertension in whom early evidence of arterial damage is found. Such evidence may be the appearance of superficial retinal hæmorrhages, a transient paresis, a mild attack of encephalopathy or the onset of dyspnoea on exertion. Only a minority of these patients progress to the fully developed stage of malignant hypertension with papilloedema and renal failure. Nevertheless various other arterial complications may occur, especially in men, and it is justifiable to give at least a limited course of hypotensive drug therapy. The aim should be to produce an appreciable lowering of blood pressure which is sustained throughout the day without excessive swings and with minimal side effects. This is probably best achieved by a combination of drugs. Therapeutic trials of these are at present being extensively carried out. The most effective combination to date is an alkaloid, *Rauwolfia serpentina* together with a hexamethonium derivative, the latter being administered orally in the first instance or intramuscularly where a rapid depressor action is required. The dose should be determined for each patient by hourly blood pressure readings over 6 to 8 hours after the administration. The effect of these drugs is potentiated by a low salt diet. It must be appreciated that hypotensive drug treatment is not without its risks. Sympatholytic drugs may produce severe hypotension which may lead to syncope and occasionally to fatal cerebral hæmorrhage or thrombosis. Where severe coronary disease is present an attack of myocardial insufficiency may be precipitated by a sudden fall in blood pressure. A serious form of pulmonary œdema which may progress to consolidation has been described after prolonged hexamethonium therapy. Paralysis of accommodation may produce considerable incapacity for some time after the administration, and dryness of the mouth may be unpleasant. The former is best relieved by spectacles worn during the period of maximum action of the drug. Constipation, dysphagia and difficulty in micturition, drowsiness or lethargy may also occur. Prostigmine may relieve some of these symptoms. Very occasionally vagal inhibition of the bowel may lead to fatal ileus. Inadequate response to the hypotensive drugs or intolerance due to severity of side effects may lead to consideration of sympathectomy. This should be carried out only in patients with incapacitating symptoms which are judged to be due to the severity of the hypertension. The results in some cases are excellent, the blood pressure falling to the normal level and remaining there for many years. In other individuals there is sooner or later a gradual rise in blood pressure to pre-operative levels, but not infrequently hypertensive symptoms do not recur, possibly because a more steady level of hypertension is maintained without the periodic exacerbations which are responsible for ischæmic episodes or minor vascular occlusions.

The fourth grade of severity is characterised by obvious complications which result from arterial degeneration. Such are cardiac infarction, hypertensive heart failure, cerebral vascular accidents and severe grades of retinal vascular damage leading to impairment of vision; the latter include extensive hæmorrhages or exudates in the macular region, or thrombosis of main branches of the retinal vessels, but without papilloedema. In patients who have sustained myocardial infarction or major cerebro-vascular accidents, treatment with hypotensive drugs or by sympathectomy is best avoided in view of the risks of lowering the blood pressure in the presence of occlusive arterial disease, but hypertensive heart failure or retinopathy may be dramatically improved by hypotensive drugs.

### MALIGNANT HYPERTENSION

**Synonyms.**—Malignant Essential Hypertension; Malignant Nephrosclerosis.

The term malignant hypertension was first used to describe a syndrome consisting of very high blood pressure, transient cerebral attacks (hypertensive encephalopathy)

and retinopathy with papilloedema, occurring in a variety of disorders such as acute and chronic nephritis, eclampsia and essential hypertension. Subsequently a number of writers applied the term exclusively as a clinical synonym for the malignant nephrosclerosis of Volhard and Fahr. Clinical and pathological studies have demonstrated, however, that the renal changes of malignant nephrosclerosis are not the cause of the hypertension, but develop during the course of the disorder. Furthermore, experimental observations in animals have provided convincing evidence that the renal changes of malignant hypertension are directly attributable to severe elevation of blood pressure. It is now recognised, therefore, that malignant hypertension (with its associated nephrosclerosis) is a syndrome which may occur in any patient with severe hypertensive disease whether essential, renal or endocrine in origin. The clinical features and the hypertensive renal lesions which result are very similar whatever the origin of the hypertension.

**Incidence and Pathology.**—It is not known what determines the transformation from the benign to the malignant form of essential hypertension. It is a feature of severe hypertensive disease that sudden exacerbations periodically occur. During these phases of very high blood pressure focal vascular damage may be produced in the brain, retina, kidneys and other viscera. The mechanism of this vascular damage is not clear, but there is strong experimental evidence that sudden increase in intravascular pressure may cause intense focal vasoconstriction and that this may lead to both vascular necrosis and perivascular tissue damage. In essential hypertension successive episodes of this character, manifested by attacks of encephalopathy, retinal hæmorrhage, heart failure or hæmaturia may be followed after a variable interval of months or years by the establishment of malignant hypertension which, in the absence of treatment, progresses steadily without remission. This change from the phasic to the fixed stage of the disease may be due to progressive renal vascular damage maintaining and even aggravating the initial hypertension.

Two clinical groups have long been recognised; in the larger group the patients present with malignant hypertension in the fourth or fifth decades without a previous history of longstanding benign hypertension. The smaller group comprises patients, usually in the sixties, in whom longstanding benign hypertension changes to the malignant type. The progress of the disease tends to be much slower in the older age group and the development of renal failure may take several years. Owing to the growing frequency of routine blood pressure determination in young subjects there is increasing evidence that even in the first group symptomless hypertension may be present for many years before the malignant termination. It is uncertain what proportion of patients with essential hypertension pass into the malignant phase. Estimates from hospital practice are almost certainly too high and it is probable that the figure is not more than 1 per cent., possibly much less.

Malignant hypertension differs from benign hypertension essentially in the intensity of secondary vascular changes. Arteriolar degeneration is more acute and characteristically takes the form of fibrinoid necrosis of arterioles with endarteritis in the larger vessels. These changes are most prominent in the kidney, the afferent arterioles of the glomeruli undergoing necrosis whilst the interlobular arteries show endarteritis. The resulting acute ischæmia produces focal necroses in the glomeruli and hæmorrhage into the capsular space. Organisation of these acute ischæmic changes leads to gross distortion of the glomerular tufts, capsular adhesions, occasional epithelial crescent formation and chronic fibrotic thickening and occlusion of the arterioles. In addition there may be chronic ischæmic lesions of the glomeruli due to longstanding benign hypertension and for the same reason the larger renal vessels may show intimal fibrosis and elastosis together with medial hypertrophy. Hyaline droplet degeneration of the tubular epithelium is almost invariably present in the acute phases. Recurrent episodes of acute hypertensive damage lead to progressive involvement of the kidney and the final stage is that described as malignant

impairment, a diagnosis of malignant hypertension should be made. In the absence of renal involvement full investigation for a space occupying lesion should be carried out.

**Treatment.**—In the later stages when renal function tests are impaired, treatment can be only symptomatic. If, however, the blood urea is within normal limits or only slightly elevated (*e.g.* to not more than 60 mg. per cent.) attempts should be made to lower the blood pressure by sympathectomy or hypotensive drugs. In older patients or in those with severe vascular complications, such as heart failure or cerebral hæmorrhage, sympatholytic drugs will be preferred. In younger patients a course of drug treatment should be given a trial, hexamethonium salts being given as described under treatment of severe benign hypertension. The result may be considered satisfactory if symptoms can be relieved, papilloedema subsides and the blood pressure is stabilised at a lower level than previously. It is usually impracticable and unnecessary to try and reduce the blood pressure to normal. If this degree of control cannot be achieved or if side effects of the drugs are incapacitating, bilateral thoraco-dorsal sympathectomy offers the only chance of delaying the progress of the disease. In general this operation should be reserved for patients under the age of 50 with normal renal function and without evidence of coronary disease or severe cerebral vascular damage. In addition to these hypotensive measures, symptomatic treatment for headaches and breathlessness and other hypertensive manifestations should be carried out as described under benign hypertension.

## PULMONARY HYPERTENSION

Systemic hypertension is not associated with a rise in pulmonary arterial pressure. Pulmonary hypertension is due to a variety of lesions all of which produce either increased peripheral resistance in the lungs or increased output of the right ventricle or both. Mitral stenosis, emphysema, pulmonary fibrosis due to any cause, primary pulmonary endarteritis and certain types of congenital heart disease are the common ætiological factors (see p. 895).

## HYPOTENSION

There is no arbitrary limit which supplies a satisfactory definition of hypotension, but in adults 100 mm. may be regarded as the lower limit of the systolic pressure. The reading may be slightly lower in the supine than in the erect position.

**Ætiology and Pathology.**—Abnormally low blood pressure may be due to myocardial infarction or reduction in cardiac output due to terminal heart failure. Reduction in cardiac output may also be due to diminished venous return in oligæmic states, *e.g.* following hæmorrhage, loss of fluid due to burns or acute gastro-enteritis. Severe toxæmia may also produce an abnormally low blood pressure and so may heat exhaustion. In vasovagal syncope hypotension is a usual feature. Low blood pressure is a characteristic of Addison's disease. Postural hypotension is a specific variety which will be described separately.

**Symptoms.**—In acute hypotension due to oligæmia the skin is cold and clammy, the pulse is usually rapid and small in volume; the blood pressure may be unrecordable or the sphygmomanometer may register the systolic but not the diastolic pressure. Hypotension with bradycardia, nausea and sweating suggests a vasovagal attack. In shock there will usually be evidence of a primary cause and the hypotension is chiefly important as an index of deterioration or recovery.

Prolonged hypotension is sometimes associated with states of unconsciousness following head injury or operations on the brain. In these and in other patients

with prolonged hypotension, renal function may be considerably impaired and elevation of the blood urea may be associated with hyperchloremic acidosis.

**Treatment.**—This depends upon the cause. Hypotension following hæmorrhage is a grave sign and usually indicates a loss of at least 25 per cent. of the blood volume. Transfusion of whole blood should be given until the systolic pressure reaches 100 mm. After this point, a further 2 pints are usually necessary to restore the blood volume.

## POSTURAL HYPOTENSION

Postural hypotension is present if the systolic pressure in the erect posture after 3 minutes' quiet standing, with the arm at heart level, is 50 mm. or more below the systolic pressure in the supine position.

**Ætiology.**—This disorder is due to impairment of the carotid sinus reflex. It may follow bilateral denervation of the carotid sinus or may be associated with neurological or endocrine disease, particularly tabes dorsalis, syringomyelia, diabetic neuritis, Parkinsonism, Addison's disease or hypoparathyroidism. It may follow extensive sympathectomy or the administration of drugs paralysing the vasoconstrictor nerves. In many cases, however, there is evidence of widespread disorder of the autonomic nervous system unaccounted for by any organic lesion. To this condition the term idiopathic postural hypotension has been given. The central lesion in such cases is above the spinal reflex level and is probably a specific autonomic degeneration resembling Parkinsonism. It is rare before the age of 40 and uncommon in women.

**Symptoms.**—The cardinal symptom is syncope, usually preceded by dizziness. It rarely occurs while the patient is sitting and never while lying down. Attacks are usually more frequent early in the day, during hot weather and on standing still after moderate activity. They are often first noticed while standing in queues or at the kitchen sink. In most cases, especially of the idiopathic type, the pulse rate is unchanged despite great variations in blood pressure. There may also be patchy or total anhidrosis, nocturnal polyuria and, in males, loss of libido and potency. Pigmentation of the skin is sometimes observed and hyperhidrosis has been reported. There may be absence of pupillary reaction to light.

**Diagnosis.**—Epilepsy is usually suspected until the postural variation in blood pressure is discovered. The presence of pigmentation may suggest Addison's disease, but again the demonstration of a gross fall in blood pressure on standing still, establishes the diagnosis.

**Prognosis.**—Postural hypotension may persist unchanged for very many years with minor disability or it may progress to a disabling affliction which confines the sufferer to a wheel-chair. Remissions rarely occur. The postural hypotension which follows dorso-lumbar sympathectomy usually passes off in 6 to 9 months. More extensive sympathectomy may be followed by a permanent, disabling, postural hypotension.

**Treatment.**—Elastic stockings and an abdominal binder are useful measures to diminish pooling of the blood. Symptoms may be improved by avoiding the supine position at all times during the day and elevating the head of the bed 18 inches at night. Treatment with vasoconstrictor drugs usually produces little if any permanent relief of symptoms, but is worthy of trial.

## PERIPHERAL VASCULAR DISEASE

The term peripheral vascular disease includes a number of obliterative arterial diseases of the limbs and a group of less common functional disorders of the small peripheral vessels.

There are two main types of obliterative arterial disease :

(1) *Chronic vascular occlusion* due to arterial degeneration or vascular spasm, or both processes in combination. The commonest variety of peripheral vascular disease is atheromatous degeneration which may be complicated by vascular spasm and by thrombosis. Detachment of thrombus from an atheromatous area may give rise to embolism in a more peripheral artery. Raynaud's phenomenon is an example of vasospastic peripheral arterial disease, but this also may in the later stages be complicated by thrombosis.

(2) *Acute obstruction* to the vessel lumen by embolism. Systemic emboli usually arise from the valves of the left side of the heart or from mural thrombi in auricle or ventricle or from thrombosis over atheromatous areas of the larger arteries.

Peripheral vascular disease of all kinds leads to ischæmic manifestations in the limbs, the chief of these being muscle pain and gangrene.

**METHODS OF INVESTIGATION.**—Since peripheral vascular disease is most commonly due to generalised arterial degeneration a complete examination of the cardio-vascular system is essential in all cases. This involves examination of the peripheral arteries of the upper and lower limbs, retinoscopy, examination of the heart and the blood pressure. Electrocardiographic investigation and radiography of the heart and aorta should be carried out, and the urine should be tested for sugar and albumin. The Wassermann reaction must be tested in all patients with indolent ulceration of the limbs. Radiographic examination of the affected parts for arterial calcification is of value in distinguishing arterial degeneration from inflammation. In all cases of deep ulceration, radiography of the underlying bones and joints is essential for the detection of osteomyelitis or destructive arthritis.

Local examination of an affected limb should be directed first to the colour of the skin, which is determined by the filling of the sub-papillary venous plexus and by the proportion of reduced hæmoglobin in the blood. Pallor is usually due to arterial occlusion or vasoconstriction, cyanosis to slowing of the blood flow, redness to capillary dilatation, which may be persistent or may be transient if due to inflammation or reactive hyperæmia. Engorgement of the superficial veins should be looked for. Inspection will also reveal the presence of œdema which may be inflammatory or may indicate venous obstruction. Oedema is sometimes present in the chronic ischæmic limb, especially where there is under-nutrition of the tissues and muscular atrophy due to disuse. Trophic lesions should be observed in their general extent and for the presence of sinuses indicating involvement of deep tissues. Associated eczema or fungus infections between the toes should be noted. The skin temperature is regulated by rate of blood flow and the comparison should be made of normal and abnormal limbs. Lowering of skin temperature indicates arterial occlusion or vasoconstriction, while increase is usually due to inflammation. Pulsation should be looked for in all the main arteries of the limb, *e.g.* in the lower limb the femoral, popliteal, posterior tibial and dorsalis pedis arteries, the two sides being compared. If there is a marked difference in pulsation the blood pressure should be compared on the two sides.

Special investigations may be carried out to determine the extent and severity of the vascular occlusion. A simple test is to elevate the lower limb and then measure the time taken for the circulation to return to the toes after hanging the leg downwards. In the normal limb, provided it is warm, this should take a few seconds, but in vascular occlusion it may be increased to half a minute or longer. The amplitude of pulsation at different points in the main arteries may be measured by the recording oscillograph. In skilled hands this may indicate the site of vascular obstruction, which is of special value when the level of amputation is being considered. Measurement of skin temperature can be used to determine whether ischæmia can be relieved by sympathetic vasodilatation. In the reflex vasodilatation test the patient is placed in a hot chamber with the affected limbs outside. Alternatively, reflex vasodilatation

may be produced by putting the arms in hot water (when the skin temperature of the feet is to be tested) until general vasodilatation and sweating occurs. With the room temperature about 20° C. reflex vasodilatation should produce in the normal a rise in skin temperature over the hand or foot to at least 30° C. Sympathetic release may also be obtained by spinal anaesthesia and this method is preferable if sympathectomy is being considered as a form of treatment. In all these investigations, if only one limb is affected, the sound limb should be used as a control.

Angiography is a valuable method of investigation. If arterial grafting is contemplated it is essential both for diagnosis and for assessment of the results of treatment. Angiography will indicate not only the site and extent of vascular occlusion, but will give some information as to the degree of collateral circulation. Satisfactory arteriograms of the limb vessels can be obtained by injection into the femoral artery of 50 per cent. diodone.

## PERIPHERAL ARTERIOSCLEROSIS

**Ætiology and Pathology.**—The all important pathological lesion in peripheral arteriosclerosis is atheroma. The commonest predisposing factors are old age, high blood pressure and diabetes; in other conditions characterised by a raised blood cholesterol, e.g. myxœdema, atheromatous degeneration may be particularly severe. Atheroma starts with the deposition of doubly refracting lipid in the deep layers of the intima; cellular infiltration and fibrosis follow, and a raised nodule is produced in the vessel wall. Cholesterol crystals are formed and calcification usually occurs. The lesion is common in areas of strain, particularly at points of bifurcation or of origin of branches of the aorta. Ulceration may occur in atheromatous areas and localised thrombosis may complete the arterial occlusion. Medial degeneration (Mönckeberg's degeneration) is a much rarer form, which leads to ring-like calcification of the media and this may be recognised radiologically. It occurs in elderly patients and atheroma is almost always present. Arterial degeneration is most common in the lower limbs and the popliteal artery is the site of election. Occasionally arteriosclerosis in the arteries of the upper limb produces ischæmic pain, numbness and blanching of the digits.

**Symptoms.**—Peripheral arteriosclerosis is five times as common in men as in women. The two cardinal manifestations are pain and ischæmic necrosis of the tissues. The usual type of pain is *intermittent claudication* (angina cruris). This consists of cramp-like pain in the calf, produced usually by a constant amount of exercise, and relieved promptly by rest. This distribution of pain is due to popliteal artery occlusion. Less frequently the obstruction is in the femoral or common iliac artery and claudication pain may then occur in the thigh or gluteal region. Claudication may first affect one side and later, as improvement occurs with the development of collateral circulation, the other limb may in turn be affected. As the disease progresses effort pain is characteristically brought on by diminishing amounts of exercise, until the patient may be unable to walk more than 10 or 20 yards. *Rest pain* is a continuous type of pain which affects the distal portions of the feet or toes. It usually comes on at night when the patient gets warm in bed, and relief may only be obtained by hanging the foot downwards out of bed. Rest pain is very often resistant to all forms of drug treatment and may be so incapacitating that amputation is necessary. The ischæmic lesion is in general very severe in these cases and gangrene is a common sequel. Rest pain may also be produced by inflammatory changes associated with gangrene, especially if there is considerable œdema or deep necrosis with involvement of bone or joints.

**Gangrene** due to arteriosclerotic occlusion is common in the lower limb but rare in the upper. It may involve one or more toes, or the distal part of the foot according

to the particular arterial branch which is obstructed. Trauma is a frequent precipitating factor, bruising of the foot leading to œdema and thereby depressing the local circulation to a point below which effective nutrition cannot be maintained. In other cases gangrene may appear or extend suddenly in a manner which indicates either embolism or acute extension of a thrombotic lesion. Gangrene may also occur over pressure points, especially the ball of the heel and the malleoli. Trophic ulceration may be observed in the absence of massive tissue necrosis. This may take the form of ulceration around the nails or between the toes and the condition may be aggravated by fungus infection or an eczematous eruption. All forms of infection tend to aggravate ischæmia by producing œdema, but the introduction of antibiotic therapy has made it possible to combat moist, spreading gangrene with satisfactory delimitation of the lesion. Vascular spasm is sometimes a prominent feature of peripheral arteriosclerosis and the appearances may resemble Raynaud's phenomenon due to other causes. Sometimes individual digits are affected (so-called "dead fingers") particularly after exposure to cold. The combination of arterial degeneration with secondary vasoconstriction may lead to symmetrical peripheral gangrene of the fingers or toes.

The physical signs which may be present in obliterative endarteritis have been discussed under methods of investigation. Pallor or cyanosis of the skin will depend on the degree of arterial occlusion. Skin temperature is lower on the abnormal side unless inflammation is present. The femoral pulses will usually be diminished in amplitude and the posterior tibial and dorsalis pedis pulses are frequently absent. It should be noted, however, that dorsalis pedis pulsation is absent in about 10 per cent. of normal young adults. Popliteal pulsation is sometimes difficult to feel in normal subjects and this sign is equivocal unless there is a definite difference between the two sides.

**Diagnosis.**—The diagnosis of obliterative arteriosclerosis is indicated by the age of the patient, generalised signs of arterial degeneration and evidence of predisposing factors such as hypertension or diabetes. The radiological demonstration of calcification is a conclusive sign of arterial degeneration. Difficulty arises over the occasional young patient in whom localised atheroma produces obliteration of a large artery in one of the limbs. The differentiation from thrombo-angitis in these cases is difficult; the absence of recurrent episodes and of associated venous thrombosis are the most important diagnostic points in favour of arteriosclerosis.

**Course and Prognosis.**—Peripheral arteriosclerosis produces a permanent and usually progressive obliteration of the arteries. After an initial attack of intermittent claudication or gangrene, considerable improvement may occur over a long period of time with establishment of collateral circulation. The treatment of infection with antibiotics, with subsidence of œdema, frequently leads to considerable healing and makes local surgery a practical measure. It is common for both lower limbs to be involved in sequence although, of course, intermittent claudication occurs only in the more affected limb. The individual prognosis is frequently determined by the consequences of arterial degeneration elsewhere in the body. Thus relief of angina cruris is sometimes followed by the onset of angina pectoris as the patient returns to normal activity.

**Treatment.**—The most essential treatment in patients with peripheral arteriosclerosis is prophylaxis. The foot should be kept clean and warm and at all costs trauma should be avoided. Thus special shoes should be fitted if necessary and warm, woollen socks should be worn. Exposure to cold and wet should be carefully avoided. When vascular occlusion gives rise to definite ischæmic changes, complete rest in bed is necessary, extremes of heat or cold should not be permitted to the affected part and bed socks should be worn. The treatment depends on the nature of the disorder. Intermittent claudication may gradually improve with the passage of time as collateral circulation develops. This may be expedited by the use



of intermittent venous occlusion, but only if treatment is continued over a long period. Sympathectomy is of uncertain value, some cases being improved, many obtaining no relief. The skin temperature response to sympathetic release gives no reliable indication of the increase in muscle blood flow and relief of symptoms which may be expected after sympathectomy. In selected cases severe claudication may be successfully treated by section of the tendo achillis. Vasodilator drugs are of little value.

Rest pain is treated by putting the patient to bed and giving analgesic drugs. Intermittent venous occlusion may be tried; occasionally this kind of pain, particularly if of sudden onset, may gradually improve with the development of collateral circulation. In intractable cases, however, amputation may be necessary.

Gangrene is now treated conservatively in the majority of cases. Rest in bed and use of antibiotics quickly lead to the subsidence of inflammation and demarcation of the area of gangrene. Necrotic tissue may then be removed and healing accelerated by means of pinch grafting. Where gangrene is superficial and when considerable improvement in the skin circulation follows reflex vasodilatation, sympathectomy may be the most effective treatment particularly when secondary vasoconstriction is a prominent feature. In resistant cases, particularly in elderly subjects with generalised arteriosclerosis or diabetes, mid-thigh amputation may be the only effective form of treatment. Recent developments in the cold preservation of human tissues have made arterial grafting a practicable form of therapy in arterial disease. This is obviously most successful where a local lesion occurs in an otherwise healthy vessel, e.g. traumatic arterial occlusion or localised degeneration.

## THROMBO-ANGIITIS OBLITERANS

**Synonym.**—Buerger's Disease.

**Definition.**—A disease characterised by acute inflammation with thrombosis affecting both arteries and veins.

**Ætiology.**—The disease has been recorded in all countries and races. The cause is unknown. It affects men almost exclusively and 99 per cent. of cases are smokers, most of them heavy smokers. Attempts to demonstrate an infective cause or an allergy to nicotine have been inconclusive. The association of non-specific inflammation of arteries and veins suggest a relationship to periarteritis nodosa and the other collagen diseases. Some patients develop visceral vascular lesions and the relationship to the collagen disorders is even more marked in these cases.

**Pathology.**—Any vessel may be affected, but the medium-sized arteries and veins of the lower limbs are most commonly involved. It is likely that the earliest change is a proliferation of the intima and infiltration with small round cells. When thrombosis has occurred there is a marked intimal proliferation with a few foci of lymphocytes. The other coats show the usual changes associated with thrombosis, fibroblastic response in the media and capillary dilatation with fibroplasia in the adventitia. As the lesion ages, fibrosis occurs in the thrombus and recanalisation follows. Characteristically only a short length of the vessel is affected and lesions in all stages, with intervening normal areas, may be found.

**Symptoms.**—These depend on the vessel involved. The most usual symptom is intermittent claudication, but patients may present with superficial venous thromboses, Raynaud's phenomenon, gangrene of the extremities or a visceral catastrophe. Venous thrombosis commonly affects the lower limb and characteristically produces episodic attacks of localised, superficial, painful swelling, particularly in the calf. Peripheral gangrene may affect the toes, or a larger part of the extremity if a main artery is obliterated. Pain in the feet at night is not uncommon, and is characteristically eased by hanging the leg downwards out of the bed, or by walking about.

Paræsthesiæ may occur. Ischæmic pain in the arms is rare but may be severe enough to prevent the patient from following his usual employment. Cardiac infarction or cerebral thrombosis may occur.

The physical signs depend on the site and age of the lesions. When a main artery to a limb is involved the skin beyond the lesion is cold, and the peripheral pulses absent. If ischæmia is induced by elevating the limb for some minutes, the return of the circulation to the skin on lowering the limb is delayed. When the flush does appear it is usually more intense than on the normal side due to reactive hyperæmia. Occasionally in bilateral disease the skin of the calf is warmer and the leg blood flow is increased on the symptomatically more affected side.

**Diagnosis.**—The disease must be distinguished from other causes of arterial occlusion including generalised atheromatous disease and isolated arterial lesions such as "idiopathic" thrombosis of the popliteal artery. The finding of obliterative arterial disease with or without gangrene in a male under 50 strongly suggests thrombo-angiitis obliterans. The association of arterial disease with superficial painful swellings due to venous thrombosis is diagnostic. Radiological demonstrations of calcified vascular lesions is strong evidence against Buerger's disease as is the finding of a raised blood cholesterol. Lesions restricted to the upper limbs should suggest the possibility of some anatomical abnormality causing compression of the subclavian artery. In an early case diagnosis may be impossible until further scattered venous or arterial lesions appear.

**Course and Prognosis.**—The course of the disease is episodic with recurrent attacks of venous thrombosis, intermittent claudication or gangrene involving several sites in succession. The outcome is unpredictable. Cardiac infarction may cause sudden death early in the disease, or the condition may progress steadily over many years with recurrent episodes of thrombosis. Although there may be considerable improvement between attacks due to partial restoration of the circulation some residual disability is usual. In many cases the disease becomes inactive after a succession of attacks.

**Treatment.**—The main disablement results from arterial obstruction. Most of the patients are young adults whose tissues withstand the effects of ischæmia well, and much can be done to avert the loss of a limb. The blocked lengths of arteries usually recanalise and in time a good collateral circulation will form. Treatment, therefore, is chiefly directed to mitigating the effects of ischæmia until the circulation recovers. In acute lesions of the hands or feet the local temperature should be kept low by exposure to cool air. This reduces the metabolic rate and so the need for oxygen. The circulation may be greatly improved by sympatholytic drugs or by sympathetic block. If gangrene occurs, treatment should be confined to local excision and pinch grafting under suitable antibiotic cover. When the main disorder is muscle ischæmia the most useful measures are rest and a cool environment. Sympathetic block has little effect on the circulation through muscle and is of little value in these cases. Once the acute stage is past, it may be possible to improve the circulation by the production of reactive hyperæmia which stimulates the development of the collateral circulation. For this purpose Buerger's exercises, intermittent venous occlusion, or the "Pavex" boot may be employed.

## RAYNAUD'S PHENOMENON

**Definition.**—Intermittent pallor or cyanosis of the extremities brought on by cold, with return of skin colour to normal between attacks.

**Ætiology.**—Very great changes in the calibre of the digital vessels occur in normal subjects in response to variations in temperature. The resulting changes in blood flow are greatest in the finger tips (where the blood flow may be a hundred times

greater in the hot finger than in the cold) and diminish progressively towards the wrist. Raynaud's phenomenon is the result of a temporary, complete occlusion of the digital arteries due to an excessive vasoconstrictor response to cold. It may occur in vessels partially obstructed by atheroma or emboli, in scleroderma when the tissue pressure is greatly raised, in the hands of workmen using vibrating tools and it may follow local injury. Syphilitic endarteritis has been recorded as a cause.

Young women frequently suffer from Raynaud's phenomenon. The explanation in these patients was shown by Lewis to be an excessive reaction to cold in otherwise normal vessels. The term Raynaud's disease is usually reserved for this type of digital asphyxia, which is five to ten times commoner in women than in men. In his original description Raynaud included cases of symmetrical gangrene which would now be attributed to organic vascular occlusion or scleroderma.

**Symptoms.**—Attacks may be brought on by any stimuli which cause digital vasoconstriction. These include handling cold objects, the heat conservation response to a cold environment, sudden fright or emotional tension. In those who work with vibrating tools the attacks are usually brought on by cold but may occur in a warm environment, for example, while in bed. In these patients there are usually signs of sensory loss. In Raynaud's disease the tips of the fingers may be first affected; in scleroderma the phenomenon is often limited to the digits most affected by the collagen disorder.

The colour of the fingers during an attack depends upon the state of venous tone. Commonly it is a pale bluish white, often white with small blue patches. In a prolonged and severe attack the fingers become waxen and shiny. If the spasm relaxes momentarily and the venules fill, the fingers may be deeply cyanosed. In this stage the fingers feel dead and often tingle. If cut, they do not bleed, or only a little dark blood oozes out.

After a period, which may be from a few minutes to 20 minutes or more, the arteries relax and the circulation returns. Pinkish patches begin to appear at the base of the finger, and whole digits become cyanosed. Finally the skin changes to a bright red (*reactive hyperæmia*) and *paræsthesiæ* are felt. There may be an unpleasant, numb, aching sensation.

**Diagnosis.**—Raynaud's phenomenon should be distinguished from chilblains, acrocyanosis, erythromelalgia and from the numbness and tingling sometimes found in erythrocyanosis. Diagnosis is certain if immersion of the hands in cold water provokes an attack. When the water is warmed the characteristic changes associated with returning circulation are seen. The localisation to the fingers is characteristic. In early scleroderma Raynaud's phenomenon may be the most prominent feature of the disease. Nevertheless characteristic skin changes are, as a rule, present at this stage, and affect parts of the body other than the fingers. In Raynaud's disease *sclerotic changes are usually confined to the fingers and develop only after many years of intermittent digital asphyxia.*

**Prognosis.**—In Raynaud's phenomenon secondary to organic arterial disease the prognosis depends upon the cause. When there is partial obstruction in the digital arteries, for example due to embolism secondary to brachial artery compression, relief of the latter will arrest the condition, but improvement is unlikely. In tool workers the attacks do not occur during work and a change of occupation does not usually prevent attacks; indeed the condition may progress. Raynaud described remissions in young women during pregnancy. In these patients the disease may remit spontaneously for many years, to return at the menopause in a milder form. After several years of severe Raynaud's attacks the fingers become thickened and the skin atrophic, a condition termed *acrosclerosis*. Superficial ulceration of the tips is sometimes seen but extensive gangrene of the digits rarely if occurs.

occlusion. The distinction is easy since oedema is prominent in venous thrombosis, the limb is warm and arterial pulsation can usually be felt. Differential diagnosis between arterial thrombosis and embolism depends on the primary disorder. Arteriosclerosis is the common cause of thrombosis and there will usually be evidence of this process elsewhere. Moreover, the popliteal artery is the common site of thrombosis in the lower limb. The symptoms of obstruction are usually less acute and less severe after thrombosis than after embolism, since previous incomplete arterial narrowing will have produced some degree of collateral circulation.

**Course and Prognosis.**—Most patients may be expected to recover with medical treatment alone; with prompt resort to surgery where necessary gangrene should rarely occur. The prognosis depends very considerably on the age and general condition of the patient. Since severe cardio-vascular disease is usually present, active treatment may be impracticable or death may supervene from other causes.

**Treatment.**—The patient is nursed in a warm room to encourage vasodilatation. The limb should be kept warm, but not overheated, and great care must be taken to avoid burns from hot-water bottles. The leg should be lowered by blocking the head of the bed. Analgesics are given as required and an attempt may be made to produce vasodilatation by injection of papaverine hydrochloride gr.  $\frac{1}{2}$  intravenously. The circulation may be improved by an alternating positive and negative pressure machine (Pavex) or if the obstruction is low enough, by intermittent venous occlusion. Anticoagulant therapy should be given at once, a suitable regime being 50 mg. heparin intravenously every 4 hours and a coumarin derivative by mouth, the dosage being regulated by the prothrombin time. If improvement in the circulation takes place, this treatment is continued for a week. *Should no improvement be observed in 3 or 4 hours, embolectomy must be undertaken if the patient is in a fit stage to undergo operation.* Although embolectomy has been successfully performed up to 24 hours after arterial occlusion, if the patient is seen soon after the onset, operation should not be delayed beyond 12 hours.

**Arterial thrombosis** is usually a complication of arteriosclerosis or thrombo-angiitis obliterans. The femoral, popliteal or posterior tibial arteries may be involved in the lower limb, or the subclavian, axillary, brachial or radial arteries in the upper limb. The symptoms and signs resemble those produced by embolism but the onset is usually more gradual and gangrene is less common and less extensive. Medical treatment as described for arterial embolism should be carried out. Since underlying arterial disease is usually present, operative interference is not advisable if the diagnosis is unequivocal.

## VENOUS THROMBOSIS (THROMBOPHLEBITIS)

Thrombophlebitis may be suppurative or non-suppurative, the latter being the common form.

**SUPPURATIVE THROMBOPHLEBITIS.**—This condition may be due to the introduction of infection into a vein, usually during prolonged intravenous infusion of blood or saline. There are usually general symptoms—malaise, fever and shivering. Pyæmia may follow if the condition is not treated promptly and effectively. Locally there is redness and pain, with swelling of the affected limb, and the thrombosed vein, if superficial, may be hard and tender. An abscess may form and local incision may be necessary. Treatment is by local application of heat and administration of an antibiotic to which the infecting organism is sensitive.

Suppurative thrombophlebitis may complicate pyogenic infection anywhere in the body. Thus mastoid infection may lead to suppurative thrombosis of the lateral sinus or jugular vein; pyogenic infection of the bowel may be followed by suppurative pyelophlebitis (p. 688).

**NON-SUPPURATIVE (SIMPLE) THROMBOPHLEBITIS.**—**Ætiology.**—Simple thrombophlebitis is a not infrequent complication of a variety of conditions which lead to venous stasis. The usual predisposing causes are chronic congestive failure, immobilisation after abdominal operations and childbirth. Thrombophlebitis complicates  $\frac{1}{2}$  to 1 per cent. of labours. Hysterectomy and other pelvic operations, herniorrhaphy, gastrectomy, cholecystectomy and splenectomy are the common operations followed by thrombophlebitis. The veins of the calf, the femoral vein or the long saphenous vein are most frequently involved, in that order. It has been assumed that venous stasis due to relative immobilisation is the primary cause of the thrombosis. This is almost certainly not the whole explanation. Other factors such as associated infection, or changes in blood coagulability due to the primary disease or to operative trauma are probably involved, but the exact mechanism is still obscure.

Thrombophlebitis occurs in other conditions where venous stasis is not a prominent feature. It may complicate polycythæmia, leukæmia or carcinomatosis. It may develop in any severe infection, especially typhoid fever. Finally, venous thrombosis is frequently encountered in otherwise healthy subjects who present no evidence of any predisposing factor. In such patients recurrent attacks may occur (thrombophlebitis migrans) and this condition may be so extensive as to produce chronic invalidism.

**Pathology.**—Venous thrombosis rapidly leads to inflammation of the vein. As a result of invasion by fibroblasts the clot becomes adherent to the vessel wall. The head of the thrombus is composed of leucocytes and fibrin (white thrombus) but the tail is lamellated due to layering of red and white clot. The tail itself becomes firmly adherent in a few hours and detachment to produce embolism rarely occurs after this interval and certainly not after 3 days. Canalisation in the organised thrombus results in partial restoration of blood flow.

**Symptoms.**—The characteristic picture is seen in so-called femoral thrombosis, in which the obstruction usually involves both external iliac and femoral veins. The whole limb becomes swollen; pain is variable and not usually conspicuous. There is congestion of superficial veins and frequently the thrombosed vein may be palpated as a tender, hard cord. Fever, malaise and tachycardia may be present at the onset. Thrombophlebitis secondary to abdominal operation usually starts in the deep veins of the calf and is observed between the fourth and fourteenth post-operative days in most cases. Local tenderness may be the only sign, although the circumference of the calf may be increased due to œdema. Passive dorsiflexion of the foot may elicit pain in the absence of other signs.

*Thrombosis of the axillary or subclavian vein* produces similar changes in the upper limb.

*Thrombosis of the inferior vena cava* may occur under the same conditions as peripheral vein thrombosis. Special causes are the pressure of abdominal masses such as liver abscess, ascites or retroperitoneal tumours, or thrombophlebitis migrans extending from the femoral veins. Swelling of both legs may be present due to associated iliac or femoral thrombosis. Distension of the venous collaterals over the lower abdomen develops later.

**Diagnosis.**—The early diagnosis of thrombosis of the calf veins after operation, described above, is particularly important. In cases without obvious precipitating cause full investigation is essential to rule out any underlying lesion, such as pelvic carcinoma involving the iliac veins or abdominal neoplasms compressing the inferior vena cava.

**Course and Prognosis.**—In the uncomplicated case œdema, pain and constitutional signs subside in 2 to 3 weeks and recovery is complete. Pulmonary embolism is the most serious complication of thrombophlebitis (p. 852). *Chronic venous obstruction* may follow femoral or axillary vein thrombosis, the chief manifestations being persistent or recurrent œdema and aching pain in the limb when standing

walking. Chronic venous distension leads to varicosities and varicose ulceration. Induration of the limb due to persistent œdema and recurrent cellulitis may produce lymphatic obstruction which greatly aggravates the swelling and further impairs the nutritional state of the tissues. Obesity, varicose veins and inadequate treatment in the early stages predispose to chronic venous obstruction.

**Treatment.**—Preventive measures against post-operative thrombophlebitis include early ambulation, leg exercises and massage, avoidance of tight bandages and pressure on the calves, and the adequate treatment of dehydration and infection. After operation and in congestive heart failure anticoagulant therapy, as described on p. 847, is given at the earliest intimation of venous thrombosis to prevent extension and pulmonary embolism. Ligation of the femoral vein or even of the inferior vena cava has been performed as a prophylactic measure against pulmonary embolism after thrombophlebitis has occurred, but these measures have not been justified by the results.

In the treatment of femoral thrombosis the patient should be kept at rest in bed until all œdema, tenderness and constitutional signs have subsided. The limb should be elevated to about 30° on an inclined plane. Hot fomentations may be applied to the limb if there is evidence of secondary vasoconstriction. Analgesics are given as required. After 3 days, active movements at all joints are encouraged. Should there be any return of œdema when the patient is allowed up, knee-length elastic stockings should be fitted; these are worn during the day and removed at night until the venous circulation returns to normal.

**THROMBOPHLEBITIS MIGRANS.**—This condition has already been mentioned as a recurrent form of idiopathic thrombophlebitis. Attacks of venous thrombosis occur over a number of years and the veins of the legs, arms, trunk and the inferior vena cava may be involved. Chronic venous congestion of the legs may lead to widespread varicosities and indolent ulceration. The cause is unknown and no effective treatment is available. In a rapidly progressive case it may be justifiable to give a course of anticoagulant therapy, but this is only a temporary measure and does not halt the progress of the disease.

## LYMPHATIC OBSTRUCTION

**Synonym.**—Lymphœdema.

**Ætiology, Pathology and Symptomatology.**—Lymphatic obstruction may be congenital (developmental or hereditary), traumatic, inflammatory or neoplastic. An idiopathic type (lymphœdema præcox) is not uncommonly seen, chiefly in girls or young women, coming on around puberty and aggravated by menstruation and a hot environment. There is often a family history.

*Congenital lymphœdema* may be present at or soon after birth. In the heredo-familial type (Milroy's disease) the condition occurs in successive generations and is usually present at birth. It may be unilateral or bilateral and the lower limbs are the more commonly affected. The fundamental abnormality appears to be stasis and dilatation (lymphangiectasis) in valveless lymphatics. The subcutaneous fat is replaced by a sponge-like mass of dilated lymph spaces and fibrous connective tissue.

*Inflammatory lymphœdema* may be due to pyogenic or non-specific chronic lymphadenitis and lymphangitis. Recurrent attacks of inflammation accompanied by malaise, fever and sometimes cellulitis, lead to progressive lymphatic obstruction and brawny swelling due to a combination of œdema and subcutaneous fibrosis. Severe lymphœdema (elephantiasis) is a feature of chronic filariasis (p. 326).

Infiltration or compression of lymphatics by new-growth may cause lymphœdema, although this type of obstruction more commonly affects the abdominal lymphatics to produce *chylous ascites*. Operative removal of lymph glands, e.g. of the axillary lymphatics for carcinoma of the breast is a common cause of lymphatic œdema.

**Diagnosis.**—Although pitting œdema is usually present, lymphœdema has a characteristic solid or brawny consistency due to its chronicity, which leads to proliferation of connective tissue and inflammatory fibrosis. The age and circumstances of onset, rate of development and presence or absence of primary lymphangitis make the diagnosis of the cause fairly obvious.

**Prognosis.**—Lymphœdema is a chronic disorder which increases gradually or by successive attacks according to the ætiology. Although partial remissions occur in the early stages, irreversible changes due to inflammation and connective tissue thickening eventually lead to permanent enlargement of the limb. Recurrent attacks of cellulitis and ulceration are then liable to aggravate the symptoms still further.

**Treatment.**—Attempts should be made to reduce the œdema by elevation of the limb and elastic bandaging. A well-fitting elastic stocking may keep the swelling down in less severe cases. If lymphangitis, cellulitis and ulceration are present every effort must be made to reduce œdema; the infection is treated by appropriate antibiotics and local application of a non-adherent (oily) dressing. Hereditary lymphœdema, if severely disabling, is best treated by superficial lymphangiectomy, the œdematous subcutaneous tissue being removed and the muscles covered with free skin grafts.

## ARTERIAL ANEURYSM

An aneurysm is a permanent dilatation of an artery due to destruction of its wall. Since the strength of the arterial wall lies in the muscular or musculo-elastic tissue of the medial coat the causes of aneurysm formation are pathological lesions affecting the media. These may be congenital, traumatic, inflammatory or degenerative.

**Congenital aneurysm** is almost entirely confined to the arteries at the base of the brain. The cause is a congenital defect of the media, leading to the formation of a "berry" aneurysm usually at some point on the circle of Willis. More than one aneurysm may be present. Pressure effects due to enlargement of the sac, and rupture, leading to intracerebral or subarachnoid hæmorrhage, are responsible for the various clinical manifestations (p. 1447). The so-called cirroid aneurysm is a developmental anomaly in which greatly dilated arteriovenous communications form a large vascular tumour, particularly in the brain.

**Traumatic aneurysm.**—This results from a penetrating injury, commonly a gunshot wound, which injures a main artery and gives rise to aneurysmal swelling. The sac may connect with the neighbouring vein, producing a so-called arteriovenous aneurysm. The main arteries of the limbs, especially the popliteal, are most frequently affected. A bruit is commonly heard over the sac. If an arteriovenous fistula is large, the pulse may be collapsing and increased cardiac output leads to cardiac enlargement. Treatment lies in closing the anastomosis and restoring continuity of the artery by local excision or grafting.

**Inflammatory causes.**—The common inflammations producing aneurysms are syphilis, bacterial endocarditis and periarteritis nodosa. The last may affect any artery, particularly the abdominal branches of the aorta, the cerebral and the limb arteries (p. 931). Syphilitic aneurysms are almost entirely confined to the aorta and its large branches (p. 858). Mycotic aneurysms in bacterial endocarditis are due to blockage of arteries by infected emboli arising from valvular vegetations. The femoral, brachial, retinal and cerebral arteries are particularly affected. Rupture of the last causes subarachnoid hæmorrhage. Mycotic aneurysms are becoming less common as a result of antibiotic therapy but may still arise when the causative organism is resistant to antibiotic control. Rupture of a mycotic aneurysm in a limb vessel may produce a large intramuscular hæmatoma, followed by great pain and swelling of the limb and even gangrene. Surgical release of tension by evacuation of clot may be necessary.

*Degenerative lesions* causing arterial aneurysms are atheroma and mucoid degeneration of the media. Atheroma produces a uniform dilatation of the aorta (so-called fusiform aneurysm) which commonly affects the ascending aorta, arch and descending thoracic aorta. Simple atheromatous dilatation of the abdominal aorta is not uncommon but true aneurysm formation, with the production of a large saccular tumour and painful erosion of the vertebral bodies, is always syphilitic. Medial degeneration is the usual cause of dissecting aneurysm.

#### DISSECTING ANEURYSM OF THE AORTA

**Incidence.**—Dissecting aneurysm is a not uncommon cause of sudden death. The subjects are almost always elderly and the incidence is reported to be five times as high in men as in women.

**Ætiology and Pathology.**—The primary cause is mucoid degeneration of the media. Atheroma is invariably present but is not itself a cause of dissecting aneurysm. The dissection occurs down the centre of the medial coat, forming a false channel between the two layers. The tear usually starts in the ascending aorta, less commonly in the descending thoracic or abdominal aorta. By rapid extension the aneurysm may reach the bifurcation of the aorta, occluding one or both renal arteries *en route*. Extension towards the heart may lead to rupture into the pericardium and sudden death. External rupture into the mediastinal or retroperitoneal tissues is less common. Very rarely the dissection may be arrested before any main arteries are involved and over a period of years there may be recurrent attacks. In most cases, however, death occurs in the first attack.

**Symptoms.**—The common presenting symptom is agonising pain in the abdomen, chest or back together with shock. The pain is persistent and may change in site as the dissection spreads. Obstruction of the renal vessels leads to pain in the loins and anuria. Occlusion of one or both common iliac arteries produces pain, numbness or coldness of the affected extremity. The patient is grey and collapsed, the pulse rapid and small, but the blood pressure is often maintained, hypertension being present in many cases. Involvement of the carotid or spinal arteries may produce paralyses, or the limbs may be pulseless and cold due to arterial obstruction. There may be some degree of improvement for a few hours, after which rupture into the pericardium may lead to a sudden attack of pain in the chest and fatal collapse.

**Diagnosis.**—The condition is most commonly mistaken for coronary thrombosis or an acute abdominal emergency such as perforation of a peptic ulcer. Diagnosis can only be made with certainty if signs of occlusion of specific arteries, *e.g.* renal, femoral, spinal or carotid can be detected. More often the diagnosis may be suspected in life but is only confirmed post mortem. There is no effective treatment.

#### COLLAGEN DISEASES

The term collagen disease was first used by Klemperer in 1942 to describe a group of disorders which had in common a general disturbance of connective tissue. This involved in particular the extracellular components of connective tissue, the collagen fibres and so-called ground substance. Included in this group are rheumatic fever, rheumatoid arthritis, polyarteritis nodosa, disseminated lupus erythematosus, generalised scleroderma and dermatomyositis. These conditions all show in different degree changes in connective tissue including fibrinoid degeneration of collagen, excessive deposition of collagen, increase and alteration in ground substance, proliferation of connective tissue with or without degenerative change and inflammatory cell infiltra-



tion. The conditions are distinguished pathologically by the degree and distribution of these particular changes.

Clinically as well as histologically these diseases have much in common and there are many cases which cannot be allocated to one or the other, but form a transitional picture between the various disorders. The pathogenesis in most instances is not clear, although there is evidence in some of the diseases of an allergic reaction to bacterial antigen. This is the case in polyarteritis nodosa. In disseminated lupus, evidence of abnormal antibodies in the circulation and hyperglobinaemia also suggest some abnormal antigen-antibody reaction. Polyarteritis nodosa, temporal arteritis, disseminated lupus, scleroderma and dermatomyositis are discussed here. Rheumatic fever and rheumatoid arthritis are dealt with elsewhere.

### POLYARTERITIS NODOSA

**Synonym.**—*Periarteritis Nodosa*.

**Definition.**—A disease in which widespread acute necrosis occurs in the arteries leading to a variety of functional disturbances involving the nervous system, heart, kidneys, lungs, blood and abdominal viscera.

**Incidence.**—The condition may occur at any age, though the maximum incidence is between 20 and 30 years. Males are affected three times as often as females.

**Ætiology and Pathology.**—The condition may be regarded as an allergic or hypersensitivity reaction to a bacterial antigen. In a considerable proportion of cases bacterial infection, particularly due to streptococci, precedes the onset of the disease. More recently polyarteritis nodosa has resulted from hypersensitivity to drugs (sulphonamides) and foreign proteins. The arterial lesions consist of necrosis with inflammatory reaction involving all coats of the arteries (pan-arteritis). There is great swelling in the intima; necrosis of the media may lead to aneurysm formation and even rupture. Intense inflammatory reaction of the adventitia (periarteritis) results. Obstruction of the lumen by thrombosis is common. Medium-sized and large vessels are characteristically affected, but arteriolar lesions may appear, especially in the viscera. The vascular lesions are essentially focal. The common sites for arterial necrosis are the kidney, abdominal viscera (pancreas, intestines, spleen, liver, gall-bladder, testis, mesentery), peripheral vessels, coronary arteries, cerebral arteries and rarely the pulmonary vessels. The disease is episodic, phases of activity being followed by periods of quiescence with healing of the vascular lesions. Organisation of the inflamed segments results in asymmetrical intimal thickening (endarteritis) with fibrosis in the other arterial coats. Pathological changes in the tissues such as infarction, hæmorrhage and peripheral nerve degeneration are the result of vascular necrosis or thrombosis. There is also severe anaemia and intense pulmonary oedema in the terminal stages. Diffuse glomerular nephritis may be an associated lesion.

**Symptoms.**—The clinical manifestations are protean and all systems may be involved. The following are the common methods of presentation :

- (1) Continued, irregular, unexplained fever. These patients present with malaise, loss of weight, progressive anaemia, muscle pains and general misery.
- (2) Polyneuritis, either local or symmetrical, may be the mode of onset and polyarteritis nodosa should be suspected in unexplained cases of wrist drop or foot drop associated with fever and anaemia.
- (3) The patient may present with hæmorrhage, either abdominal due to a ruptured aneurysm, cerebral or renal.
- (4) Paroxysmal attacks of bronchial asthma with transient non-specific pneumonitis.
- (5) Occasionally the mode of onset resembles some other disease; there may be polyarthritides suggestive of rheumatoid arthritis or a typical attack of acute diffuse nephritis or the development of malignant hypertension.

**Signs.**—Fever, tachycardia, wasting and anæmia are common to all forms. The temperature is irregular and moderately raised, but in severe cases may be very high. The general attitude of the patient, particularly in the later stages, is one of progressive depression and misery. Subcutaneous nodules may occasionally be discovered along the course of small arteries in the limbs or in the abdominal wall. Skin rashes are common and include purpura, urticaria and macular or maculo-papular erythema. Joints may show evidence of acute arthritis. There may be signs of pulmonary congestion and œdema and there is sometimes a marked element of bronchospasm. Hypertension is often absent in the early stages but with the appearance of renal involvement there is usually a moderate rise in blood pressure; very occasionally malignant hypertension develops during the course of the disease. Heart failure is a frequent late complication.

Abdominal signs are often vague, but may be due to hæmorrhage, perforation of the gut, or involvement of the gall-bladder or appendix by vascular lesions. Peripheral neuritis may be present as a "mononeuritis multiplex" or as symmetrical polyneuritis; cerebral lesions such as thrombosis or rupture of an aneurysm may lead to focal paralyses of wide variety. The kidneys are usually involved at some stage of the disease and albuminuria and hæmaturia are common. Rapid renal failure may develop as a result of progressive occlusion of the renal vessels.

Examination of the blood shows polymorphonuclear leucocytosis in 70 per cent. of cases and eosinophilia in less than one-fifth. The sedimentation rate is raised. Anæmia is nearly always present and is often severe.

**Diagnosis.**—If a subcutaneous nodule is discovered it should be removed for histological examination; otherwise diagnostic muscle biopsy should be carried out, as large a piece of muscle as possible being removed. Typical arterial necroses are found in the majority of cases by this technique. The differential diagnosis includes a wide variety of conditions, particularly other cause of obscure fever, nephritis, malignant hypertension, other forms of polyneuritis, cerebro-vascular disease and other collagen disorders. Diagnostic proof depends on the demonstration of the typical acute or chronic pathological changes in the arteries.

**Course and Prognosis.**—Phases of activity alternate with remissions during which the patient may be afebrile and free from symptoms. Occasionally recovery occurs spontaneously from a focal attack, e.g. a vascular lesion in the appendix or gall-bladder, and after an interval of perhaps a year the symptoms of generalised polyarteritis appear. In the absence of treatment the majority of patients run a progressive course, terminating in renal failure, hæmorrhage, pulmonary œdema or cerebro-vascular accident.

**Treatment.**—Cortisone or corticotrophin offer the only possible effective treatment. The use of these drugs is followed by prompt remission of fever with relief of symptoms and recovery of anæmia. Renal, cardiac or neurological damage may be arrested, but many of the results of vascular necrosis are irreversible. Cortisone may be used continuously or may be discontinued during remissions and resumed in full doses (100 to 300 mg. daily by mouth) whenever a relapse occurs. The ultimate outcome of this form of therapy is uncertain but it is apparent that the hormone may modify the disease in the active phases by preventing vascular complications, so that life may undoubtedly be prolonged.

#### TEMPORAL ARTERITIS

This condition was first described by Jonathan Hutchinson in 1890. It is an affliction of elderly subjects, usually over the age of 60, and the incidence is the same in both sexes.

**Ætiology and Pathology.**—The pathological process so closely resembles polyarteritis nodosa that a similar pathogenesis seems likely, but evidence of any pre-

cipitating factor is lacking. The lesion may be localised to one segment of the temporal artery or may extend along the vessel producing obstruction at several points. Histologically there is organised thrombosis, intimal proliferation, medial necrosis with giant cell reaction and adventitial inflammatory infiltration. Other arteries, including the cerebral, retinal and peripheral vessels, are occasionally similarly involved.

**Symptoms.**—These are general and local. There may be fever, malaise, anorexia, weakness, weight loss, night sweats and progressive anaemia as in polyarteritis nodosa. Pain over the temporal artery is a constant feature and may be associated with severe generalised headache. Involvement of other arteries may produce various symptoms such as impairment of vision or cranial nerve palsies. On examination there is tenderness over the inflamed artery, which is usually prominent, hard and nodular; pulsation may be absent; both temporal arteries may be affected. Blood examination shows an anaemia with variable leucocytosis and elevated sedimentation rate.

**Prognosis.**—The condition usually improves gradually and completely over the course of several months, although obliteration of the arteries is permanent. Relapses occasionally occur.

**Treatment.**—The majority recover without any residual disability. In view of the possibility of permanent visual impairment or paralysis when the retinal or cerebral vessels are involved, cortisone therapy may be tried in severe cases. Favourable results after this form of treatment have been reported.

#### DISSEMINATED LUPUS ERYTHEMATOSUS

**Definition.**—A diffuse disease of connective tissue characterised by a variable combination of the following manifestations: fever, increased sedimentation rate, symmetrical erythema, visceral lesions, hyperglobulinæmia and a specific serum factor which produces abnormal phagocytosis in leucocytes.

**Incidence.**—Eighty to 90 per cent. of cases are women of child-bearing age, but before puberty the sex incidence is equal.

**Ætiology and Pathology.**—The ætiology is unknown but various factors which may exacerbate the disease suggest the presence of a bacterial or chemical hypersensitivity reaction. Such factors are infection, drugs (especially sulphonamides), sunburn, exposure to X-rays or injection of foreign proteins. There are certain elements in the picture such as glomerular and arteriolar lesions in the kidney, polyarthritis and the episodic nature of the disease which relate it to other collagen disorders. Pathologically there is widespread involvement of the connective tissues although it is difficult to define any specific histological lesion. Fibrinoid necrosis of arterioles may be widespread in the viscera and there is fibrinoid change in collagen with increase in ground substance, particularly in serous membranes, synovial membrane, endocardium (so-called verrucous endocarditis), lymph glands, spleen and skin. Thickening of the capillary basement membrane of the renal glomeruli presents a characteristic wire-loop appearance. Pneumonitis, pleural effusions and hepatitis may be present.

**Symptoms.**—The course of the disease is one of remissions and relapses which may prove fatal in a few months or may continue for many years. Acute, subacute and chronic forms have been described but these courses merge into one another and merely reflect the great variations in intensity of the disorder. The name disseminated lupus over-emphasises the importance of the skin lesion which is variable in character and distribution and may be absent. In about one-fifth of the cases the disseminated lesion develops on a pre-existing discoid lupus. The characteristic picture is a red, slightly raised, sometimes œdematous eruption affecting particularly exposed areas, i.e. the backs of the hands and upper part of the front of the chest, with a butterfly distribution on the face. The rash may, however, be pleomorphic

or purpuric and splinter hæmorrhages of the nails are sometimes seen. There may be a low-grade, irregular fever or a swinging temperature, according to the intensity of the disease. Tachycardia, wasting and progressive anæmia are usual. Many cases present with obvious polyarthritis resembling rheumatoid arthritis; the fingers are particularly affected and are often cold and blue, suggesting Raynaud's phenomenon. The joint condition may be transient like that of rheumatic fever or more acutely inflammatory like infective polyarthritis; sometimes there is persistent severe joint pain with little objective change. Verrucous endocarditis produces few if any clinical signs in the heart although a systolic murmur may be due to organic mitral disease. Heart failure is usually a late development but isolated cardiac involvement, without other manifestations of the disease, has been described. Pericarditis is not infrequent. Dyspnoea is a prominent symptom and may be extreme in the early acute case; the usual cause is acute pulmonary congestion or a pneumonitis resembling "rheumatic pneumonia". Pleurisy with a small or moderate effusion often develops and pleuritic pain is a common complaint. A variety of lesions may appear in the abdominal viscera. The spleen is frequently enlarged and this may be associated with generalised enlargement of superficial lymph glands; both may subside dramatically when the temperature falls during a remission. Hepatitis may occur at any stage of the disease and clinically may differ from infective hepatitis only in the persistent high temperature. Abdominal pain, nausea, vomiting and diarrhoea and even gastro-intestinal hæmorrhage may occur, but are not common. Albuminuria indicates the development of glomerulonephritis which is an irreversible lesion and eventually leads to uræmia. The mental state of the patient is often labile, psychotic changes are common, and convulsions occur in about a quarter of the cases; both these may be presenting symptoms. The optic fundi occasionally show exudates, hæmorrhages or even papilloedema.

Special investigations are of great value in diagnosis. The blood sedimentation rate is always raised and often exceeds 100 mm. (Westergren). Hyperglobulinæmia is almost always present and at some stage there is a leucopenia with a total white count less than 5000 per c.mm. The anæmia may be non-specific and normocytic or hæmolytic, and platelets may be reduced. The serum should always be examined for the "L.E. phenomenon", which is positive in the great majority of cases. If serum from a patient with lupus erythematosus is incubated with leucocytes (from his own or from normal blood) characteristic inclusions appear in the cytoplasm of the polymorphonuclear leucocytes. These bodies are depolymerised desoxyribose-nucleic acid, presumably of nuclear origin. The *in vitro* phagocytosis of such inclusions is dependent on a gamma globulin fraction of the plasma proteins, possibly antibody in nature. More recently phagocytosis of this material has been shown to depend on an additional factor derived from platelet breakdown. These "L.E." cells are characteristic of the disease but are not entirely specific since the phenomenon has been observed in patients sensitised to penicillin and other drugs. The abnormal plasma globulin may produce a "false" positive Wassermann reaction (in about 20 per cent. of cases), which can be distinguished from a true positive by the treponema immobilisation test. Recent work has shown that an appreciable proportion of Wassermann tests carried out routinely give this false positive reaction and the L.E. phenomenon may be present in a small number of these cases; clinical manifestations resembling disseminated lupus may develop. Other patients with a false positive W.R. may subsequently suffer from a variety of symptoms whose relation to disseminated lupus is not yet clearly understood.

**Diagnosis.**—This depends on the association of the various clinical features described above with increased sedimentation rate, hyperglobulinæmia and the presence of the L.E. cell factor in the serum.

**Course and Prognosis.**—In fulminating cases death may occur from exhaustion, toxæmia, infection or convulsions after a few months. Most cases exhibit remissions

and relapses for several years and a few run a very chronic course. Where the condition follows discoid lupus the course is less severe and the outcome more favourable. The appearance of albuminuria is a bad prognostic sign.

**Treatment.**—Cortisone or corticotrophin are the only drugs which offer any possibility of controlling the disorder. In the active stage cortisone in adequate dosage produces prompt fall in temperature, subjective improvement, resolution of the rash and improvement in joint signs and pulmonary symptoms. The L.E. phenomenon often persists even though a full clinical remission follows treatment. The current practice is to raise the daily dose of cortisone rapidly (up to 400 mg. or more) until fever is controlled, and then to lower it gradually to a satisfactory maintenance dose. In severe cases the typical facies of Cushing's syndrome may be expected to develop before control is adequate and remission occurs. The appearance of psychotic changes or convulsions should not lead to discontinuance of treatment. A low sodium diet should be given together with potassium chloride to prevent salt retention and hypopotassæmia; œdema may develop in spite of low salt intake and is best treated by intramuscular injection of mercurial diuretics. Secondary infection is a serious hazard during cortisone therapy and appropriate antibiotics (*not* sulphonamides) should be given at the first sign of this complication. The treatment of disseminated lupus with cortisone is at present under extensive trial. Although a dramatic remission may be observed during an acute attack there is no improvement in the renal lesion once it has occurred, nor is there yet evidence that complete recovery may be produced.

#### GENERALISED SCLERODERMA

**Definition.**—A widespread disorder of connective tissue and blood vessels producing a progressive thickening of the skin and subcutaneous tissues. The heart, lungs, kidneys and other viscera may be involved.

**Ætiology and Pathology.**—The disease affects women more often than men, the usual age of onset being 30 to 50. No definite cause or precipitating factor is recognised. Occasionally circumscribed scleroderma (*morphea*) may develop into the generalised disease. Histologically there is great increase and thickening of collagen fibres, with slight fibrinoid change, affecting the skin, lungs, heart, gastrointestinal tract and joints. Some degree of atrophy and lymphocytic infiltration of skeletal muscle is found. Endarteritis obliterans occurs in the affected organs and severe fibrinoid necrosis of the glomerular arterioles may lead to renal failure.

**Symptoms.**—The disease commonly presents with swelling of the fingers, hands and face. The features become immobile and expressionless, the fingers pale and blue, and frequently the typical Raynaud phenomenon occurs with minimal scleroderma. As the process develops the skin is at first tense and swollen, then becomes stiff, hard and adherent to deep structures; finally, general tissue atrophy produces the fully developed picture to which the names *acrosclerosis* and *sclerodactyly* have been given. Ulceration of the finger-tips is usual in this stage and may be followed by gangrene of the fingers, which tends to be bilateral. The process may spread over the trunk and lower limbs and there may be extensive calcification in the sclerotic areas. Pigmentation of the skin is usually present and melano-leukodermia is sometimes seen. The joints are often stiff and painful and the muscles become weak and atrophied. Visceral involvement should always be looked for. Involvement of the œsophagus causes dysphagia due to loss of peristalsis and to the development of stenosis at the lower end. The heart is less commonly affected, but pericarditis or cardiac enlargement may be present and myocardial fibrosis may lead to heart failure. The electrocardiogram may show partial A.V. block with low voltage in the absence of clinical signs. Fibrosis of the lungs and bronchi may cause cough and dyspnoea. After albuminuria appears, acute arteriolar and glomerular necroses in the kidneys

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are apt to lead to the rapid development of uræmia without hypertension. Fever is present only in those cases which come on acutely; weakness and exhaustion occur in the chronic stages. Apart from the specific changes due to visceral lesions, special investigations reveal little of note except elevation of sedimentation rate and variable anæmia.

**Diagnosis.**—Raynaud's phenomenon occurs early in scleroderma and the distinction from Raynaud's disease rests on the presence of thickening of the skin in sites other than the fingers, *e.g.* on the face or trunk. Acrosclerosis occurs late in Raynaud's disease and it is always confined to the areas of digital asphyxia. Skin biopsy shows no specific histological changes; in the early stages there is œdema and perivascular infiltration, in the later stages, great increase in collagen.

**Course and Prognosis.**—Spontaneous recovery is very rare. Occasionally the disease runs an acute course with fever, marked constitutional changes and death from heart failure or secondary infection within a few weeks or months. In general, however, the onset is insidious and the course slowly progressive over a number of years. The later stages are often distressing as the patient becomes immobilised by the increasing rigidity of the skin and subcutaneous tissues. Fixation of the chest may lead to broncho-pneumonia. Uræmia, myocardial failure and inanition due to dysphagia may all contribute to the fatal outcome.

**Treatment.**—There is no effective specific therapy. Sympathectomy may relieve symptoms due to the Raynaud phenomenon in the hands or feet, but the symptoms usually returns after an interval of a year or less. Improvement with cortisone or corticotrophin therapy has been reported but in chronic scleroderma little more than slight subjective benefit can be expected.

#### DERMATOMYOSITIS

**Definition.**—A connective tissue disorder in which muscle necrosis is the most prominent feature, with increase in collagen in the skin, joints and viscera.

**Ætiology and Pathology.**—The borderline between scleroderma and dermatomyositis is ill-defined and both may be varieties of the same collagen disorder. The age of onset is usually between 10 and 50, the distribution is equal between the sexes, and there is no known ætiological factor apart from a possible association with malignant tumours. Histologically there is great increase and thickening of collagen fibres, with slight fibrinoid change in skin, joints and heart as in scleroderma. The affected skeletal muscles show severe necrosis with inflammatory cell infiltration.

**Symptoms.**—The onset may be sudden or insidious and the disease may be rapidly fatal or may run a chronic course with frequent remissions and relapses. Presenting symptoms are weakness, stiffness and aching pain in the muscles, involvement of which is usually bilateral and symmetrical. Fever is present in the acute phases. Weakness may be so extensive and severe as to suggest acute polyneuritis. Later, muscular atrophy occurs and contractures may develop. Involvement of the muscles of the larynx and pharynx may produce difficulty in talking and coughing, dysphagia and nasal regurgitation. Weakness of the diaphragm and intercostal muscles may lead to respiratory failure. Joint changes, with stiffness and peri-articular swelling, particularly affecting the fingers, resemble rheumatoid arthritis. An erythematous rash on the face and arms is common in the early stages and there may be œdema of the eyelids and hands. Thickening of the skin, as in scleroderma, may follow. Cardiac involvement is unusual except as a terminal event, but there may be electrocardiographic evidence of myocardial damage at an earlier stage.

Examination of the blood usually shows some elevation in sedimentation rate, and in the acute stage a considerable polymorphonuclear leucocytosis may be present. The urine sometimes contains albumin and always a marked excess of creatine.



Muscle biopsy reveals diagnostic changes in the form of muscle necrosis and inflammatory cell reaction.

**Diagnosis.**—The differentiation from scleroderma is impossible in some cases without muscle biopsy. In a severe acute attack polyneuritis may be suspected, but the absence of sensory changes, the pain and tenderness of the muscles and the finding of an erythematous rash or œdema of the face should make the diagnosis clear; if doubt remains, a positive muscle biopsy is conclusive.

**Treatment.**—In the acute stages cortisone or corticotrophin may produce a prompt and sustained remission. Special precautions should be taken to prevent respiratory infection and to deal with respiratory paralysis should it appear. In the chronic stages of the disease little benefit can be expected from hormone therapy.

CLIFFORD WILSON.

## SECTION XIII

### DISEASES OF THE RESPIRATORY SYSTEM

#### DISEASES OF THE NOSE

##### ACUTE CATARRHAL RHINITIS

(See The Common Cold, p. 147)

##### EPISTAXIS

**Ætiology.**—The causes of epistaxis may be classified as follows :

**Local causes.**—Trauma, including blows on the nose, fracture of the base of the skull, surgical operations and foreign bodies, small septal erosions, atrophic rhinitis when crusts separate, malignant disease, "bleeding polypus" of the septum and hereditary hæmorrhagic telangiectasia. Epistaxis may be an early symptom of leprosy.

**General causes.**—Hypertension, chronic nephritis, cirrhosis of the liver, violent exertion, extremes of heat and cold, congestion at the menstrual period or "vicarious menstruation", venous congestion, as in mitral stenosis, tumours in the thorax or root of the neck, emphysema, bronchitis and whooping-cough, blood conditions, such as pernicious anæmia, leukæmia, purpura, scurvy and all the acute infectious fevers, especially in the prodromal stage. To these may be added rarefaction of the air, as in aeroplane ascents and mountaineering, and poisoning by some drugs, especially salicylates and quinine.

The *source of the bleeding* is, in the large majority of cases, in a region called Little's or Kiesselbach's area, situated on the front and lower part of the septum just beyond the vestibule.

**Treatment.**—Severe epistaxis should always be treated, though it is of comparatively little importance in healthy young people. In older patients with high blood pressure the loss of blood may be beneficial, but the occurrence is so distressing and alarming to the patient that steps must be taken to control the bleeding. It is wrong to lay patients down; they should be propped up in bed with the head inclined slightly forward so that blood cannot enter the pharynx and larynx and add to their embarrassment.

The source of the bleeding is usually so far forward that a pledget of wool introduced for less than an inch into the naris, and held by compressing the nostril, will generally control it temporarily. To arrest it and prevent recurrence the bleeding spot must be found, controlled by application of cocaine and adrenaline on a plug of wool, and sealed by the galvano-cautery at dull-red heat. In obstinate cases the bleeding may recur from another spot or from the opposite naris, when the treatment must be repeated. As in other forms of hæmorrhage, a rapid, excited heart's action, associated with restlessness and fright, is often present, and an injection of morphine is of great value. If the bleeding is from the usual situation, formal plugging of the nose is seldom called for, but sometimes it is so profuse or the bleeding point is so far back that its situation cannot at first be determined. In such cases the naris should be evenly packed with ribbon-gauze introduced on forceps under direct vision. The older method of plugging the posterior nares is seldom required, and carries the risk of causing otitis media. Nasal plugs quickly become septic, and should ordinarily be removed in 24 hours; but if ribbon gauze impregnated with sulphanilamide powder is used this may safely be left *in situ* for 3 days

## ALLERGIC RHINITIS

**Ætiology.**—This is among the commonest and most obvious manifestations of allergy. As in other examples of this condition, the patient is susceptible to very minute doses of some substance, usually a protein, to which he has become sensitised but to which normal people are completely immune. It is thought that histamine or some closely allied substance is liberated which by altering cell permeability causes mucosal swelling. The substances which may cause allergic symptoms are numerous and diverse, and enter the body by various routes :

A. By inhalation : 1. Vegetable particles : the pollen of certain plants, especially grasses ; powdered orris-root, until recently a component of toilet powders ; moulds, especially dry-rot and the spores of some fungi ; and even the scent of such flowers as roses, though here association probably has a psychological effect. 2. Animal emanations : the dandruff of animals, horses, cats, dogs and others ; the feathers of poultry, which have their chief opportunity of acting when used to fill pillows and mattresses. 3. House dust, which may contain any of the above substances.

B. By ingestion : Numerous common and uncommon articles of diet, such as eggs, strawberries and fish, especially shell-fish, may produce allergic sensitisation ; the rhinorrhœa and skin-eruptions caused by the iodides and some other drugs may be of allergic origin.

C. From a focus of infection, most often from disease of the paranasal sinuses. The affection is distinctly hereditary and is often associated, either in the patient or his relations, with such other symptoms of allergy as asthma, urticaria, angio-neurotic œdema or chilblains. It often shows itself in early adolescence and tends to improve with advancing age, though it is not unusual for symptoms to commence in the second or third decade. Males and females are equally affected. It is most frequent among the upper classes. A mental shock is sometimes the starting-point of the attacks, and a psychogenic influence is often apparent.

**Symptoms.**—The nasal mucosa is swollen, pale and waterlogged. Fits of sneezing are associated with profuse watery discharge, irritation of the nasal and conjunctival mucous membrane, and often much depression and prostration. The nasal airway may become almost completely obstructed, and this is liable to happen when the patient enters a hot, stuffy room. Sudden clearing of the obstruction may occur when he goes out into the open air. The rapidity with which the symptoms come and go is sufficient to distinguish them from the ordinary coryza. The predominating cells found on examining a nasal smear are eosinophils, and eosinophilia is often evident on blood examination.

Sensitisation to pollen is the commonest variety of allergic rhinitis, and is known as "hay-fever" ; it is seasonal and, when caused by the pollen of grasses, the attacks begin about the end of May and cease in August, and those due to heather continue a few weeks longer.

**Treatment.**—The determining factors, which should receive attention, are heightened irritability of the nervous system, occasionally some intranasal abnormality which increases the sensitiveness, and the specific irritant. Hay-fever patients are better in a locality as free as possible from pollen ; some remain comparatively well at the seaside, others only on board ship and a few have to spend the best days of the year in a darkened room. It is only rarely that benefit results from correction of some nasal anatomical abnormality ; indeed, surgical treatment is only of real value when polypi in the ethmoid region cause so much crowding that nasal obstruction is almost complete (chronic nasal œdema). Cauterisation of the so-called sensitive areas, which comprise the septal mucosa opposite the middle turbinate and the mucosa on the anterior end of inferior turbinate gives but temporary relief in a small proportion of cases. Ionisation of the nasal mucosa with sulphate of zinc is also

employed. True hay-fever patients may have their susceptibility to pollen lessened by inoculation with dilute extract of pollen; the use of these extracts gives excellent results in a proportion of cases, and attempts are being made with varying success to test susceptibility to, and to immunise against, other proteid poisons. The antihistamine drugs must take their place in the symptomatic treatment of allergic rhinitis. Though they do not cure the condition they are of value in alleviating severe nasal obstruction. This is especially the case when dealing with seasonal allergy (hay-fever), phenindamine (Thephorin) 25 mg. may be given in the morning and promethazine (Phenergan) 25 mg. in the evening. These drugs are much less effective in cases of perennial nasal allergy. The conjunctivitis often needs attention; a simple lotion may be used with an eye-bath or as drops: acid. borici gr. 4, zinci sulph. gr.  $\frac{1}{2}$ , aquam dest. to fl. oz. 1; 1 drop of adrenaline, 1 in 1000, also gives great though transient relief. Dark glasses, too, are very helpful.

### ACCESSORY-SINUS SUPPURATION

**Ætiology.**—In the large majority of cases infection reaches the accessory sinuses from the nasal cavity, and may result from a simple coryza or from one of the acute infectious fevers. Influenza is especially liable to produce disease of the sinuses. Badly maintained swimming baths are often responsible for initiating the disease. In addition, antral suppuration is caused by infection from the teeth, particularly the second bicuspid and first two molars, whose roots are in closest proximity to the antral floor. When one sinus becomes infected, spread to other sinuses is to be expected if appropriate measures are not taken in the early stages.

**Symptoms and Diagnosis.**—If the ostium of a suppurating sinus be occluded pus is secreted under pressure and the local symptoms are severe, whereas if the secretion can escape freely there may be no symptoms except discharge. The former class of case has been called "closed" and the latter "open" empyema. The difference between the two is, however, only relative, and many cases are alternating, the severe symptoms being relieved by periodical discharge. As the pressure of pus in the cavity depends on the rapidity of its secretion and the degree of occlusion of the ostium by inflammatory swelling, it follows that the closed and open cases correspond generally to acute and chronic suppuration; acute suppuration is usually fairly obvious, but some chronic cases with scanty discharge are only to be detected after very careful examination and may be for long the undiscovered cause of post-nasal catarrh, pharyngitis or chronic toxæmia. In all doubtful cases a radiograph should be taken.

The symptoms are pain, tenderness and discharge, together with the secondary effects of the suppuration. Pain is often severe in acute cases, and in chronic suppuration there may be a heavy feeling over the face. Frontal pain of an intermittent character relieved by a sudden gush of discharge from the nose is highly characteristic of sinus disease, as also is a peculiar periodicity, for it tends to begin regularly at the same time every morning and to get better during the afternoon. Tenderness can usually be elicited in frontal empyema by percussion over the anterior wall, and especially by pressing upwards against the floor of the cavity; in antral disease tenderness over the canine fossa is uncommon. Discharge into the nose is the most important, and often the only, symptom. A localised stream of pus which reappears after removal is, in the absence of a foreign body or malignant disease, conclusive evidence of suppuration in an accessory sinus. Further assistance is afforded by transillumination and skiagraphy, though transillumination is a somewhat unreliable test. A good radiograph will usually demonstrate clearly the extent of the disease, and puncture of the antrum with trocar and cannula should be carried out in doubtful cases. Fœtor, both subjective and objective, is not common, and when present it must arouse the suspicion that the primary cause is dental.

**Complications.**—These include pharyngitis, laryngitis, bronchitis and otitis media; the swallowed pus causes various forms of gastric and intestinal disorders. *Acute septicæmia and pyæmia are rare, but symptoms of chronic poisoning are common, and include anæmia, arthritis, fibrositis and even mental aberrations.* A very important series of complications results from extension of the inflammation to surrounding parts: orbital abscess or cellulitis, osteomyelitis of the frontal bone, cerebral abscess, meningitis, thrombosis of the cavernous sinus.

**Treatment.**—This in the most acute stages entails complete rest in bed. Inhalations are of little value and give rise to much unnecessary exhaustion. It is useful to promote shrinkage of mucosa in the middle meatus by prescribing ephedrine, 0.5 per cent. in normal saline, dropped into the nose when the head is bent backwards, or introduced by means of an atomiser. Analgesics and hypnotics should not be withheld. Antibiotics should be prescribed for severely ill patients in the acute stage, especially if the frontal sinus is known to be involved. Penicillin is usually effective though there is some evidence to show that chloramphenicol is even better. In recent cases of antral suppuration the cavity should be punctured and washed out with saline, a procedure which in most cases must be repeated every 3 or 4 days until the washings are returned clear.

Acute frontal sinusitis is scarcely ever seen in the absence of an infected antrum on the same side. If the antrum is successfully treated the frontal sinus will almost always recover spontaneously, though it may be necessary when the more acute stage has passed to rectify anatomical or pathological conditions which interfere with the patency of the fronto-nasal duct. Thus, the anterior end of a middle turbinate may have to be inflected or even removed, or the septum may have to be straightened. Cases which fail to recover under such treatment have entered upon the chronic stage and sooner or later will require an external operation.

## DISEASES OF THE NASO-PHARYNX

### ADENOIDS

**Ætiology.**—By this term is implied chronic enlargement of the lymphoid tissue in the naso-pharynx. This is normally present in childhood and disappears by the age of 20 or thereabouts. The precise stage at which enlargement becomes pathological can only be determined by the symptoms; these usually become manifest between the ages of 3 and 8, but occasionally show themselves at or soon after birth. The incidence of adenoids is universal, but it is in damp temperate climates that the child population is most affected. Lymphoid tissue may hypertrophy during an attack of measles or scarlet fever, and a series of severe colds will lead to permanent hypertrophy.

**Pathology.**—The adenoid, as it should really be called, or enlarged pharyngeal tonsil, is a mass of lymphoid tissue of definite anatomical shape; it is thickest above and tapers away below, and presents a series of ridges which radiate from below upwards and slightly outwards. In older patients the mass is firmer and more fibrous, and the ridges are often adherent in places, leaving deep clefts and furrows in which secretion can collect and decompose.

**Symptoms.**—The symptoms of adenoids are many and various, and include those due to nasal obstruction, those caused by infection and by the extension of inflammation, and reflex processes attributable to irritation and lowered vitality. In infants nasal obstruction interferes with sucking and a serious degree of malnutrition will result unless the baby be carefully spoon fed. Older children snore at night, breathe heavily in the day, and either bolt their food or eat very slowly owing to the

necessity of breathing through the mouth. Lack of oxygen induces restless sleep, patients wake unrefreshed and develop an inability to concentrate. Persistent nasal obstruction during the period of growth mechanically produces permanent deformities of the jaws and face which narrow the nasal passages, prevent the mouth from closing naturally and thus perpetuate mouth-breathing. When the mouth is habitually held open, the *alae nasi* are pulled downwards with the cheeks, become narrow and slit-like and fall in like valves with each inspiration; this "alar collapse" is an important cause of obstruction in neglected cases of adenoids. The palate is narrow and highly arched; the dental arch is narrow and V-shaped, so that the upper incisors, crowded and prominent, look outwards rather than forwards and are not covered by the short upper lip; the lower jaw retains its infantile obtuse angle, and the lower incisors lie behind the upper; the chin is receding and, in the worst cases, when the molar teeth come into contact on biting, the incisors cannot meet. Only a proportion of cases of adenoids show these deformities, and there is, indeed, considerable uncertainty as to the importance of adenoids in their ætiology; undue softness of the bones, such as occurs in rickets, is doubtless an additional factor, and also in the causation of the malformations of the chest which result from obstruction to the entry of air. The long narrow unexpanded chest with acute costal angle and prominent scapulae is the commonest deformity. Harrison's sulcus, a transverse depression corresponding to the attachment of the diaphragm; pigeon-breast, a prominent sternum with depressed costal cartilages; and funnel-breast, a sharp depression at the lower end of the sternum, are also encountered.

Various infective processes result from the spread of inflammation, and if the naso-pharynx be large, are not necessarily associated with nasal obstruction. The common catarrhal and suppurative affections of the ear in children are, in an overwhelming majority of cases, the result of adenoids. Blepharitis and phlyctenular conjunctivitis are also associated with adenoid vegetations. Feverish attacks, often with tender enlargement of the cervical glands, are caused by infection of the adenoids and tonsils, and tuberculous disease of the glands is usually due to passage of the bacilli through these portals; in such cases the tonsils and adenoids may remain unaffected or may themselves show tubercles when examined under the microscope. Chronic or recurrent bronchitis frequently results from the infection spreading to the lower air-passages. The mucus secreted by the adenoids is swallowed in large quantities, and produces derangements of stomach and intestines with failure of growth and general health. Finally, mouth-breathing predisposes to dental caries. The irritation of these vegetations, and their effect on respiration and the general health, account for numerous reflex and nervous disturbances, such as cough, laryngitis with spasm, and laryngismus stridulus; more remote conditions, stammering, night terrors and nocturnal enuresis, are sometimes ascribed to adenoids, but are by no means always cured by their removal.

**Diagnosis.**—Tractable children usually permit the use of a small post-nasal mirror through which a satisfactory view of the naso-pharynx can be obtained. An irregular convex mass can be seen, sometimes so large that other landmarks are obscured. In nervous children, if the symptoms point strongly to adenoids it is wiser to give an anæsthetic for examination, being prepared to remove the vegetations if present. Digital examination of the naso-pharynx without an anæsthetic is cruel and should not be undertaken. Infection of one or both antra is not uncommon in small children; such infection may coexist with hypertrophy of adenoids and tonsils. Disappointment after operative removal of tonsils and adenoids can often be explained by the fact that antral infection has not been discovered. Some rhinologists go so far as to have all children radiographed before operation; if infection is confirmed antral lavage can be carried out under the same anæsthetic. In the mongolian type of idiocy the tongue is large and the mouth persistently open, and in microcephaly the extremely undeveloped naso-pharynx causes nasal obstruction; cases of both these

types of maldevelopment are often brought to the doctor in the hope that removal of their adenoids will cure their "backwardness", and care should be taken not to fall into the error of performing a useless operation. On the other hand, adenoids can be present and produce serious secondary effects without causing nasal obstruction or any appearance of the typical "adenoid facies".

**Treatment.**—The normal naso-pharyngeal tonsil becomes swollen during coryza, and such temporary swelling should not be diagnosed as "adenoids".

When the enlargement frequently recurs or has gone on to chronic hypertrophy, operative removal is the only treatment, and this is especially called for when any aural symptoms supervene, or when cervical adenitis is present. If the *alæ nasi* are collapsing, or the chest narrow, breathing exercises are important and should be started forthwith.

## DISEASES OF THE LARYNX

### ACUTE LARYNGITIS

**Ætiology.**—This affection most often occurs during the course of a cold, the inflammation spreading downwards from the nose and naso-pharynx. Over-use of the voice will precipitate an attack, especially if voice production is faulty. It arises in the course of acute infectious fevers such as influenza, measles or scarlatina. Predisposing causes are nasal obstruction, infection of sinuses, tonsils or teeth and sedentary occupations in ill-ventilated overheated rooms. Acute laryngitis of a non-tuberculous nature is not uncommon in patients with pulmonary tuberculosis.

**Symptoms.**—The symptoms consist of hoarseness, local discomfort varying from dryness or tickling to a burning sensation or actual pain and irritating cough. There is little expectoration, unless the trachea and bronchi are involved. At the onset there may be slight feverishness and malaise. The degree of hoarseness is by no means proportionate to the objective appearances; the voice may be quite good in cases of decided hyperæmia, and may be completely lost when little abnormal is to be seen. A muscular man may retain a strong voice with a degree of inflammation which would render a weakly woman almost aphonic—indeed some women lose the voice with every slight cold, so that it becomes difficult to differentiate between laryngeal catarrh and "functional aphonia". On the other hand, in some voice-users redness of the cords appears to be the normal condition and causes no interference with function. This variable effect on the voice is to be observed in all forms of laryngeal disease. In children, acute laryngitis is a serious affection. They show a far greater tendency to œdema and to spasm and, as the glottis is not only absolutely but relatively smaller than in adults, dangerous dyspnoea may ensue with great rapidity. The larynx is reddened, and this is most obvious on the parts usually pale—the epiglottis and vocal cords, the vessels on the former being unduly prominent. The cords may be red or salmon pink, or may merely have lost their bright pearly lustre. A small amount of mucous secretion is generally present, but no large accumulations or strings of mucus, such as are seen in chronic laryngitis.

**Treatment.**—The patient should be confined to a warm (65° F.), well-ventilated room, preferably in bed, and must not attempt to use the voice. Steam inhalations are of value and may be used from an inhaler or from a jug round the mouth of which a towel has been wrapped in the shape of a cone. The water should be at a temperature of 130° to 140° F., and fl. dr. 1 or 2 of tinct. benzoin co. (Friars' balsam) should be added to the pint. This simple prescription cannot be improved upon though it is sometimes worthwhile incorporating menthol gr. 10. Inhalations should only be prescribed when the patient is confined to his room. At a later stage instruction

may be given in the use of an atomiser of the de Vilbriss pattern charged with protargol 10 per cent. Internally, expectorants are indicated; tinctura ipecacuanhæ, min. 10, or vinum antimoniale, min. 5, potassium iodide, gr. 2 or 3, ammonium carbonate, gr. 4, every 4 or 6 hours. If cough is severe it should be restrained by means of a tincture containing codeine phosphate gr.  $\frac{1}{2}$  or liquor morphinæ, min. 2 to 4 to each drachm.

## ŒDEMATOUS LARYNGITIS

**Synonym.**—Œdema of the Larynx.

**Ætiology.**—Œdema of the larynx is not a disease but a pathological condition due to a variety of causes. Non-inflammatory œdema may be mentioned here for the sake of completeness; it occurs, though rarely, as part of the general anasarca of renal and cardiac disease. Angio-neurotic œdema sometimes occurs in the larynx, in which event it produces rapid and sometimes fatal dyspnœa (see p. 1255). The swelling which occasionally results from administration of potassium iodide in susceptible subjects may be placed in the same category.

Inflammatory œdema seldom results in adults from a simple catarrh, but it may do so in children; it more often occurs as part of an acute septic infection of the pharynx, trachea and bronchi, "acute fulminating laryngo-tracheo-bronchitis" (*q.v.*). Œdema may follow various forms of trauma, the drinking of corrosive poisons, inhalation of irritating vapours such as the poison gases of warfare, the lodgment of foreign bodies or rough or unduly prolonged bronchoscopy. Scalding, from attempts to drink from a kettle-spout, is a common cause among children. In other cases it is a sequela of typhoid fever, pneumonia, scarlet fever or small-pox, and is a local complication of syphilitic, tuberculous, cancerous or traumatic ulceration.

**Symptoms.**—If part of a septic pharyngo-laryngitis, the general symptoms are severe. The chief local symptom is dyspnœa with inspiratory stridor and the associated symptoms of asphyxiation; there is hoarseness or aphonia, local discomfort and tenderness and sometimes dysphagia. The aryteno-epiglottidean folds are enormously swollen, appearing as pale or purple translucent flask-shaped masses; if the epiglottis be œdematous it forms a sausage-shaped swelling of the same appearance. The mucosa of the vocal cords is too adherent to permit much swelling, and "œdema of the glottis" is therefore a misnomer. The subglottic region is lax and may become swollen; indeed, the œdema may be confined to this region and then appears as a red swelling below each vocal cord. In children œdema may be inferred from the steadily increasing dyspnœa without the rapid increase and decrease typical of spasmodic laryngitis.

**Treatment.**—Patients should be nursed in a semi-sitting position. In slight cases, the swelling may be reduced by sucking ice and by the application of an ice-bag to the neck; the latter is inadmissible in young children. A spray of adrenaline, 1 in 1000, may be used. Hypodermic injections of pilocarpine, gr.  $\frac{1}{2}$ , are recommended, and for the œdema produced by iodides, large doses of bicarbonate of soda. When œdema is the result of an acute streptococcal infection, full doses of sulphonamides and penicillin should be given without delay. Scarification of the œdematous tissues with a curved bistoury, which was accepted practice in the past, is now not recommended because of the disturbance it causes to patients, the danger of blood entering the trachea and the chances of giving rise to secondary infection. Tracheotomy should be performed before respiratory embarrassment is too great; intubation is not recommended. Angio-neurotic œdema should be treated by a spray of adrenaline, but as this condition is often allergic in origin it is logical to prescribe full doses of one of the "anti-histamine" drugs such as promethazine or phenindamine. Intravenous calcium gluconate is excellent treatment. Very rarely tracheotomy may be necessary.



## MEMBRANOUS LARYNGITIS

The formation of false membrane in the larynx is nearly always part of an attack of diphtheria which is discussed elsewhere, but the term "membranous laryngitis" implies formation of membrane of non-diphtheritic origin. Apart from traumatic cases, due to irritating chemicals and scalds, inflammation of the larynx accompanied by membrane may be caused by streptococcal infection. The affection occurs especially in children between the ages of 2 and 8 years (see *Acute Laryngo-Tracheo-Bronchitis*, p. 946). The diagnosis from diphtheria is only possible by bacteriological examination, and pending the report the case should be treated with antitoxin. It may be noted that the pharynx is nearly always involved in diphtheria, whereas in membranous laryngitis the disease is often primary in the larynx. The prognosis is grave and worse than that of diphtheria since the introduction of antitoxin.

## ACUTE LARYNGEAL CONDITIONS AFFECTING CHILDREN

In the past it has been customary to describe a group of acute laryngeal conditions occurring in early childhood, all of which are associated with dyspnoea. A great deal of unnecessary confusion has arisen because there has been (and still is) some uncertainty as to the mechanism of such conditions. An unfortunate nomenclature has been evolved which is muddling and unhelpful.

An attempt will be made to clarify the situation by confining description to acute laryngitis in children, acute laryngo-tracheo-bronchitis, congenital laryngeal stridor and laryngismus stridulus.

For years the expression croup has been used so universally that many have wrongly supposed that the term denoted a definite disease. The word dates from a period when diagnosis of diseases of the throat was far from exact and the meaning was obstructive dyspnoea. The adjective "croupy" may still be used to describe noisy inspiratory stridor, itself a symptom of diverse laryngeal affections.

## ACUTE LARYNGITIS IN CHILDREN

In young children the larynx is small whilst the cartilages are soft and yielding. The mucosa is rather loosely connected to subjacent tissues so that effusion can take place more readily. It seems that the controlling nervous mechanism is somewhat unstable and that glottic spasm is more easily evoked. For these reasons laryngitis in children is always a serious condition, and alarming symptoms, especially dyspnoea and cyanosis, may develop with extreme rapidity. A child, save for a slight cough, may seem well during the day and then at night may suddenly develop laryngeal spasm and become seriously ill. Acute laryngitis with spasm is a better name than the old-established "laryngitis stridulosa", a term which, though accurate enough, has served to confuse generations of medical students.

**Treatment.**—The time-honoured treatment has been "an emetic and a purge". Emetics are certainly helpful in some cases and tincture ipecacuanhae, min. 60, may assist in the removal of obstructing secretions. An aperient may be given, remembering that there is no specific virtue in calomel. It is well to put up a steam kettle, and there are occasions when oxygen will be required. Antibiotics will not directly relieve laryngeal spasm but may be indicated to control the primary infection. Very rarely indeed is tracheotomy required. When the acute attack has passed the child should be examined with a view to eliminating unhealthy adenoids or tonsils.

## ACUTE LARYNGO-TRACHEO-BRONCHITIS

**Ætiology.**—This severe disease usually occurs in children under 3 years of age and is rarely seen after the age of 6. Weakly children are most often affected and the mortality even now is about 15 per cent. The responsible organisms may be streptococci, staphylococci, pneumococci or influenza bacilli. There is redness and swelling of the arytenoid region and gross subglottic swelling which spreads down into trachea and bronchi. An exudate is poured out into the tracheo-bronchial tree and quickly becomes thick and tenacious; its expectoration is often beyond the strength of the patient. Pneumonia and atelectasis from plug formation form a prominent part of the clinical picture.

**Symptoms.**—In most cases the disease develops comparatively slowly; only occasionally is an infant rapidly prostrated. The following graphic description is quoted from F. C. Emery. "As the disease progresses these patients become dehydrated, prostrated and finally present a picture of complete collapse. The cyanosis disappears, leaving an ashen pale skin and anoxic coma, with all the remaining energy being spent on breathing. Retraction may be so great that the sternum and thoracic spine seem to meet with each gasping inspiration."

**Treatment.**—Humidification of inspired air is important and a steam kettle can be used with advantage. Almost all cases must be at some time nursed in an oxygen tent; a mixture of helium and oxygen has been recommended by Jackson. Sleep is a grave problem as drugs given to ensure sufficient rest damp down the cough reflex. On the other hand, continual coughing may so sap the patient's physical strength that some opiate must be given. In theory causative organisms should be isolated and tested for sensitivity to the various antibiotics and sulphonamides, but time should not be wasted whilst waiting for the bacteriologist's report. Penicillin is generally useful, but evidence is mounting which suggests that chloramphenicol is substantially more effective. Every effort must be made to keep up the fluid intake.

Bronchoscopy often becomes an urgent necessity, for this may be the only practical method of ridding a patient of tenacious secretions and pseudo-membranous sloughs. Sometimes even this procedure is inadequate and an emergency tracheotomy is indicated. It must be remembered that obstruction to respiratory exchange may be as great below the tracheotomy as above it, but an opening in the trachea facilitates lavage and suction.

## CONGENITAL LARYNGEAL STRIDOR

In this condition there is an exaggeration of the infantile shape of the upper aperture of the larynx; the epiglottis is sharply folded laterally, the ary-epiglottic folds are almost in contact, and the opening is thus reduced to a narrow vertical slit. As these parts are very flaccid in infancy, they become sucked together during inspiration and, by their vibration, produce the characteristic stridor. This stridor is noticed very soon after birth, it is inspiratory, of a peculiar purring or even musical character, and is most marked during active breathing and crying. The voice is unaffected, and there is remarkably little sign of dyspnoea or distress. These characteristics distinguish the condition from other forms of obstruction found in infants, such as laryngeal webs or papillomata, or "thymic asthma". Symptoms tend to disappear during the second year of life, but the prognosis must be guarded in early infancy, for an attack of bronchitis is more than ordinarily dangerous and kills a proportion of these patients.

## LARYNGISMUS STRIDULUS

**Ætiology.**—This is a condition, clinically similar to glottic spasm, occurring in children. It is far commoner than the spasm of adults, and it has been suggested that the asphyxial attacks of laryngismus are caused by collapse of the soft and yielding cartilaginous framework of the larynx, and not solely by spasm of the muscles. It is commonest between the ages of 6 months and 2 years, but may persist later; it occurs in ill-nourished unhealthy children, often in association with rickets, and practically always in association with adenoids.

**Symptoms.**—The onset is sudden and attacks usually occur at night. The child wakes gasping for breath, and a series of short noisy inspirations is followed by complete cessation of breathing; a long crowing inspiration terminates the attack. There are retraction of the lower ribs and epigastrium, cyanosis and great terror and distress and, in severe cases, carpo-pedal contractions, convulsions and evacuation of urine and faeces. When the attack is over the child is perfectly normal and there is no hoarseness. Slighter and less typical attacks often occur.

**Diagnosis.**—This is easy if the symptoms are carefully noted; the sudden attack of dyspnoea, with complete absence of symptoms in the intervals, is quite distinctive.

**Prognosis.**—The prognosis is somewhat grave in severe cases; an infant rarely dies in an attack, but is often worn out and eventually succumbs to collapse of the lungs.

**Treatment.**—During the attacks the face and chest may be freely sponged with cold water, and the inhalation of amyl nitrite from a capsule broken in a handkerchief may be tried. The child should be supported sitting up, and the quickest relief can usually be obtained by drawing the tongue forward with a finger passed into the mouth to its base, a manoeuvre easily performed by the mother or nurse. The attacks are so short and sharp that there is no time for the hot bath or administration of bromides frequently recommended.

**Prevention** involves the control of rickets with vitamin D, fresh air, wholesome food and correction of digestive disturbances. Attention should be given to eliminating infection in the nose, and drops of protargol, 2½ per cent., may be instilled when the child is in the head-down position. It is particularly important to remove adenoids even if they are only moderately enlarged.

## CHRONIC LARYNGITIS

**Ætiology.**—The causation is similar to that of acute catarrhal laryngitis; indeed, chronic laryngitis is often the result of recurrent acute attacks. The principal factors which predispose to chronicity are nasal obstructions and discharges, dental infections and chronic tonsillar sepsis, dusty occupations and lack of fresh air, over-use of the voice and faulty voice production, and the abuse of alcohol or tobacco; consumptives are particularly liable to non-specific catarrhal laryngitis. Almost any cause of general ill health may be included among the predisposing causes.

**Symptoms.**—The only constant symptom is impairment of the voice, which is hoarse, easily tired or, rarely, almost completely lost. It is sometimes weakest when tired in the evening, but is often at its worst on rising in the morning or after a rest. There is frequently a sensation of aching, dryness, tickling or of a lump in the throat, and there is usually some cough, but little expectoration unless the trachea and bronchi are involved.

The objective appearances vary with the severity of the affection. The larynx generally is of a deeper red than usual, and the vocal cords have lost their normal, pearly lustre and are pink; they are usually somewhat thickened at the edges, enlarged vessels may be visible on their surface; the vocal processes are often prominent and may be reddened or show up white against the hyperæmic cord. Strings

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of sticky secretion may stretch between the cords, or a little globule of mucus may form on the centre of the cord during phonation; adduction is frequently imperfect. When the epiglottis is reddened, its yellow edge stands out clearly and enlarged vessels are visible; the ventricular bands are often swollen so as to hide the outer part of the cords. The mucous membrane in the inter-arytenoid space is seen to be thrown into folds on adduction of the cords, and may form a mass large enough to prevent their complete approximation. The general picture is one of symmetry, a useful point in diagnosis when tuberculous laryngitis is in question.

A patient suffering from atrophic rhinitis may develop an unusual form of chronic laryngitis known as *laryngitis sicca*, in which small brown scabs adhere to the cords and posterior commissure, but occasionally the disease itself spreads to the larynx, which is covered by large greenish or brownish-black fetid crusts; more rarely still the crusts extend into the trachea and cause severe dyspnoea.

*Pachydermia laryngis* is an uncommon variety of chronic laryngitis, occurring principally in middle-aged men. It is frequently ascribed to alcoholism, though perhaps on insufficient grounds and the diagnosis between pachydermia and tuberculosis or syphilis is often a matter of difficulty. The characteristic epithelial thickenings are probably of the nature of corns, resulting from frequent cough and continued irritation. There is hoarseness of a rough raucous character, but no particular discomfort. The epithelial thickening is pink or whitish and occupies the posterior region of the glottis from the vocal processes backwards to the posterior commissure. A circumscribed swelling appears on each vocal process, with a small cup or depression at the apex; the approximation of the cords is better than would be expected, because the prominence on one vocal process fits into the depression at the other. The epithelium of the inter-arytenoid space is thrown into ridges, which fill up the angles between the arytenoid and the posterior commissure, but leave a depression in the middle line. These firm, opaque, symmetrical swellings, without ulceration, are distinguishable from the soft irregular granulations of a tuberculous lesion.

**Treatment.**—The detection and correction of the ætiological factors are the most important part of treatment. Any constitutional disturbance, such as anæmia, rheumatism, gout or dyspepsia, should receive attention. Over-indulgence in tobacco or alcohol, lack of ventilation and exposure to dust must be considered, and with teachers the blackboard chalk is a common source of irritation.

Incorrect voice-production is a factor of great importance and a good speech therapist can often provide substantial help.

Almost always some infection is discovered in nose, sinuses, tonsils or teeth. Elimination of such infection is the most important step in treatment.

Locally, treatment must begin with rest of the voice, which should be absolute in the case of professional voice-users. Where there is much secretion a saline lotion may be used in a spray—sodium bicarbonate, borax, sodium chloride, gr. 10 of each, glycerin, 60 min., water to 1 oz. Oily solutions are usually preferred, such as menthol gr. 5, camphor gr. 2, chlorbutol gr. 5, or oil of eucalyptus in similar proportions, to 1 oz. of liquid paraffin. The direct application of pigments is not often called for, and is to be recommended only when pachydermatous changes are present. Dundas Grant advised an alcoholic solution of salicylic acid, beginning with 1 per cent. and increasing to 6 or 8 per cent.

Internally, small doses of potassium iodide, gr. 2 or 3 three times a day over long periods, is of value.

## TUBERCULOUS LARYNGITIS

**Ætiology.**—In all cases the disease is secondary to pulmonary tuberculosis, of which it is an important complication. It is probably caused by infection from the

sputum, is commoner in men than in women, and is most frequent between the ages of 20 and 40. St Clair Thomson found that the difference in sex-incidence is occupational, and that women working in office and factory are as susceptible as men.

**Symptoms.**—The disease attacks, in order of frequency, the vocal cords, arytenoid region, inter-arytenoid space, ventricular bands and epiglottis; in general the glottis is invaded before its upper aperture. The typical infiltration is finely nodular, pallid and soft in appearance; ulcers are shallow, with a smooth speckly base and pale ill-defined margin. On the vocal cord the disease chiefly attacks the posterior half and especially the vocal process, where ulceration readily reaches the underlying cartilage and may produce a deep triangular excavation. Thickening in the inter-arytenoid region is common; infiltration of the ary-epiglottic folds results in typical pale semi-translucent flask-shaped swellings, while the epiglottis appears as a firmer red sausage-shaped mass.

The voice is weak and has not the raucous quality associated with syphilis. Sometimes voice production is actually painful. Cough and expectoration are mostly due to the pulmonary disease and not in any considerable degree to the larynx. Pain on swallowing is common and often very intense; there may also be actual obstruction to deglutition and, in a late stage, entry of food into the larynx. Dyspnoea is rare.

**Diagnosis.**—Although signs of pulmonary tuberculosis are helpful in diagnosis, it is obvious that any kind of laryngeal disease may occur in a consumptive patient.

**From simple laryngitis.**—In the earliest stage of invasion tuberculous laryngitis may exactly resemble catarrhal laryngitis, but redness of one cord only is certainly not due to catarrh, and the latter quickly improves under treatment. Inter-arytenoid infiltration resembles pachydermia, but the latter is opaquely white, firm and symmetrical.

**From lupus,** typical tuberculosis differs completely. The former is painless, affects first the epiglottis and upper aperture, is never accompanied by œdema, and tends to cicatrization. But there is a chronic "lupoid" form of tuberculous laryngitis which attacks the epiglottis and is very similar to lupus.

**From syphilis.**—The tuberculous ulcer has an ill-defined margin without surrounding hyperæmia; the base has a yellow speckled appearance, and on healing there is little scarring or contraction. The superficial syphilitic ulcer has a well-defined hyperæmic margin, with a smooth, flat base; the deep ulcer is "crateriform", with thickened punched-out edge, and, on healing, leaves a dense scar and marked deformity. In general, syphilitic lesions attack the anterior half of the larynx, tuberculous the posterior; the former look firm and dense, the latter, soft, translucent and ill-defined.

**From neoplasms.**—Only the rare tuberculomata resemble innocent tumours. Occasionally tuberculosis attacks one vocal cord in an elderly patient, and may then easily be mistaken for epithelioma, especially when, as often happens in such cases, the pulmonary signs are inconclusive and tubercle bacilli absent from the sputum.

**Prognosis.**—This has greatly improved in recent years due to advances in the chemotherapy of tuberculosis.

**Treatment.**—Tuberculous laryngitis is but a complication of pulmonary tuberculosis, and by far the most important part of the treatment is that of the general infection. Complete vocal rest has in the past been the mainstay of treatment; this is a severe and depressing measure and it is now not always necessary to enforce complete silence. Streptomycin, combined with isoniazid or sodium aminosalicylate (P.A.S.) not only promotes healing of laryngeal lesions but within a very short time abolishes pain and dysphagia. It should now never be necessary to use a galvano-cautery or to insufflate analgesic powders, let alone to inject alcohol around the internal laryngeal nerve. In these days one no longer sees the desperate case of tuberculous

laryngitis in which the airway becomes obstructed and tracheotomy is called for. There have, however, been rare cases of cicatricial stenosis following "successful" chemotherapy.

## PARALYSIS

Paralysis of a vocal cord occurs in association with various diseases of the thorax and of the nervous system. The early form, unilateral abductor paralysis, causes no symptoms, and can only be recognised by laryngoscopic examination.

The original function of the laryngeal muscles is that of a sphincter to prevent the entrance of fluid into the lungs, and this sphincter, or adductor, is the only muscle present in the larynx of primitive air-breathing animals; the abductors are a later addition. In progressive lesions involving the nerve pathways the abductor muscles are first affected whilst the adductors continue to function for a variable time. The function of phonation, much more recently acquired, is associated with adduction and is under direct control of the will. Functional disturbances, therefore, always cause adductor paralysis, while organic lesions first affect the movement of abduction.

### ORGANIC PARALYSIS

The crico-thyroid muscle is supplied by the superior laryngeal nerve, and when this is injured the affected cord remains slack on phonation, but owing to the short course of the nerve isolated paralysis of this muscle is extremely rare; it results from surgical or suicidal wounds, and may occur after diphtheria. In lesions of the vagus above the origin of this branch the signs of this paralysis are obscured by that of the other muscles of the cord. The recurrent laryngeal nerves supply all the other muscles. In any progressive lesion of the nerve pathway the muscles become paralysed in a definite order; the abductors are first affected, then the internal tensors or thyro-arytenoidei and finally the adductors. This is known as Semon's Law.

There is but one muscle on each side which acts as an abductor of the vocal cord, namely, the crico-arytenoideus posticus (often, for convenience, alluded to as the posticus muscle). This muscle not only moves the vocal cord away from the mid-line during respiration, but its most posterior fibres brace back the arytenoid cartilage and stretch the aryepiglottic fold. The cartilage of Wrisberg is incorporated in the fold and helps keep it taut in an upright position. Thus it is that in "posticus" paralysis the aryepiglottic fold droops inwards and the cartilage of Wrisberg tilts forwards and inwards with it. Yet another thing happens, the arytenoid cartilage is free to slide and tilt forwards so that the cord appears shortened and tends to lie at a slightly lower level. This forward tilting and apparent prominence of Wrisberg's cartilage is of help in diagnosis.

### ABDUCTOR PARALYSIS

The affected cord lies immobile in the midline, being held there by the unopposed action of adductor muscles (crico-arytenoideus lateralis and inter-arytenoideus). On phonation the unaffected cord swings over to meet its immobile fellow so that the voice is unaltered. It is not quite true to say that during phonation the larynx appears normal, for on the sound side Wrisberg's cartilage seems to move forward in front of its fellow. The glottic aperture is reduced but dyspnoea is only noticed on exertion.

Bilateral abductor paralysis is a serious condition, particularly if the onset is sudden, as both cords lie together in the middle line, leaving a mere chink. Inspiratory



embarrassment is extreme, but the conical shape of the subglottic region allows expired air to blow the glottis open. The voice is quite good, though the patient must constantly pause in a vain attempt to fill the lungs. Were it not for forward displacement of the arytenoid cartilages referred to above, thus allowing a chink, patients would asphyxiate.

#### COMPLETE PARALYSIS

When only the recurrent laryngeal nerve is involved the affected cord assumes a "paramedian" position for the crico-thyroid muscle, an external tensor and weak adductor, is still acting. The cadaveric or intermediate position can only be assumed when this muscle also is paralysed, as in a lesion of the main vagus trunk above the superior laryngeal nerve from which it derives its innervation. The true cadaveric or intermediate position is half-way between abduction and adduction, whereas the paramedian position is somewhat nearer the midline. Few observers could distinguish such a small positional difference were it not for the fact that when the crico-thyroid muscle is acting there is still some cord tension, and when paralysed tension is absent, so that the cord presents a wavy appearance. The affected cord during respiration appears shorter and lies at a slightly lower level, and the cartilage of Wrisberg seems unduly prominent. The reasons have already been given when discussing the effects of posticus paralysis.

In a unilateral case, whether the lesion is true recurrent nerve palsy or high vagus palsy, there is at first inefficient closure of the glottis and a feeble husky voice results; air waste on phonation is characteristic. As time goes on the voice may improve because the unaffected cord compensates and swings right across the midline on phonation. At first there may be some overflow of water or food into the trachea but this also improves as time goes on.

When complete paralysis is bilateral there can be no hope of efficient glottic closure. The voice is feeble and "breathy," whilst spilling over into the trachea is a constant source of worry. Breathlessness is usually only evident on exertion. Bilateral complete paralysis is fortunately very rare.

**Diagnosis.**—The diagnosis is almost entirely a matter of accurate inspection. Obliquity of the laryngoscopic image, due to faulty position of the mirror, may cause confusion. In nervous subjects the cords are sometimes adducted on inspiration, but they will abduct naturally during the involuntary inspiration which follows a prolonged phonation. The only condition which really imitates paralysis is the fixation of the arytenoid cartilage which results from disease in or around the joint; its complete immobility with the presence of swelling or scarring often aids the diagnosis, but in old-standing cases of paralysis secondary fixation frequently occurs. In cases of arytenoid fixation there is no "dropping forward" of the cartilage of Wrisberg.

**Ætiology.**—The movements of the cords are represented bilaterally in the cortex cerebri, and stimulation of either centre produces movement (adduction) of both cords, from which it follows that no unilateral lesion above the bulbar nuclei can paralyse the larynx, and clinically we find that it is never affected in cases of hemiplegia. The bulbar centres lie in the floor of the fourth ventricle, and here a lesion of one centre causes paralysis of the cord on the same side which, in a gradually progressive lesion, affects first the abductor muscle. Thence the nerve fibres pass in the roots of the bulbar-accessory to the vagus and recurrent laryngeal nerve; the cause of the paralysis may, therefore, be situated (1) in the medulla, (2) at the base of the skull, (3) in the vagus or (4) in the recurrent laryngeal nerve.

Paralyses of bulbar origin are often, but by no means always, bilateral. In lesions here and at the base of the skull neighbouring nerves are liable to be involved; thus, paralysis of a cord and of the palate on the same side may coexist (syndrome of Avellis), or paralysis of cord, palate, trapezius and sternomastoid from involvement of the

spinal accessory roots, or persistent tachycardia due to damage of the cardio-inhibitory centre or nerves. *Tabes dorsalis* is the most frequent cause of paralysis of central origin; it may effect one or both cords and may be associated with anæsthesia, paræsthesia or the spasmodic attacks called "laryngeal crises". In general paralysis of the insane laryngeal palsy is not uncommon. It is the rule in bulbar paralysis, and is usually bilateral, but appears late in the disease. Syphilitic nuclear disease, pachymeningitis and gummata at the base of the brain are now rare causes, and here the ocular muscles, especially the external rectus, are often attacked.

Peripheral causes usually act by compression of the recurrent nerve, the most frequent being aneurysm, enlarged glands, tuberculous or malignant, and cancer of the œsophagus. Other causes are thyroid tumours, usually but not necessarily malignant, mediastinal tumours, cancer of the lung, pleurisy and pulmonary tuberculosis in which the nerve, usually the right, may be involved in a lesion at the apex of the lung or by tuberculous bronchial or tracheal glands. Neuritis is a cause of laryngeal paralysis; it may be produced by the toxins of diphtheria, or by organic poisons, especially lead, and more rarely arsenic and alcohol. Finally, the condition is not uncommonly the result of trauma, more especially surgical operations on the thyroid gland and lung.

**Prognosis.**—Paralysis of one cord is not in itself dangerous to life; but when the cause is undiscovered the prognosis must be guarded, for this paralysis may be for a long time the only sign of serious disease; on the other hand, the recurrent laryngeal nerve may be involved in some non-progressive lesion, such as a fibrotic bronchial gland, and such cases have been under observation for 20 or 30 years without change.

**Treatment.**—This depends on the cause. In most cases it is but a symptom of disease elsewhere and does not call for special treatment. In cases due to neuritis, strychnine and the local application of the faradic current by means of an intra-laryngeal electrode are indicated. Tracheotomy is advisable in bilateral abductor paralysis. A specially designed tube in which a valve is incorporated is used; this valve allows air to enter freely on inspiration but closes during expiration so that the voice remains unaffected. Operations devised to fix one arytenoid cartilage and vocal cord in a more lateral position sometimes give satisfactory results.

All patients suffering from laryngeal paralysis must be forbidden to swim.

#### FUNCTIONAL PARALYSIS (FUNCTIONAL APHONIA)

**Ætiology.**—Functional aphonia is a common manifestation of hysteria and occurs chiefly in young women. Many cases were encountered amongst men during the War of 1914–1918 and the War of 1939–1945, men whose terrifying experiences had driven them into a state of "battle exhaustion". Anæmia, debility and local inflammatory conditions may predispose to an attack of aphonia, but it seems clear that the condition would not materialise without some hysterical background. It is true that some women are rendered aphonic by acute laryngitis of moderate severity, but it is not the inflammatory process which prohibits cord approximation.

**Symptoms.**—Paralysis of the adductors presents a totally different clinical picture from organic paralysis. It is always bilateral; the larynx appears normal while at rest, but, on attempts at phonation, it is seen that the cords do not adduct into the position necessary for the production of the voice. Occasionally the internal tensors alone are working inefficiently, an elliptical chink is left between the cords anteriorly. If the crico-arytenoidei laterales are paretic, the entire glottis remains open to a variable extent, and, very rarely, the arytenoideus is affected alone, when a triangular aperture is left behind the vocal processes. The paralysis is hardly ever complete; indeed a considerable amount of movement is usually seen, though insufficient to produce phonation. In purely hysterical cases onset and recovery are sudden and

the voice when regained is clear, though perhaps at first less powerful than usual. Whilst examining the larynx through a mirror it is well to ask the patient to cough : if the cords remain separated during attempted phonation and come together on coughing the diagnosis of functional aphonia is not in doubt.

When a patient assailed by some great emotional disturbance is "struck dumb", she is not even able to whisper, for the whole speech mechanism is paralysed. This is called "hysterical mutism".

**Treatment.**—In patients suffering from debility the cause should be found and treated. Predisposing local inflammatory conditions should be sought for and appropriately treated. It is well to remember that patients suffering from chronic phthisis sometimes speak very softly and may become almost aphonic.

Although in some cases of true functional aphonia the voice can be temporarily restored by powerful local stimulation, this form of treatment is not recommended for aphonia will usually recur. The most difficult patients to treat are those who have been unsuccessfully subjected to such local treatment.

The physician must be sympathetic yet firm and confident, and it is his first duty to explain that there is no serious disease. The patient may be told that the trouble results from muscular inco-ordination.

The best long-term results are obtained when the voice can be restored during the first interview, and it is imperative that no relation or friend should be in the room. A good plan is to suggest that one group of muscles in the larynx is in spasm and that without complete body relaxation it is difficult to break down this spasm. The patient may be asked to lie on a comfortable couch and told to relax as though about to go to sleep. It is surprising how many patients will in fact go straight into a semi-hypnotic state. The "laryngeal box" may be moved from side to side across the vertebral column and suggestions made that by breaking down the spasm in this way the voice will be fully restored. More often than not when told to rouse herself and recite "God Save the Queen" the patient will do so in a normal voice. Should the voice be not fully restored the physician must retain his attitude of complete confidence, and assure his patient that there has been encouraging improvement, and that restoration of normal function can and will be attained in a short space of time. When the voice is restored it should be freely exercised. Really difficult cases must be referred to an expert for psychiatric treatment.

## SPASMODIC AFFECTIONS

### SPASM OF THE GLOTTIS

Spasm of the laryngeal muscles produces adduction of the cords, for, though the abductors are probably affected, they are overpowered by the stronger adductor muscles.

**Ætiology.**—(1) In the majority of cases the spasm is a reflex set up by local irritation : foreign bodies, including the laryngoscopic mirror, irritating gases and inflammation, ulceration or tumours in or near the larynx. (2) Spasm is also caused by irritation of the recurrent laryngeal nerves by mediastinal tumours and, especially, by aneurysm. (3) Central nervous lesions, especially tabes. (4) Functional disturbances, frequently hysterical, and sometimes excited by sexual disturbances.

**Symptoms.**—The attacks vary much in different subjects in severity and duration. The patient clutches some support or rushes to the window. The respirations are rapid and shallow, with loud inspiratory stridor, and, in the height of a severe attack, are completely arrested with all the signs of asphyxia. The subjective sensations include a horrible feeling of anxiety, but consciousness is not lost. Many cases are less acute but persist longer, even for several hours.

**Prognosis.**—The attacks are practically never fatal, unless a foreign body or tumour be present.

**Treatment.**—During the attack amyl nitrite or chloroform may be inhaled, and ampoules of these drugs should be kept at hand. Between the attacks sources of irritation should be sought for and removed, the upper air-passages brought to a healthy condition and the general health and mode of life should receive attention. Administration of bromides may be required when the attacks recur frequently.

W. I. DAGGETT.

## DISEASES OF THE TRACHEA

### INFLAMMATION OR TRACHEITIS

#### ACUTE TRACHEITIS

Acute tracheitis may occur from any condition leading to irritation of the mucous membrane of the trachea. When it occurs as a result of bacterial or chemical agency, the whole of the upper air-passages are usually involved in greater or less degree, and the clinical manifestations are not confined to the trachea. In some cases, however, the stress of the resultant reaction falls upon this tube, and the condition therefore requires separate consideration.

**Ætiology.**—1. *Microbic invasion.*—This is the commonest cause. The bacteria usually found associated with tracheitis are the so-called catarrhal organisms, such as *Neisseria catarrhalis*, the pneumococcus, the Friedländer pneumo-bacillus and *Hæmophilus influenzae*. It is probable that the primary organism in many cases is a virus. Frequently a streptococcus may be found, either alone or in association with one or more of those just mentioned. As with catarrhal inflammation of other parts of the upper air-passages, damp, cold or foggy climatic conditions predispose to tracheitis. It is more common in young and middle-aged adults than in infancy or in old age. Mouth-breathers are more liable to this condition. Exposure to sudden changes of temperature may be a factor in its onset.

Tracheitis may also occur as part of the clinical picture in some of the acute specific diseases, such as enteric fever, diphtheria, whooping-cough and measles. It is often a troublesome and distressing association or sequel of true influenza.

2. *Chemical agencies.*—Irritating or poisonous fumes and vapours may lead to a very acute form of tracheitis. It may therefore occur in certain occupations, unless adequate precautions are taken. The use of "poison gases" in warfare has drawn widespread attention to this form of the condition, since tracheitis was an almost constant result of certain forms of "gassing". The chief chemical irritants used in the War of 1914–1918 were chlorine, phosgene and dichloro-diethyl sulphide, commonly known as mustard gas. Of these the last was perhaps the most irritant to the trachea, and fatal cases invariably showed tracheal lesions. Direct inhalation of steam may also induce an acute tracheitis.

3. *Mechanical causes.*—The presence of a foreign body, or the invasion of the trachea by extension from malignant growth in adjacent structures may lead to a local or even to a general tracheitis. It is noteworthy, however, that the trachea is frequently spared in occupations involving the respiration of dusty air, which leads to deposits in the lungs and bronchial glands with resulting pneumoconioses. Although a coal miner's lungs are black, yet his trachea may be practically normal.

**Pathology.**—The changes found in the trachea vary from simple catarrhal inflammation to intense destructive changes with ulceration, and in some cases croupous

or membranous exudate. In the catarrhal forms, the mucous membrane shows changes similar to those in bronchitis. It is at first swollen, red and dry, the vessels running across the trachea being engorged and clearly visible. Then, owing to increased activity of the mucous glands, excessive mucoid secretion occurs and the mucous membrane becomes moist, after which resolution may take place, or the process may proceed to a muco-purulent stage, when the fluid on the membrane coheres to form yellowish or green tenacious pellets. Occasionally numerous red blood cells are extruded and the tracheal exudate becomes streaked, tinged or uniformly pinkish.

In some inflammations, such as those induced by poison gases or inhaled steam, the mucous membrane may be intensely engorged and actual destruction may occur, involving even the deeper structures and the cartilages, so that greyish yellow sloughs result, which on separation leave ulcers. In diphtheria the characteristic false membrane composed of necrosing fibrin, leucocytes and bacilli may be found loosely attached to the mucous membrane, as in other localisations of this process. It may be primary or secondary to faucial or laryngeal diphtheria, either by direct extension or through diphtheritic infection of a tracheotomy wound.

In influenza the pink appearance of the trachea is of such constancy in fatal cases that it has come to be regarded as one of the most characteristic post-mortem changes found in this disease. The bright injection generally involves the lower half of the trachea, but it may occur along the whole length of this tube.

In whooping-cough the inflammatory reaction is usually less acute.

In typhoid fever small ulcers may occasionally be found in the trachea similar to those occurring more commonly in the larynx.

**Symptoms.**—Acute catarrhal tracheitis usually begins more or less acutely, like the common "cold", of which it is to be regarded as one form, with malaise, slight headache and a mild degree of fever, the temperature being usually between 99° and 100° F., rarely 101° F. The patient soon experiences a sensation of irritation behind the sternum, rapidly leading to a harsh, dry cough of noisy character. The cough aggravates the retrosternal discomfort, which develops into a sensation of rawness or soreness, making the cough very painful and distressing. If the larynx is involved at the same time, the voice becomes hoarse and sometimes lost, or reduced to a raucous whisper. In tracheitis alone the voice is usually unaffected. After from 12 to 24 hours the condition passes into the mucoid stage. The cough becomes looser and less painful, and small pellets of tenacious mucus are coughed up, usually greyish or black in town-dwellers, whitish in those in rural conditions; in either case, the mucus may be streaked with blood or even tinged a uniform pink colour; in the more acute forms it sometimes becomes yellow and more purulent. In the mucoid stage, the retrosternal soreness becomes less, the constitutional symptoms abate, while the temperature subsides and becomes subnormal. The patient often feels weak and out of health for some days, and is sometimes left with a noisy morning cough and tracheal irritation which may last for days or weeks. The aspect of the patient shows nothing characteristic. There is the general appearance of fever, malaise and discomfort. The rise of temperature and increase in pulse-rate are usually moderate. In the early stages physical examination of the chest shows no abnormality, but when exudation occurs a coarse wheeze may be audible over the trachea, particularly when the patient takes a deep breath or just before a cough occurs.

**Diagnosis.**—The association of catarrhal symptoms with a dry, harsh cough and retrosternal soreness, without signs of bronchitis, is almost pathognomonic. In some cases the diagnosis can be established with the laryngoscope or by endoscopy, but in most the discomfort which these examinations entail is unnecessary.

**Prognosis.**—This is almost invariably good, except in debilitated subjects or in those with cardiac or renal disease, in whom the process may spread to the larynx,

dysphagia and sometimes laryngeal paralysis reveal the origin of the tracheal symptoms when they occur. In this case copious frothy mucoid expectoration is frequent, and when ulceration develops with perforation, food particles may enter the trachea, excite cough and soon lead to inhalation broncho-pneumonia or gangrene. When the growth is near the bifurcation, urgent dyspnoea is the rule, and spasmodic attacks may occur, causing extreme distress. In most cases of tracheal growth the characteristic clanging brassy cough (gander cough) of tracheal obstruction can be heard. The trachea may be pushed to one side and its lumen distorted and obstructed by growth in the cervical glands or in the thyroid gland. In mediastinal new-growth invading the trachea, the pressure signs and symptoms characteristic of that disease usually render the explanation of the tracheal symptoms apparent.

**Diagnosis.**—Intratracheal growths have to be differentiated from other causes of tracheal obstruction, and the diagnosis is considered in detail under that condition. Endoscopy affords valuable confirmation if it is practicable or desirable. In oesophageal and mediastinal new-growths invading the trachea, radiographic examination may assist in diagnosis.

**Course.**—This is generally rapidly progressive.

**Prognosis.**—This is hopeless, death occurring from asphyxia or from some complication or by asthenia.

**Treatment.**—Treatment can be palliative and symptomatic only. In obstruction, it may be possible in rare cases to give temporary relief by a low tracheotomy, but, as a rule, this is impossible, owing to the presence of obstruction below any point where the trachea is accessible.

## THE INFECTIVE GRANULOMATA

### SYPHILIS

The trachea may be affected in both the congenital and acquired forms.

In congenital syphilis, a progressive cicatrisation may occur, leading to stenosis. In acquired syphilis, during the secondary stage, the mucous membrane of the trachea may become generally hyperæmic, or small raised mucous patches may develop locally. In the tertiary period, gummata may occur in the trachea, the commonest site being towards the lower end. Degenerative processes, leading to necrosis and softening, eventually result in ulceration, sometimes with local sloughing of parts of the tracheal rings. In the process of cicatrisation a progressive stenosis may develop.

**Symptoms.**—Symptoms are those of chronic tracheitis and tracheal irritation in both the secondary and tertiary manifestations, but in the latter, signs of tracheal stenosis may develop when scarring and healing are in progress. Laryngeal involvement occurring at the same time tends to distract attention from the tracheal lesions or to obscure them.

**Diagnosis.**—The diagnosis of syphilis of the trachea depends upon a careful study of the history of the case, indications of tracheal irritation, laryngoscopic or endoscopic examination, the coexistence of other manifestations of syphilis, and in their absence, a positive Wassermann reaction.

**Prognosis.**—If the condition is recognised early, excellent results may be obtained by treatment, but it is obvious that where deep destructive changes have resulted, medicinal measures can only palliate.

**Treatment.**—Antisyphilitic treatment should be administered vigorously. In cases of stenosis of the trachea from cicatrisation, dilatation of the stricture by means of bougies introduced through an endoscope may be practicable and afford useful help.

## TUBERCULOSIS

Tuberculosis of the trachea may be found post mortem in advanced cases of pulmonary tuberculosis, usually in those with extensive laryngeal involvement. Primary tracheal tuberculosis is unknown. Secondary lesions in the trachea and bronchi are found not infrequently on systematic endoscopic examination.

**Pathology.**—Tuberculous lesions may occur at any part of the trachea, but they are more frequent in the lower part and on the posterior wall. When they occur they are usually numerous. There may be some general hyperaemia, or small tubercles, varying in size from a pin's head to a split pea, may be visible. Later, superficial ulceration occurs, forming irregular punched-out ulcers. Occasionally, the process may extend deeper, and erosion of the cartilages may occur, with the formation of sinuses and even fistulous communication with the oesophagus.

**Symptoms.**—Since tracheal tuberculosis is usually a late manifestation of advanced disease, its clinical indications are slight and are usually obscured by the more obvious laryngeal and pulmonary symptoms and signs, though if the process extends deeply and produces sinuses and fistulous tracks, it may become apparent. The actual tracheal symptoms are those of cough and retrosternal soreness.

**Diagnosis.**—This condition has to be distinguished from other chronic tracheal lesions, and a diagnosis can only be made from a careful review of the history, the general evidence of tuberculous disease, and by the tracheal involvement which may be visible by endoscopy.

**Treatment.**—American observers have treated the lesions by cauterisation with silver nitrate. Streptomycin and isoniazid are usually effective.

## LEPROSY

In some cases of this disease, granulomatous lesions occur in the trachea, and these may eventually give rise to tracheal stenosis, owing to the contraction of new-formed fibrous tissue. The diagnosis can only be made from the occurrence of tracheal symptoms in a case with established lesions of leprosy in other parts.

The treatment is symptomatic.

## SCLEROMA

Although in most cases this condition affects the nose only, scleromatous lesions may be found in the trachea as a pathological curiosity. The disease in any form is rare in England, and occurs chiefly in Poland and Austria. The nodules of granulomatous tissue in the trachea may cause partial obstruction mechanically, or, on contraction, lead to actual stenosis.

## TRACHEAL OBSTRUCTION

Obstruction to the lumen of the trachea may be produced by foreign bodies, by conditions originating in the trachea, and by pressure from without.

## FOREIGN BODIES IN THE TRACHEA

The commonest route by which foreign bodies enter the trachea is through the mouth and larynx, in the acts of breathing, laughing, yawning, sighing, or before and after coughing, when food or some foreign substance is in the mouth. A piece of bone, a stud, button, false teeth, chewing gum, peas, articles of food, nuts, grains of wheat, beads or blades of grass are among the substances which may gain entrance

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**Diagnosis.**—The diagnosis of syphilis of the trachea depends upon a careful study of the history of the case, indications of tracheal irritation, laryngoscopic or endoscopic examination, the coexistence of other manifestations of syphilis, and in their absence, a positive Wassermann reaction.

**Prognosis.**—If the condition is recognised early, excellent results may be obtained by treatment, but it is obvious that where deep destructive changes have resulted, medicinal measures can only palliate.

**Treatment.**—Antisyphilitic treatment should be administered vigorously. In cases of stenosis of the trachea from cicatrisation, dilatation of the stricture by means of bougies introduced through an endoscope may be practicable and afford useful help.



## TUBERCULOSIS

Tuberculosis of the trachea may be found post mortem in advanced cases of pulmonary tuberculosis, usually in those with extensive laryngeal involvement. Primary tracheal tuberculosis is unknown. Secondary lesions in the trachea and bronchi are found not infrequently on systematic endoscopic examination.

**Pathology.**—Tuberculous lesions may occur at any part of the trachea, but they are more frequent in the lower part and on the posterior wall. When they occur they are usually numerous. There may be some general hyperæmia, or small tubercles, varying in size from a pin's head to a split pea, may be visible. Later, superficial ulceration occurs, forming irregular punched-out ulcers. Occasionally, the process may extend deeper, and erosion of the cartilages may occur, with the formation of sinuses and even fistulous communication with the œsophagus.

**Symptoms.**—Since tracheal tuberculosis is usually a late manifestation of advanced disease, its clinical indications are slight and are usually obscured by the more obvious laryngeal and pulmonary symptoms and signs, though if the process extends deeply and produces sinuses and fistulous tracks, it may become apparent. The actual tracheal symptoms are those of cough and retrosternal soreness.

**Diagnosis.**—This condition has to be distinguished from other chronic tracheal lesions, and a diagnosis can only be made from a careful review of the history, the general evidence of tuberculous disease, and by the tracheal involvement which may be visible by endoscopy.

**Treatment.**—American observers have treated the lesions by cauterisation with silver nitrate. Streptomycin and isoniazid are usually effective.

## LEPROSY

In some cases of this disease, granulomatous lesions occur in the trachea, and these may eventually give rise to tracheal stenosis, owing to the contraction of new-formed fibrous tissue. The diagnosis can only be made from the occurrence of tracheal symptoms in a case with established lesions of leprosy in other parts.

The treatment is symptomatic.

## SCLEROMA

Although in most cases this condition affects the nose only, scleromatous lesions may be found in the trachea as a pathological curiosity. The disease in any form is rare in England, and occurs chiefly in Poland and Austria. The nodules of granulomatous tissue in the trachea may cause partial obstruction mechanically, or, on contraction, lead to actual stenosis.

## TRACHEAL OBSTRUCTION

Obstruction to the lumen of the trachea may be produced by foreign bodies, by conditions originating in the trachea, and by pressure from without.

## FOREIGN BODIES IN THE TRACHEA

The commonest route by which foreign bodies enter the trachea is through the mouth and larynx, in the acts of breathing, laughing, yawning, sighing, or before and after coughing, when food or some foreign substance is in the mouth. A piece of bone, a stud, button, false teeth, chewing gum, peas, articles of food, nuts, grains of wheat, beads or blades of grass are among the substances which may gain entrance

to the trachea in this manner. Surgical operations in the mouth and throat may lead to the inhalation of a tooth, a piece of tonsil or a mass of adenoid tissue. Material vomited from the stomach, such as food, blood clot or intestinal worms, may be inhaled into the trachea. A large blood clot in hæmoptysis may temporarily obstruct it. Foreign bodies, such as small projectiles embedded in old wounds of the neck, peices of new-growth or tuberculous glands may also gain access by ulceration through the tracheal wall.

Unless it becomes impacted, or is too large to enter one of the two main bronchi, a foreign body rarely remains long in the trachea. It either causes death with dramatic rapidity, is coughed out again, or passes down into one or other of the large bronchi or their secondary divisions, where it produces results which are described in the section on diseases of the bronchi.

**Symptoms.**—These depend upon the mode of entry, the size of the foreign body, and the degree of obstruction to the air current which it induces, but in general the tracheal symptoms are less urgent than those of laryngeal obstruction, and less serious than those of obstruction of one or other main bronchus. There may be intense dyspnœa, with great discomfort and alarm during the actual passage through the larynx of a small foreign body, especially if it is temporarily arrested there; but when it enters the trachea there is an almost instantaneous cessation of the acute distress, though some degree of dyspnœa may persist. The type of dyspnœa is inspiratory in the main, though a minor degree of expiratory difficulty may be apparent if the foreign body is of considerable size. There may be a definite stridor with both phases of respiration, but it is more pronounced in inspiration. If the foreign body remains loose in the trachea, which may occur if it is rounded and too large to engage in one of the main bronchial divisions, a sound of vibratory character may be heard on auscultation of the trachea, sometimes described as the *bruit de grelottement*. This may be produced by friction of the foreign body against the tracheal wall, or more commonly by the air passing over it during respiration. A paroxysmal cough may occur, caused by the foreign body irritating the sensitive posterior wall of the trachea, and during such an attack the foreign body may be forced up to the larynx, obstruct it, or cause reflex spasm with intense dyspnœa and cyanosis and a risk of suffocation, unless it drops back, is coughed out, or removed. When sudden rupture of caseous material into the trachea occurs, the lumen may be blocked and death take place rapidly.

**Diagnosis.**—The history of disappearance of some object from the mouth during coughing, breathing or laughing should give rise to suspicion of an inhaled foreign body, and this may be confirmed by seeing the object directly by endoscopy, or indirectly by means of the radiograph.

**Course.**—A foreign body impacted in the trachea may give rise to septic inflammation of its walls, with subsequent cicatrization after removal, or it may lead to secondary infective processes in the lungs, such as purulent bronchitis and bronchopneumonia.

**Prognosis.**—This depends in the main on the nature of the foreign body, and the time elapsing before its removal. An irregular, rough or soft foreign body is more likely to induce septic complications than a smooth, hard substance. Apart from rapidly fatal results, the prognosis is better with intratracheal foreign bodies than with those reaching the bronchi. If removal is effected within 24 to 36 hours, recovery is usually rapid and complete.

**Treatment.**—Treatment consists in rapid removal with as little damage to the trachea and larynx as possible. This may be effected by means of forceps passed through a bronchoscope, or rarely by tracheotomy alone, when the foreign body may be coughed out through the opening or be easily removed by forcep. Inversion of the patient in the hope that gravity may assist the expiratory efforts of cough is dangerous and should only be attempted after tracheotomy has been performed. Where

rupture of a caseous gland or softening new-growth occurs into the trachea, an immediate tracheotomy may be necessary.

#### OBSTRUCTION FROM CICATRISATION OF THE TRACHEAL WALLS

**Ætiology.**—This may result from any condition leading to ulceration of the tracheal walls, with subsequent healing, such as a syphilitic gumma, or less commonly other granulomata, such as tubercle, leprosy or scleroma. Another cause is cicatrization from wounds of the trachea, accidental, suicidal or after tracheotomy, when the incision has been made too near the cricoid, or when the wound has become infected or the tube left in too long. Scarring from damage to the trachea by the inhalation of boiling or caustic liquids or even by inhaled gases may lead to stenosis.

**Pathology.**—The deformity of the trachea and the obstruction of its lumen depend upon the situation and the extent of the cicatricial contraction of its walls. It may be local, producing an hour-glass constriction, or involve a long extent of the tube. Occasionally, especially in syphilitic lesions, stenosis may occur at two different levels.

**Symptoms.**—These depend upon the degree of stenosis, the rapidity with which it develops, and the condition of the larynx, bronchi and lungs. When the stenosis is produced gradually, as in cicatrization, a degree of obstruction may result, greater than would be compatible with life if suddenly induced. In the early stages of a progressive stenosis, slight dyspnoea may be present on exertion, and during sleep a faint stridor may be audible, disappearing when the patient is awake. As the contraction progresses, the dyspnoea becomes more marked, and a definite and persistent stridor develops, at first inspiratory only, though expiration may become both noisy and obstructed. The patient may experience a sensation of obstruction referred to the neck or under the sternum, accompanied by pain and irritation, leading to cough, which may be dry, noisy and metallic, or accompanied by more or less frothy sputum, if the primary condition is associated with widespread tracheitis. The voice may lose tone and volume, and the patient talk more quietly than normal and with some evident effort. In advancing stenosis, sudden and alarming attacks of dyspnoea may occur, leading to cyanosis and threatening suffocation. These attacks are usually due to an accumulation of mucus at the site of the stenosis. The patient in advancing degrees of obstruction cannot lie down, and generally sits leaning forward with chin depressed. It may be noted that the extraordinary muscles of respiration contract forcibly, and yet the laryngeal excursions may be small or hardly noticeable, in contrast with those of laryngeal obstruction in which they are maximal. This distinguishing sign was first pointed out by Gerhardt, and is of value, but unfortunately it is not absolute and cannot, therefore, be regarded as pathognomonic. On auscultation over the trachea, a noisy roar may be audible, of maximum intensity near to the obstruction, whereas the breath-sounds over both lungs may be deficient, although the stridor may be conducted bilaterally.

**Diagnosis.**—Tracheal obstruction from cicatrization has to be distinguished from laryngeal obstruction, in which the symptoms are usually more acute and more urgent. Gerhardt's sign described above may also be suggestive. It has also to be differentiated from obstruction due to pressure from without (*vide infra*). The only reliable method of distinction is by direct inspection with the bronchoscope.

**Course.**—The course of cicatricial stenosis is usually progressive, unless arrested by treatment, and the dyspnoeic attacks become more frequent and alarming.

**Prognosis.**—Early syphilitic stenosis may be arrested by appropriate antisymphilitic treatment. Obstruction due to other granulomatous conditions varies with the severity and extent of the primary lesions. Caseous material or degenerated growth ulcerating

into the trachea is usually immediately fatal, or leads to death within a few days from pulmonary complications.

**Treatment.**—Rest should be advised, with avoidance of exertion, smoking and alcohol. The patient's fears should be allayed and symptomatic treatment ordered, such as sedative inhalations or a linctus to check useless cough. In syphilitic stenosis vigorous antisyphilitic treatment should be given. A low tracheotomy may be necessary for an intractable stricture high up in the trachea. In some cases where an ordinary tracheotomy cannot be performed below the stricture, it may be possible to insert Koenig's long tracheotomy tube through an opening in the trachea made above it. In other cases, dilatation of a fibrous stricture by bougies passed through an endoscope may be feasible.

#### OBSTRUCTION FROM EXTERNAL PRESSURE

Pressure on the trachea may occur in the neck or in the mediastinum.

*Causes of pressure in the neck.*—Strangulation, throttling and garotting lead to death by occlusion of the trachea and suffocation. Enlargement of both lobes of the thyroid body may cause lateral compression of the trachea, until eventually its lumen is reduced to a narrow slit—the so-called "scabbard trachea". Irregular or unilateral enlargements, on the other hand, cause deviation of the trachea, with linking of its lumen. Other less common causes of compression of the trachea are enlargement of the cervical glands from tuberculosis, malignant disease, Hodgkin's disease or leukaemia. The trachea may be pressed on from behind by a foreign body impacted in the œsophagus, or by a bony tumour arising from the vertebrae.

*Causes of pressure in the mediastinum.*—An aneurysm of the aortic arch may press directly upon the trachea at, or near, the bifurcation and cause obstruction. Similarly deep pressure may be caused by a retrosternal goitre, a persistent and enlarged thymus, or a thymic abscess, mediastinal glands enlarged from any cause, usually malignant disease, a dermoid cyst or a bony tumour originating in the sternum.

**Symptoms.**—The symptoms are in the main identical with those of stenosis of the trachea from intrinsic causes, with the special symptoms due to the primary external condition superadded.

**Diagnosis.**—This may be simple and obvious, as in those cases due to pressure from tumours in the neck, whereas, in those due to mediastinal pressure, it is usually only possible after a careful survey of all the symptoms, and is in brief identical with that of aneurysm or mediastinal new-growth, to which reference should be made. In some cases radiographic examination may give valuable information.

**Prognosis.**—This is good in obstruction due to causes in the neck other than malignant disease, but it is grave, almost hopeless, in obstruction due to mediastinal causes, with the exception of abscess, goitre, dermoid cyst and some thymic conditions.

**Treatment.**—The treatment is that of the primary condition. In goitre and tuberculous glands, in simple tumours, cysts and some thymic conditions, operation may be possible and may effect complete cure. In those due to mediastinal pressure, especially from aneurysm or new-growth, treatment, in most cases, can be only palliative or symptomatic, and directed to the relief of pain, dyspnoea, cough and distress.

#### INJURY

Direct violence to the trachea has been known to cause rupture when the chin is raised upwards and the trachea is thereby extended.

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## DISEASES OF THE BRONCHI

## BRONCHITIS

Inflammation of the bronchi, or bronchitis, is one of the commonest maladies and may be induced by a variety of causes. These, in the main, fall into three groups: bacterial, chemical and mechanical, similar to the causes of tracheitis, which is, indeed, in many cases, a concomitant or antecedent of bronchitis, so that tracheo-bronchitis would be a more accurate designation of the majority of cases. At the same time it should be recognised that the trachea may be alone or predominantly affected, while, on the other hand, in many cases of bronchitis of the smaller tubes, the trachea may escape, or be only slightly involved.

Bronchitis is so varied in its extent and in the form and severity of its manifestations that a satisfactory classification is somewhat difficult to formulate. We propose to consider the clinical manifestations of bronchitis according to the following classification:

1. ACUTE FORMS.—(a) Catarrhal bronchitis, (1) of the larger tubes, (2) of the smaller tubes; (b) suppurative; (c) secondary bronchitis; (d) bronchitis due to mechanical and chemical agencies; (e) fibrinous.

2. CHRONIC FORMS.—(a) Catarrhal, (b) suppurative, (c) secondary, (d) due to mechanical agencies and (e) fibrinous.

## 1. ACUTE BRONCHITIS

## ACUTE CATARRHAL BRONCHITIS OF THE LARGER TUBES

**Synonyms.**—This condition is often called *Bronchial Catarrh*, or *Acute Tracheo-bronchitis*.

**Ætiology.**—*Predisposing causes.*—Climate undoubtedly plays an important part. Catarrhal bronchitis is rare in polar and arctic regions and near the equator, but is very prevalent in damp and foggy climates. In England, attacks are common in late autumn, winter and early spring. Owing chiefly to greater exposure, the disease occurs more frequently in men than in women. It is most common at the extremes of life, infancy and old age, but it is not infrequent at any age. Fatigue and privation play their part, and exposure to cold, wet or fog so frequently seems to initiate the attack that it is often regarded as the exciting cause. Scoliosis, kypho-scoliosis and other malformations or deformities of the chest predispose to bronchitis, and some of them are induced or aggravated by bronchitis early in life. Chronic cardiac and renal disease both render their subjects more liable to bronchitis, as do also conditions of the nose and pharynx which lead to mouth-breathing, in consequence of the inhalation of air which is unwarmed and unfiltered by the nose. There is a popular idea that a child may "cut its teeth with bronchitis" but the combination is probably coincidental.

The exciting cause is not really known. There is a suspicion that the infection is primarily viral in origin. Pneumococci, streptococci, *Neisseria catarrhalis*, staphylococci, *Hæmophilus influenzae*, Friedländer's bacilli (*Kl. pneumoniae*) are found in the sputum or tissues but they are probably secondary invaders.

**Pathology.**—The changes induced in the bronchi are similar to those in the nasal mucosa in coryza and in the trachea in tracheitis. Three stages may be described: An initial dry stage, when there is active hyperæmia of the bronchial mucosa, with exudation into the submucous layer, causing temporary diminution of the bronchial secretion from occlusion of the mucous ducts. The second or mucoid stage is associated with copious discharge of mucoid secretion, owing to increased

**Pathology.**—A very intense inflammation occurs in the medium-sized and small bronchi, leading to an exudate rich in leucocytes. The inflammatory process may extend to the alveoli, which then contain a fibrinous fluid, with entangled red cells. The condition occurs in both lungs and is usually almost universal, no portion being spared. Post mortem the lungs are heavy and red in colour. On section the bronchi are found to contain a thick yellow purulent fluid. Small areas of collapse and sometimes of broncho-pneumonic consolidation are seen, and there is usually œdema of the bases. Plastic pleurisy is not infrequent, and the glands at the root of the lungs are enlarged.

**Symptoms.**—The onset is usually abrupt, often in young people apparently in robust health. A definite chill may occur, or only coryza and general malaise, with aching of the muscles. The temperature rises quickly and may reach 104° F. early in the disease. A cough soon develops and extreme dyspnoea is a characteristic feature. Expectoration starts early, often on the second or third day. At first it may be streaked with blood, but it soon becomes yellowish green and nummular; it consists of almost pure pus; there is often as much as 5 or 6 oz. in 24 hours. In most instances there is great prostration. In grave cases the patient becomes unconscious and loses control of the sphincters.

There is intense cyanosis, the face, lips and ears being purple. The respirations are rapid, 30 or 40 per minute, and the accessory muscles are often in full action. Palpation and percussion may not show any abnormality though slight dullness is sometimes present at the bases. At first no signs may be discovered on auscultation, but soon the breath-sounds become largely obscured by medium-sized bubbling râles, often audible from apex to base, both front and back. The pulse is frequent, the right heart may dilate and the heart-sounds become weak.

**Complications and Sequelæ.**—In severe cases recurrent bronchitis, broncho-pneumonia, fibroid disease or emphysema may follow.

**Diagnosis.**—The early occurrence of marked dyspnoea and cyanosis, the expectoration of copious pus, and the widespread râles without dullness are very suggestive of acute suppurative bronchitis. The disease must be differentiated from other conditions described as acute suffocative catarrh that are associated with extreme dyspnoea and cyanosis.

Acute pulmonary œdema is usually afebrile, and the sputum is albuminous, frothy and copious. The condition leading to it, such as cardiac or renal disease, may be apparent.

Capillary bronchitis or broncho-pneumonia may give rise to difficulty, but in these conditions the sputum is scanty, tenacious, sometimes rusty and but rarely purulent; moreover, cyanosis and dyspnoea develop late and depend upon the extent of the disease and the condition of the right side of the heart.

Pneumonia of the wandering type may simulate this condition, but the character of the signs, with dullness and tubular breathing, and the rusty sputum, usually render diagnosis easy.

**Course.**—In favourable cases complete restoration to health results. In severe cases the course is rapid, the patient becomes comatose from toxæmia, expectoration ceases and death occurs from exhaustion in 2 or 3 days from the onset. In other cases the disease may last for 6 weeks and proceed to recovery or death.

**Prognosis.**—This is very grave. The mortality is high, often as much as 50 per cent. Cases extending to 3 weeks or more with swinging temperatures usually recover.

**Treatment.**—The disease is highly infectious and the patients should be isolated. In the 1916, 1917 and 1918 epidemics death occurred earliest and most frequently in those who walked about while infected. Immediate rest in bed is essential and oxygen should be given from the beginning by double nasal catheter or B.L.B. mask. Penicillin or other suitable antibiotic, as indicated by the sputum, should be tried from the start.

## SECONDARY BRONCHITIS

**Ætiology.**—Bronchitis, usually of catarrhal type—indistinguishable as regards symptoms and signs from primary acute catarrhal bronchitis—occurs as a definite part of many acute infectious diseases and as a complication in others. Among these may be mentioned measles, whooping-cough, influenza, the enteric group, small-pox, diphtheria, malaria and plague. Acute nephritis of infective origin is often accompanied by acute bronchitis. Other conditions associated with bronchitis are pulmonary tuberculosis, glanders, secondary syphilis, pleurisy and gunshot wounds.

**Diagnosis.**—Bronchitis is easy to recognise, but it is important not to overlook the fact that it may not be the primary condition. In all cases of bronchitis in the early stages, the possibility of a primary acute specific infection should be borne in mind. The diagnosis is also of importance in regard to treatment—for example, in malaria, nephritis and syphilis, in which treatment directed to the primary condition may be more helpful than the ordinary treatment of catarrhal bronchitis.

## BRONCHITIS DUE TO MECHANICAL AND CHEMICAL AGENCIES

**Ætiology.**—*Mechanical.*—Attacks of acute bronchitis may be caused by the inhalation of dust-laden air. In occupations where the worker is liable to inspire fine particles of carbon, silica, steel, iron, asbestos or kaolin, acute bronchitis may result, but more often these conditions lead to chronic bronchitis and pneumoconiosis. Some industrial dusts are especially irritating: manganese dioxide and basic slag and certain fine wood dusts from West Africa are examples of these.

*Chemical.*—Acute bronchitis may follow the inhalation of chemical irritants, either as a result of occupation, accidents, attempts at suicide or the use of poison gases in warfare. Special attention has been drawn to this subject by the large number of cases of "gassing" dealt with in the War of 1914–1918. Death not infrequently occurred, much acute suffering was caused, and some permanent damage has resulted in many cases which recovered. Mustard gas produces its chief effects upon the skin, the eyes and the bronchi. A fibrinous exudate forms on the mucosa as a false membrane, which separates as a slough. The suffocative gases chlorine and phosgene affect the alveoli primarily and more intensely. Chlorine inhaled in a concentration of 1 in 10,000 causes a rapid alveolar flooding with a serous and highly albuminous fluid, and if the victim does not die at once he is liable to suffer from an acute bronchitis. A condition called bronchiolitis fibrosa obliterans may occur as a sequel. It is often associated with asthmatic dyspnoea. Lewisite produces much the same effect on the lungs as mustard gas. The only noxious gases likely to be met with in civilian life are nitrous fumes, chlorine and ammonia.

**Symptoms.**—These are similar to those of acute catarrhal bronchitis, but there is great pain, distress and almost constant cough, often with copious expectoration.

The treatment is referred to under the heading of Tracheitis, and is, in the main, symptomatic and directed to the relief of pain, useless cough and distress. If there is cyanosis, oxygen should be given continuously if necessary by double nasal catheter, B.L.B. mask or oxygen tent.

## ACUTE FIBRINOUS BRONCHITIS

**Synonym.**—Acute Plastic Bronchitis.

**Definition.**—A comparatively rare acute disease in which there is inflammation of the bronchi, with the formation of casts. These may be hollow or solid and are coughed up in the expectoration.

There are some who deny that this is a disease *sui generis* and who maintain that it is but a condition found occasionally in bronchitis. It appears to have been known to the ancients and in more recent times was well described by Osler and McCrae and more recently by Davidson. Both these accounts describe it as a separate entity.

**Ætiology.**—It is more common in males, and is met with both in children and

in adults. It may begin as a primary catarrhal bronchitis, or develop as a complication of enteric fever, measles or pulmonary tuberculosis. Such organisms as the pneumococcus or a streptococcus may be found in the casts.

**Pathology.**—The casts may involve the main bronchi only, or more frequently the smaller ones and the bronchioles. They are greyish white, solid or tubular, and when large, bear the impress upon their exterior of the bronchial walls in which they have been enclosed. Thus, when a cast extends up to the lower portion of the trachea, the indentations made by the tracheal rings may be seen impressed upon it. The fine terminations generally show a spiral moulding. Chemically, they consist of fibrin or of fibrin and mucin. Post mortem the casts may be seen in some places *in situ*; in other areas the bronchi from which they have been expelled may be recognised. The bronchial mucous membrane is at times acutely inflamed, red in colour, with the lining epithelial cells desquamating, or it may appear pale and unaffected. There is usually a certain degree of emphysema, and there may be collapse of lung tissue beyond the site of obstruction.

**Symptoms.**—The disease generally begins somewhat abruptly with a cough and malaise. In the course of a few days the patient becomes considerably worse, dyspnoea develops and a certain degree of pyrexia, but the temperature is often not more than 99° or 100° F. The dyspnoea becomes more intense, and is the prominent and all-important symptom. The face is seen to be cyanosed, the *alae nasi* and the accessory respiratory muscles are in violent action, sometimes with retraction of the intercostal spaces. There may be diminished movement of the chest, either bilateral or unilateral. If there is unilateral pulmonary collapse the heart may be slightly displaced towards the same side. Vocal fremitus may be normal or locally diminished. The percussion note is somewhat hyper-resonant over the anterior chest-wall, but behind there may be some degree of dullness over one or other lobes. If the bronchi are unilaterally affected there may be dullness limited to one lower lobe, with diminution of air entry and no adventitious sounds. Vocal resonance over the affected area is lessened. There is usually some diffuse bronchitis, as indicated by the presence of rhonchi or râles. Marked stridor is sometimes heard with respiration. A special sign, the "bruit de drapeau", has been described when the cast lies free in the bronchial lumen. It is a dry clicking sound, caused by the flapping of the cast against the wall of the bronchus as the air passes over it. The ordinary sputum does not show any peculiarities. It may, however, show Curschmann's spirals, Charcot-Leyden crystals and eosinophil cells, and it may be absent until the crisis occurs. This consists in the expectoration of the cast after a violent fit of coughing. The cast may be stained with blood, or there is sometimes actual hæmoptysis. The peculiar nature of the expectoration often escapes notice, unless it is examined by floating in water, when a large intact cast is revealed. The dyspnoea ceases immediately after the cast has been expelled.

**Complications and Sequelæ.**—Emphysema may occur as the result of the violent coughing, or the disease may become chronic, recurring at intervals of varying duration. The most serious complication is laryngeal obstruction, caused by the cast becoming impacted between the vocal cords.

**Diagnosis.**—The stridor and respiratory obstruction are suggestive of œdema of the glottis, but auscultation will show that the site of the lesion is lower down the respiratory tract. Asthma, and all causes of laryngeal and tracheal obstruction, must be excluded. The dyspnoea and the presence of signs localised to one lobe may suggest an active lobar collapse, or a lobar pneumonia, but the dyspnoea is more intense than is met with in either of these conditions. Casts are expectorated in diphtheria, pneumonia, chronic disease of the heart, pulmonary tuberculosis and hæmoptysis. The casts of acute fibrinous bronchitis are firmer than those found in these affections, and are expectorated in long pieces, showing the many branches and bifurcations of the bronchial tree.



**Course.**—The disease is generally self-limited, terminating with the separation and expectoration of the cast. The acute stage does not, as a rule, continue for more than 12 to 24 hours.

**Prognosis.**—The immediate outlook is fair. Death may occur in the first attack, or recurrences may take place, which lead to an increasing degree of emphysema, with its usual results. The ultimate prognosis is, therefore, not good.

**Treatment.**—The patient should be kept in bed and treated as a case of acute bronchitis. Inhalations of medicated vapours often afford relief. Potassium iodide is believed to expedite the separation of the cast. Bronchoscopic removal is sometimes necessary and tracheotomy instruments should be available in case of laryngeal obstruction.

## 2. CHRONIC BRONCHITIS

Chronic bronchitis is perhaps even more difficult to classify than the acute varieties, each one of which may have its counterpart in chronic form, so that the same classification may be followed. At the same time it must be admitted that, especially in the catarrhal forms, the clinical manifestations are somewhat varied.

### CHRONIC CATARRHAL BRONCHITIS

**Ætiology.**—The causes are practically identical with those of the acute form, of which it is in most cases a sequel.

This affection may commence at any age, although it is more common in middle life and with advancing years. Men are more frequently affected than women. It seems also to have a special incidence in some families. It is more common in damp and foggy climates, and is favoured by urban conditions and by dusty occupations. It starts each winter with a more or less acute catarrhal attack, but each year the summer intermission becomes shorter, until the bronchitis persists throughout the year. It tends to produce emphysema and is aggravated in turn by this condition. It is especially favoured by cardiovascular lesions, such as valvular defects and arterial disease; also by gout, chronic nephritis, syphilis and alcoholism. Conditions associated with chronic cough predispose to it, notably emphysema, asthma, arrested pulmonary tuberculosis, mouth-breathing and cigarette-smoke inhaling.

The bacteria found are practically identical with those in acute bronchitis, the commonest being the pneumococcus, Friedländer's pneumobacillus, *N. catarrhalis*, streptococci and staphylococci. Mixtures of two or more of these may be present.

**Pathology.**—The bronchi show chronic inflammatory changes of a catarrhal nature. The walls are thickened from chronic hyperæmia and also from productive changes in the connective tissues. The mucous glands may be hypertrophied or atrophied, and there may be widespread desquamation of the ciliated epithelial lining of the bronchi. In long-standing cases there is usually some peribronchitis, leading to cylindrical bronchiectasis and distortion of the bronchi by fibrosis. There is almost invariably a greater or less degree of emphysema, which may be generalised or only marginal. Post mortem, the lungs are generally red and somewhat engorged, but if much emphysema has resulted they may be paler than normal. On squeezing the lung after section, pus or muco-pus exudes from the cut bronchi, and there is usually some evidence of œdema at the bases.

**Symptoms.**—A patient with chronic bronchitis complains of cough, expectoration and shortness of breath on exertion. The cough varies greatly in its severity. During the warm weather the patient may be completely free, and yet suffer for years from a winter cough. It may occur frequently throughout the day and in attacks at night, or only in the mornings and evenings.

The expectoration varies considerably in quality and quantity, so much so that

the old classifications of chronic bronchitis were based on this factor. Thus, there may be practically no sputum or only small tenacious pellets, the "*crachats perlés*" of Laennec; on the other hand, there may be a profuse expectoration resembling unboiled white of egg diluted with water. Usually the sputum is mucous or mucopurulent and contains greyish-black particles mixed with a frothy fluid. The dyspnoea is largely due to the accompanying emphysema, and so indicates the degree of chronicity of the disease. At first the patient may only notice that he gets out of breath on going upstairs or on mounting slopes, but later even walking on the level causes dyspnoea.

Slight rises of temperature occur in the acute exacerbations of the catarrhal process. Slight cyanosis is frequently observed, especially after exercise, when the accessory respiratory muscles are called into play. Sometimes rhonchal fremitus is felt. Movement of the chest is restricted by emphysema, and the percussion note then becomes hyper-resonant. On auscultation, expiration is prolonged and sonorous or sibilant rhonchi are heard all over the lungs, with bubbling râles if there is thin secretion in the smaller bronchi. On the other hand, rhonchi may be scanty or only occasionally heard. Voice conduction is unaffected. The fingers may be slightly clubbed, and further evidence of venous obstruction may be apparent in the dilated venules on the cheeks or along the costal attachments of the diaphragm.

**Complications and Sequelæ.**—The following changes may occur in the lungs—peribronchial fibrosis, bronchiectasis and emphysema. Asthma or attacks of bronchial spasm sometimes form a complicating factor in chronic bronchitis, especially in the cases of so-called bronchorrhœa. Emphysema may lead to pulmonary hypertension and right heart failure. Late in the disease, as the result of the cyanosis, a peculiar form of confusional delirium is met with, which is worse at night.

**Diagnosis.**—Chronic bronchitis must be distinguished from pulmonary tuberculosis, bronchitis secondary to heart failure, and from bronchiectasis. In tuberculosis with bronchitis there is generally wasting, and often flattening of the chest-wall, owing to fibrosis of the lungs. In all cases where the summer intermission of the symptoms fails suddenly rather than lessens gradually, tuberculosis should be suspected. The diagnosis is clinched by the presence of tubercle bacilli in the sputum. In bronchitis secondary to heart failure, in addition to the cardiac signs, the râles in the lungs are chiefly basal and the rhonchi are not so universally distributed. In bronchiectasis the signs are usually characteristic and often limited to one lobe. The radiograph will afford useful aid in diagnosis.

**Course.**—The disease once firmly established, unless relieved by suitable climatic treatment, remains chronic and becomes progressively more severe as further damage is wrought in the lungs with each hibernal exacerbation. As the emphysema develops, a vicious circle is initiated, the aerating power of the lungs diminishes and finally cardiac failure ensues.

**Prognosis.**—The immediate prognosis is good, the ultimate is bad. Much depends upon the patient's social condition and opportunities for treatment, especially in respect to climate. The expectation of life of a patient suffering from chronic bronchitis is considerably shortened.

**Treatment.**—Those subject to chronic bronchitis derive benefit from life in a warm, equable climate. In England the south-western districts are best. Well-to-do patients can sometimes prolong their useful life by wintering in warmer climates. avoided if emphysema is present or if there are cardiac wet and chill is dangerous. The question of occupation should be spent out of doors, provided that the patient of the elements; and, further, the work under muscular efforts, or the inhalation of dusty or irritant

an outdoor occupation conforming with these

desiderata, consequently light indoor work in a good atmosphere should be advised. Clothing should be warm but light, and afford special protection to the chest without overloading, as some patients are liable to do. Excesses in diet are to be avoided, also alcohol and heavy smoking. The general nutrition should be well maintained, and many patients, especially those of spare habit, seem to derive great benefit from cod-liver oil during the winter months.

If cough is troublesome and expectoration tenacious or scanty, various combinations of expectorant remedies are useful, such as ammonium carbonate or chloride, tinct. ipecacuanha, preparations of squills or senega, with tolu, liquorice or Virginian prune as flavouring agents. A simple saline mixture such as R. Sodii bicarb., gr. 10; sodii chlorid, gr. 3; sp. chlorof., min. 5; aquam anethi dest. ad fl. oz. 1, taken with an equal quantity of hot water in the morning or at night, may help to "clear the tubes" and give the patient a spell of freedom from cough. In older patients the ether and ammonia mixture may be given, and in cases with bronchial spasm potassium iodide with anti-spasmodics, such as stramonium, lobelia, belladonna or grindelia, may be of great value. Various antiseptic drugs, such as turpentine min. 10, terebene min. 5 to 10, creosote min. 3 in capsules or perles, have been recommended, and the linctus thymi et diamorphin. B.P.C. min. 60. Sedative lozenges, such as compound liquorice, heroin or codeine, are often useful in checking useless cough. Intercurrent attacks of acute bronchitis must be treated on the principles described under that condition and the patient kept indoors or in bed, as may be necessary. When an advanced degree of emphysema coexists the treatment appropriate to that condition should be applied. When failure of the right heart ensues, the treatment must be modified suitably as described under emphysema. Cultivation of the sputum and testing the organisms for sensitivity may indicate appropriate antibiotic treatment which can ameliorate the condition and suppress some of the infecting agents. Breathing exercises often cause great improvement for both physical and psychological reasons.

#### CHRONIC SUPPURATIVE BRONCHITIS

**Synonym.**—Fetid Bronchitis.

**Ætiology.**—This condition is not sharply defined and is not a specific and separate nosological entity, but it is a convenient group in which to include cases with fetid purulent sputum. In some forms of chronic bronchitis the secretion may from time to time accumulate in the bronchi and prove offensive on expectoration. In some instances this condition becomes chronic and the expectoration is fetid up to the time of death.

**Pathology.**—There is chronic inflammation of the bronchi, with marked peribronchial thickening. The bronchial secretion becomes purulent, and ulceration of the bronchial wall or dilatation of the lumen may occur. Post mortem the lungs are soft, and on section some broncho-pneumonic areas, with œdema of the bases, may be seen. Pus of an offensive nature exudes from the cut ends of the bronchi.

**Symptoms.**—These resemble those found in chronic bronchitis, with, in addition, the unpleasant characteristics of the sputum, in which Dittrich's plugs may be found. These are small, yellowish bodies, with an intensely offensive odour, composed of compact secretion.

**Complications and Sequelæ.**—Ulceration of the bronchial walls, abscess or gangrene of the lung, and areas of broncho-pneumonia may develop. As with bronchiectasis, pyæmia sometimes ensues, with the formation of secondary abscesses in the brain.

**Diagnosis.**—The sputum is offensive in abscess and gangrene of the lung, bronchiectasis and interlobar empyema. Radiographic examination of the chest is of great value in revealing these conditions, and lipiodol investigation will usually serve to distinguish between them.

**Course.**—The disease is progressive, but in the early stages there may be long remissions in which the sputum is not offensive although the bronchitis persists.

**Prognosis.**—As the disease becomes firmly established the patient's strength is gradually undermined from the absorption of toxins, and death ensues in the course of a few years, either from exhaustion, toxæmia or pyæmia.

**Treatment.**—An endeavour should be made to diminish the degree of the infection and the quality of the sputum. Cultivation of the sputum will show the organisms concerned and their sensitivity to various antibiotics will decide the appropriate treatment. Postural drainage is usually helpful. Apart from this, treatment is as for chronic bronchitis. The offensive odour can be partially altered or masked by creosote given by mouth or by inhalation.

### CHRONIC SECONDARY BRONCHITIS

Chronic bronchitis is a common association of chronic cardiac and renal disease. Its clinical characters do not need special description. It is only necessary to emphasise, as in the acute forms, the importance of recognising that the bronchitis is not the essential condition, and that treatment must be directed especially to the primary disease.

### CHRONIC BRONCHITIS FROM MECHANICAL AND CHEMICAL AGENCIES

This usually proceeds to interstitial changes in the lung, and these results may be studied more conveniently under the heading of the pneumoconioses.

### CHRONIC FIBRINOUS BRONCHITIS

Acute fibrinous bronchitis has been described above. In certain cases of chronic catarrhal bronchitis a fibrinous exudate may occur from time to time, with the formation of intrabronchial casts. There is then cough and dyspnoea, which abate with the expectoration of the cast. It therefore very closely resembles acute fibrinous bronchitis, and the treatment indicated is that described above.

## TUMOURS OF THE BRONCHI

Tumours arising in the bronchi may be (a) simple or (b) malignant.

(a) *Simple tumours.*—The following varieties occur: Adenoma, lipoma, myxoma, papilloma and chondroma. Any of these may lead to bronchial obstruction and, in consequence, to collapse or bronchiectasis. Adenoma is of sufficient frequency and importance to require separate description.

(b) *Malignant tumours.*—Primary carcinoma or sarcoma may originate in the bronchi. Although the majority of primary malignant tumours within the lung originate in the bronchi, either from the lining epithelium or from the cells of the mucous glands, their pathological effects and clinical manifestations are in the main pulmonary, and it is therefore more convenient to describe them as tumours in the lung (see p. 1041).

### ADENOMA OF BRONCHUS

**Ætiology.**—Adenoma of the bronchus occurs about equally in the two sexes, with a slight bias to the female sex, and usually in adults below the age of 40.

**Pathology.**—The tumour is at first small and of polypoid form, as a rule, arising in a main bronchus, but not infrequently in the branch to the lower lobe. It is about twice as common on the right side as on the left. The bulbous end is generally directed towards the trachea. The surface is usually smooth and shiny, but may be

nodular. An erroneous diagnosis of carcinoma was not uncommon in the past owing to differences of staining of certain of the constituent cells and their irregular distribution in the connective tissues. Metastases, however, are unknown. An adenoma often projects through the bronchial wall, giving it a dumb-bell or cottage-loaf conformation.

**Clinical Features.**—Often the earliest symptom is hæmoptysis, and this may be slight or profuse, since adenomata are very vascular and bleed easily. In other cases the tumour causes bronchial obstruction with resultant cough and wheezing, proceeding later to pulmonary collapse or bronchiectasis. Dry pleurisy may be an early result of infection, and at times pleural effusion or empyema may conceal the underlying cause.

**Diagnosis.**—Other causes of hæmoptysis must be considered, such as pulmonary tuberculosis, mitral stenosis, dry bronchiectasis or bronchial carcinoma. Pulmonary collapse may suggest an unresolved pneumonia. In cases with pleural effusion or empyema the diagnosis is liable to be overlooked. The injection of lipiodol, or tomography, will often reveal a blocked or deformed bronchus, but the diagnosis can only be established by microscopical examination of a portion of the tumour removed through a bronchoscope.

**Prognosis.**—This varies with the stage at which the diagnosis is established. If the condition is recognised early, and treated before the growth has extended outwards through the bronchial wall and before bronchial obstruction and septic infection have occurred, the outlook is favourable.

**Treatment.**—Lobectomy, or if necessary, pneumonectomy is now the treatment generally adopted, especially if secondary bronchiectasis or fibrosis has developed. Piecemeal removal through a bronchoscope is now seldom employed owing to the risks of hæmorrhage and of local recurrence.

## THE INFECTIVE GRANULOMATA

**SYPHILIS.**—During the secondary stage, a generalised hyperæmia of the bronchial mucous membrane may occur, giving rise to slight bronchial catarrh with the usual symptoms and signs, a condition that has been called syphilitic bronchitis. It is frequently beneficially influenced by antisyphilitic treatment. In the tertiary stage, gummata may form in or near the large bronchi. They tend rather to fibrosis and contraction than to softening and ulceration, although the latter processes may occur. Contraction may lead to bronchial stenosis, with the symptoms and signs described below, or to extensive peribronchial inflammation and bronchiectasis. If the gummata extend into the lung, as may happen in rare instances, destructive lesions with cough, expectoration and hæmorrhage may result. This condition is more fully described in the section on pulmonary syphilis (see p. 1040).

**TUBERCULOSIS** of the bronchi occurs as part of pulmonary tuberculosis and does not require separate description. It may lead to bronchial stenosis, pulmonary collapse and bronchiectasis.

**LEPROSY.**—The bronchi may be involved in this disease, with the production of cellular infiltration and even nodule formation. At first, these lesions may produce bronchitis, and they are progressive, leading to cough, expectoration, wasting and asthenia. The general clinical picture may simulate chronic pulmonary tuberculosis, from which it is distinguished by the presence of leprosy lesions elsewhere, and the absence of tubercle bacilli from the sputum.

## BRONCHIAL STENOSIS AND OBSTRUCTION

Obstruction of the main bronchi or of their subdivisions within the lungs may arise from causes within the bronchi or from conditions outside them, and these

require separate consideration. It is important to emphasise the fact that in both conditions the symptoms differ according to whether the obstruction is sudden and complete, in which case collapse of the corresponding lung is the rule, or whether it is partial and more gradual, when bronchiectasis usually results. Obstruction of the smaller bronchi may result from spasm as in asthma (see p. 977) or from disease as in small-tube and capillary bronchitis (see p. 965).

### (a) INTERNAL CAUSES

These are most conveniently considered in two groups—(1) Foreign bodies; (2) those due to disease or cicatrisation of the bronchial walls.

#### (1) FOREIGN BODIES IN THE BRONCHI

These usually gain access through the larynx and trachea by inhalation. Any inhaled foreign body that is small enough to pass down the trachea may reach a main bronchus, more commonly the right, or if it is small it may pass into one of the secondary bronchi. It may at once become impacted, or be moved by cough, but unless it is expelled in this way, it is sooner or later drawn into the smallest bronchus that will receive it, and there becomes impacted.

The recorded varieties of foreign body thus reaching the bronchi are very numerous, but among the more common are pieces of bone, beads, pins, coins, ear-rings, studs, pencils, fruit stones, grains, grasses, beans, nuts, teeth and pieces of tonsil or adenoid growths after tonsillectomy. Even a living fish has been inhaled into a bronchus. Foreign bodies may reach the bronchi through a tracheotomy wound, or a gland may ulcerate into the lumen of a bronchus. Broncholiths and pneumoliths, calcareous particles originating in the bronchi and lungs respectively, may be inhaled into a bronchus instead of being expectorated.

**Pathology.**—The pathological changes resulting from a foreign body in a bronchus depend upon the nature of the foreign body, the duration of its stay, the size of the bronchus obstructed by it and the degree of obstruction induced. If the foreign body is smooth and comparatively little septic, and if it be removed within 24 hours or so, complete recovery after a very mild local inflammatory reaction may be expected. If, on the other hand, the foreign body is rough, or soft and laden with septic organisms, acute pneumonic processes, often septic in character, may develop very rapidly. A soft type of foreign body may swell and completely obstruct the bronchus it reaches, leading to complete collapse of the corresponding lung area, often the whole or half of the lower lobe. If the stay of any foreign body is prolonged to days, weeks, months or longer, irreparable damage almost invariably results. The forms this may take are numerous. Collapse and septic pneumonia have already been mentioned. If the obstruction is partial, septic bronchitis, with stagnation of the bronchial exudate and pus behind the obstruction, leads in turn to peribronchitis, bronchiectasis and fibroid induration of the corresponding lung area. In other cases gangrene of the lung results. Not infrequently an empyema may occur and the foreign body may be found in the empyema cavity. Suppuration round a foreign body may lead to localised intrapulmonary suppuration or abscess. Simple bronchial obstruction, uncomplicated by sepsis, may lead to bronchiectasis, owing to the resultant lowering of intrapleural pressure.

**Symptoms.**—During the passage of the foreign body through the larynx and trachea urgent symptoms may occur which leave no doubt as to what has happened; but this is not invariable, and the patient may not be sure whether he has inhaled or swallowed it. In any case, after a bronchus has been reached, there may be a latent period which engenders a false sense of security and leads to delay in treatment.

In most cases pain, discomfort and cough develop rapidly. The cough may lead to the expulsion of the foreign body, or may cause dyspnoea if it forces it up to the larynx. The cough soon becomes noisy, often paroxysmal, and if local septic changes are set up expectoration occurs, sometimes mucoid and copious, at others mucopurulent. *Hæmoptysis is not uncommon.* Pain may be absent, but is often severe. The temperature is generally normal for the first few hours, but soon rises, especially if bronchitis, pneumonia or broncho-pneumonia develop. The further symptoms are those of the reactive changes and complications which ensue.

The physical signs naturally depend upon the bronchus affected and upon the degree of obstruction. They are at first those of deficient air entry. The affected side may show less movement, and there may be some recession of the lower intercostal spaces in young people. If a large bronchus is involved and collapse results, there is some displacement of the heart to the affected side. Vocal fremitus may be diminished or absent, the percussion note impaired, and the breath-sounds and voice-sounds weak or absent over the whole or part of one lung, almost invariably the lower lobe. If the obstruction is valvular—*i.e.* allowing air to pass during inspiration and not during expiration—the lung behind the obstruction may become blown up and give the physical signs of localised emphysema. The presence of an obstruction in a bronchus may cause a localised wheeze or rhoncus. When bronchiectasis, empyema or other conditions develop, their characteristic signs become apparent.

**Complications and Sequelæ.**—These have been enumerated in describing the pathological results. Sometimes septic meningitis or cerebral abscess develops.

**Diagnosis.**—The history of disappearance of some article from the mouth in the act of laughing, breathing, yawning, coughing or sighing, should always arouse suspicion of an inhaled foreign body. If signs indicating bronchial obstruction are found, the diagnosis is almost certain. In every suspicious case radiographs of the chest should be taken in two different directions, in case the shadow may be merged in that of the scapula or of the ribs. The possibility of a foreign body should always be borne in mind in cases of unilateral basic bronchiectasis, especially if no obvious cause can be found. When such unilateral lung signs develop after an anæsthetic, or after operations on the mouth or naso-pharynx, the possibility of some inhaled material should always be remembered.

**Course.**—Spontaneous relief may occur in two ways, either by the foreign body being coughed up, as may happen within a few hours or days or after an interval of months or years, or the foreign body may track through the lungs and pleura, and be discharged in an abscess bursting through the chest wall. In both cases, if an interval of more than days occurs, irrecoverable damage may have resulted. Apart from these occurrences and from successful treatment the course is very variable. Death may occur quickly from some of the septic complications, or after a longer or shorter interval from bronchiectasis, gangrene or cerebral abscess.

**Prognosis.**—This is grave unless the foreign body is removed within 36 hours, owing to the various dangerous complications that may ensue. Excluding the few cases in which cure occurs by spontaneous discharge of the foreign body, about 50 per cent. of cases left untreated die within 1 or 2 years.

**Treatment.**—This consists in removal, if practicable, as soon as possible after the diagnosis is established. If the foreign body is in a main bronchus or one of its principal divisions it can usually be removed by means of the bronchoscope and appropriate forceps. In case of failure the question of pneumotomy may have to be considered. If this is decided on, every effort must be made to localise the foreign body by radiographic examination. If intra-pulmonary or pleural suppuration has occurred, this must be dealt with surgically, and sometimes the foreign body can be removed at the same time. The medical treatment of the cases consists in that of the various conditions resulting.

nant growth, aneurysm of the aorta, mediastinal abscess, pericardial effusion and œsophageal new-growths. (2) *Intra-pulmonary causes*, generally primary or secondary new-growths.

**Symptoms.**—These are practically identical with those just described, but in addition there are those of the condition causing the pressure.

**Diagnosis.**—This has been discussed in the previous section. The bronchoscope should not be employed where there is any suspicion of an aneurysm.

**Prognosis.**—This is extremely unfavourable, except in cases due to tuberculous glands and pericardial effusion, and in some cases of mediastinal suppuration.

**Treatment.**—This can only be palliative in the majority of cases. Useless cough may be checked by a sedative linctus of diamorphine (heroin) or morphine. Dyspnoea when due to spasm may be lessened by inhalations of creosote and spirits of chloroform, or by administration of oxygen. Pain may be relieved by aspirin or other analgesic drugs. Deep X-ray therapy is of value in some of the malignant cases and should be tried in Hodgkin's disease or lymphosarcoma.

## ASTHMA

The term asthma has been loosely employed to denote any form of dyspnoea of expiratory type occurring in paroxysms. For all conditions other than that now to be described some descriptive qualification should be employed to avoid confusion.

Asthma or true spasmodic asthma is a paroxysmal affection, occurring most frequently in patients of neuropathic inheritance. It manifests itself in attacks of severe expiratory dyspnoea due to excessive vagal discharges, set free by peripheral irritation, chemical agencies or cerebral influences.

**Ætiology.**—Probably no other disease shows such a varied and complex causation, but studies of idiosyncrasy and anaphylaxis have served to explain many of the obscurities.

**Predisposing causes.**—*Age.*—The first attack may occur at any age, even as early as the period of the first dentition. The majority of cases begin before the age of 25.

*Sex.*—Asthma is generally stated to be nearly twice as frequent in the male sex as in the female.

**Heredity.**—Asthma certainly runs in families. The heredity is not always direct, the nervous instability sometimes being evidenced in other generations by migraine, epilepsy or hysteria. The view that hypersensitiveness to certain proteins is inherited is now discredited, and it is believed that an unduly irritable bronchial centre is the factor transmitted by heredity.

**Other diseases.**—Bronchitis not infrequently leads to paroxysms in patients with asthmatic tendencies. Tuberculosis of the lung occasionally induces it, but here again it is probably in patients with the asthmatic diathesis.

**Climate and locality.**—Asthmatics seem very sensitive to both of these, but no general relationship can be proved, as the effects are most variable. Some patients are better in dry, others in damp, foggy climates, and in regard to locality each patient is a law to himself.

**Conditions of the nose and naso-pharynx.**—Nasal obstruction from swelling of the turbinates, deflection of the septum, spurs and polypi, and conditions of the naso-pharynx, such as adenoids and enlarged tonsils, undoubtedly predispose to asthma, and may also be exciting causes of the actual paroxysm.

**Exciting causes.**—Chemical substances.—The emanations from certain animals may be the determining cause. The best known of these are the horse and cat, but rabbits, hares, guinea-pigs, deer, dogs and monkeys may have a similar effect. Even human hair appears capable of discharging the paroxysm. The dust from some substances, such as corn, rice or oats, the smell of certain drugs, such as ipecacuanha,



and the scent and the pollen of grasses and flowers may act in a similar fashion, as also may articles of diet, and many drugs. It is claimed that at least 50 per cent. of asthmatics show hypersensitiveness to various protein antigens obtainable from animals, grains, bacterial bodies, foods and drugs, and over a hundred are now available for routine testing of these patients. The analogy with the causation of hay fever and paroxysmal sneezing is obvious. This group has been referred to as "allergic" asthma.

*Peripheral irritation.*—As already mentioned, irritation of the nose, naso-pharynx and bronchi may be asthmogenic in those of asthmatic tendency.

*Gastro-intestinal disturbance.*—This is well recognised as a cause, and most asthmatics find by experience the penalties of a heavy late meal and of indigestible articles of diet. It is possible that actual metabolic errors may be a factor, as in the so-called "week-end asthma", due to altered conditions of diet and exercise at this period.

*Ovarian disturbance.*—Asthma may occur fairly regularly about 10 days before the onset of each period. This is probably due to lack of progesterone, from a primary ovarian defect or from an insufficient production of the gonado-tropic luteinising hormone produced in the pituitary. Satisfactory results are usually obtained by the injection of a preparation such as Synergon, 1 ml. containing 10 mg. of progesterone and 1 mg. of œstrone per ml. This may be injected every other day during the 8 days before the period is due.

*Cutaneous.*—Asthmatics are peculiarly liable to urticaria and eczema, although these conditions usually alternate with the asthmatic attacks.

*Nervous factors.*—Fatigue, emotion and nervous shock may precipitate an attack. This factor cannot be ignored, even in cases due to protein hypersensitiveness, as is shown by a well-known case in which a patient susceptible to roses developed asthma when handed an artificial rose.

*Pathology.*—Numerous theories have been propounded to explain the asthmatic paroxysm. Among these may be mentioned vascular turgescence of the bronchial mucous membrane, spasm of the bronchial muscle and increased secretion of the mucous glands. Spasm of the diaphragm or of the inspiratory muscles has also been suggested. That bronchial spasm plays the major part seems to have been established by the experiments of Brodie and Dixon, and this view is strongly supported by their observations on the effects of drugs on the bronchial musculature. Muscarine, pilocarpine and physostigmine produce bronchial constriction and asthmatic symptoms in animals, while atropine, hyoscyamine and chloroform abolish these effects.

There can now be little doubt that the broncho-constrictor fibres of the vagus are the channel by which the impulses discharging the asthmatic paroxysm reach the bronchi, although the possibility that impulses leading to vaso-dilatation and to increased bronchial secretion are also concerned, must be admitted.

*Anaphylaxis.*—The important part played by extraneous proteins in the genesis of asthma and the obvious analogy between the asthmatic paroxysm and the symptoms of anaphylactic shock have suggested that in many cases, if not in all, asthma is an anaphylactic phenomenon. Evidence is accumulating in support of this view. It has been shown that the lungs of the guinea-pig killed in anaphylactic shock show extreme constriction of the bronchioles. Asthmatics are well known to show anaphylactic tendencies, and especial care in the administration of antitoxic serums is necessary with them. It is of some interest to note that the Eppinger and Hess group of vagotonics show urticaria, dermatographia, eosinophilia and liability to anaphylactic shock, all conditions which occur in asthmatics. It is tempting, therefore, to assume that the foreign protein or toxin produces the asthmatic attack by inducing vagotonicity. Further research is needed before it can be accepted that anaphylaxis accounts for all cases of asthma, but it is almost certainly an important factor in many.

*Symptoms.*—The asthmatic paroxysm most commonly commences about 2 a.m. or later, but it may sometimes develop in the daytime. There are often preliminary indications some hours beforehand, constituting the "asthmatic aura". These

include restlessness, irritability, mental exaltation, less frequently depression, itching of the nose or chin, flatulence or polyuria. Some attacks are ushered in by coryza. Such warnings are not constant, and the sufferer usually wakes from sleep with a feeling of suffocation. In early attacks great restlessness, anxiety and alarm occur. The difficulty in breathing and the sense of suffocation increase; the patient sits up in bed, or gets up to throw open the window, and fixes his arms to bring into action all possible muscles of respiration. Respiration, although laboured and difficult, is often slow, inspiration being short while expiration is greatly prolonged. Both are accompanied by loud wheezing sounds, audible at a distance from the chest. The patient appears pale, but the lips are dusky and the expression is anxious and distressed. The jugular veins are distended and prominent. The accessory muscles of respiration are seen to be in violent action, notably the sterno-mastoids, scalenes and pectorals. The skin is moist and there may be marked sweating. The chest is much distended, and at each violent attempt at inspiration very little further enlargement occurs, while there is often sucking-in of the supra-clavicular and lower costal regions.

Percussion reveals marked hyper-resonance and encroachment on the cardiac and hepatic dullness. On auscultation inspiration is short and high-pitched, expiration very prolonged, and both are obscured by abundant sonorous and sibilant rhonchi, and later by bubbling râles at the bases. The pulse is small, quick and sometimes irregular. There is usually marked epigastric pulsation. A differential blood count during an attack may show an eosinophilia of as much as 35 per cent. Cough does not develop until late in the paroxysm, and is quickly followed in many cases by the expectoration of small pellets, called "perles" by Laennec, and often likened to boiled sago or tapioca. These were carefully studied by Curschmann, and when examined on glass on a black background, prove to consist of a central highly refractive mucinoid coil, with masses and threads of mucin wrapped spirally around it. Microscopically leucocytes, mostly eosinophils, may be seen entangled in the mucus. The sputum frequently contains Charcot-Leyden crystals, which are now accepted as spermin phosphate. With the onset of expectoration the dyspnoea quickly lessens, and the attack subsides. The patient often passes a large quantity of pale urine and then may sleep until morning, awaking in apparent comfort. More frequently he appears pale, tired and anxious.

**Diagnosis.**—This involves the differentiation from other forms of dyspnoea, particularly those of spasmodic expiratory type. The chief forms of paroxysmal expiratory dyspnoea are:

1. *Bronchial asthma or spasmodic dyspnoea complicating chronic bronchitis and emphysema.*—This condition is sometimes a late result of true asthma, but may occur independently. The dyspnoea is more persistent and is more definitely related to the bronchitic attacks, being therefore more common in the winter.

2. *Cardiac dyspnoea or cardiac asthma.*—This, like true asthma, is usually nocturnal, but the signs of failure of compensation in association with valvular or myocardial disease usually make the nature of the dyspnoea clear.

3. *Uræmic dyspnoea or renal asthma.*—This is also not infrequently nocturnal and may be almost indistinguishable from true asthma. Examination of the urine, the urea and non-protein nitrogen content of the blood, usually enable the distinction to be made with certainty. Cardio-vascular changes with high blood-pressure are frequently but not invariably present.

4. *Hay asthma* is probably only a severe form of hay fever and is to be regarded as a variety of true asthma.

5. *Pulmonary tuberculosis may be associated with asthmatic dyspnoea.*—The differentiation may not be easy during the attack, but the persistence of apical signs in the interval may give a clue. It is a wise precaution to X-ray the chest of all patients with asthma when first seen and at intervals if there are suspicious symptoms.

The dyspnoea of laryngeal or tracheal obstruction and of mediastinal pressure can

usually be recognised by the fact that it is chiefly of inspiratory type, and may be associated with stridor, instead of wheezing. In all cases of doubt the chest should be examined radiographically to exclude aneurysm, retrosternal goitre, or new-growth.

**Course, Complications and Sequelæ.**—Such an attack may last from a few minutes to several hours, and may remit and then return. When the spasm is very severe and prolonged into hours, with little or no remission, the condition is often termed "status asthmaticus". The patient may be extremely ill, and death may occur unless the attack remits spontaneously or as a result of treatment. More often the attacks recur at the same time each night for a considerable period extending to weeks, and then pass off, after which the patient may enjoy a period of freedom of weeks or months. The intermissions may become shorter with successive attacks, and increasing emphysema may develop. This in turn leads to secondary bronchitis, which persists, together with some degree of permanent œdema of the bases. Later still the cardio-vascular changes incidental to emphysema occur as sequelæ, namely, engorgement of the right heart, tricuspid regurgitation, venous stasis, ascites and œdema. Chronic asthmatics frequently present a characteristic appearance. Of thin build, with sallow complexion, anxious expression and nervous manner, they often have a long neck, high straight shoulders and a forward stoop. Asthma necessarily imposes limitations upon those who suffer from it at all severely, although many asthmatics lead active, useful lives in spite of their disease.

**Prognosis.**—When the disease starts in childhood or in early adult life it may stop spontaneously or be relieved permanently when some causal condition is discovered and treated. During a severe attack the aspect of the patient may be so alarming that a fatal issue may seem imminent, yet death rarely occurs. In chronic cases, the ultimate prognosis is made more serious by the complicating emphysema and bronchitis, and in spite of popular belief, the asthmatic has less than the normal expectation of life.

**Treatment.**—(a) *During the attack.*—The list of anti-spasmodic drugs and measures employed is a long one, and it is impossible to foretell which will be efficacious, for asthmatics vary as widely in their response to drugs as they do in regard to asthmogenic causes. Drugs may be administered for this purpose by inhalation, by nasal sprays, by the mouth or by hypodermic injection. Adrenaline hydrochloride, in doses of 2 to 5 minims of a 1 in 1000 solution hypodermically, may act with dramatic efficacy if administered sufficiently early, but it should be given cautiously to elderly asthmatics. It may also be combined with pituitary extract, as in the special preparations Evamine, Pitrenalin and Kadamysin. In status asthmaticus, the procedure suggested by Hurst may give relief. A syringe of 1 ml. capacity is filled with adrenaline solution 1 in 1000. This is slowly injected over a period of several minutes to half an hour or until the spasm relaxes. When relief has been obtained a preparation with a more prolonged action may be used such as adrenaline mucate (hyperduric adrenalin) or adrenaline combined with chlorbutol and glycerin (adrenutol). An intramuscular injection of 0.5–1.0 ml. of one of these will help to prevent a recurrence for 6–8 hours. Ephedrine hydrochloride, in tablets of gr.  $\frac{1}{2}$  to  $\frac{3}{4}$ , has proved itself a useful substitute for adrenaline in some cases and can be given by the mouth. Pseudo-ephedrine in doses of gr.  $\frac{1}{2}$  to 1 is often helpful where ephedrine fails. Adrenaline often proves helpful as a nasal spray, especially in combination with Chlorotone. Intravenous injections of 50 or 100 mg. of nicotinic acid may give relief when adrenaline fails. An oxygen tent is sometimes of great value in the treatment of status asthmaticus. Intravenous aminophylline in doses of 0.25 g. in 10 ml. of distilled water is often effective, especially when intramuscular adrenaline has failed. It may also be given in doses of 0.5 g. per rectum.

It is often advisable to move cases in status asthmaticus to hospital or nursing home. The change of surroundings and the different psychological atmosphere often relieves the condition.

Cortisone and corticotrophin are sometimes said to be most efficacious. The value of these substances in this condition is not fully established but they should be tried if relief is not given by other remedies. The recommended dose of cortisone by mouth is 300 mg. on the first day, 200 mg. on the second day, 100 mg. on the third day and thereafter 75 mg. daily.

Many expectorant and anti-spasmodic drugs have been used in treatment; potassium iodide and bicarbonate with tincture of stramonium, hyoscyamus or lobelia is sometimes found comforting. Suitable sedatives are paraldehyde, phenobarbitone or sodium amytal in moderate doses. Morphine should never be given to an asthmatic at any stage. In an early stage it will cause addiction, in an advanced stage it may and often does cause death.

(b) *Between the attacks.*—General advice.—Asthmatics should be taught to live as normal a life as is possible under the circumstances. There is usually no reason to restrict either their activities or diet, although patients who have nocturnal attacks find that heavy meals at night precipitate attacks and they may therefore find it advisable to have their main meal in the middle of the day. Attempts to find health by changing houses and occupation are not usually successful in themselves. Migrants from the towns in search of health are crossed by migrants from the country with similar intentions and the benefits derived from the change seem to be equally divided between the two groups.

It has been observed that some patients are sensitive to contact with certain allergens mostly of a protein nature, such as pollen, animal and vegetable hair, house dusts and similar substances. From this observation has risen the suggestion that nearly all cases are attributable to one or more sensitisations of this nature: that these sensitisations can often be detected by performing skin tests with a wide range of protein substances and that desensitisation can be carried out by injecting small doses of the sensitising agents and by increasing the dose until desensitisation is achieved. The theory of this treatment is an attractive one and a vast literature has grown up on the subject.

Similar importance has been given to treatment with autogenous vaccines prepared from the sputum or with stock vaccines. It is doubtful whether either of these two methods of treatment have anything more than a psychological value and while apparent improvement frequently takes place during such treatment, it is more often due to the psychological effect of an impressive treatment and the personality of the doctor than to any desensitising effect.

Attempts are made to treat patients by special diets. Children are the especial victims of this form of "therapy". There is little evidence that bronchial asthma is ever caused by the ingestion of any particular food substance, although such ingestion occasionally causes alimentary symptoms. The effect of these diets is often to make patients even more introspective than they naturally tend to be.

Exaggerated attempts are sometimes made to render allergen-free the atmosphere in which the patient lives or sleeps. Such measures condemn the patient to discomfort and disappointment. The fact that many sufferers from asthma also suffer from rhinorrhœa, have nasal polyps, deflected septa or sinus infection has led to many misguided surgical and electrical misadventures. All these treatments and many others had and have their strong adherents amongst doctors and even patients.

There is an especial difficulty in assessing the value of any special treatment in asthma since the natural history of the disease is so variable and sufferers from it are so susceptible to suggestion. In default of any specific treatment, there are general measures and advice which are helpful. The patient should be advised to try and not let his asthma dominate his life. Children should go to normal schools and play games as normally as possible. There is no need for a special diet except that patients are usually well advised not to have a heavy meal in the evening as a full stomach, when recumbent, appears to cause attacks. They should avoid dusty house-cleaning

and keep out of dusty atmospheres. If they are sensitive to horse dandruff, vegetable pollens or other single substances they should avoid them, and the patients usually recognise these substances without having to have skin tests to identify them. They should receive instruction in the use of ephedrine, or if this is ineffective or loses its effect, adrenaline by injection or by inhalation. Knowledge that one has the means of relief at the outset of an attack often means that the attack will not develop. Many of the proprietary inhalants and patent inhalers are quite effective if used early enough. Most patients benefit from instruction in expiratory breathing exercises which may, of course, act by suggestion but which also have a manifest effect on the mobility of the chest and the respiratory excursion.

Advice to change a patient's home or occupation should not be given lightly. Such steps are rarely effective unless there is some very real and obvious domestic or occupational hazard.

Cortisone and corticotrophin are not usually required in the treatment of chronic asthma but they have been used with great benefit at times when all other measures have failed. Cortisone may be administered orally in such cases in the form of cortisone acetate tablets. An initial dose of 200 mg. followed by 100 mg. daily for 2 or 3 days may be necessary at the commencement of treatment. Thereafter symptoms can usually be controlled by quite small doses; 25 mg. to 50 mg. at bedtime usually being sufficient.

## BRONCHIECTASIS

**Definition.**—Bronchiectasis is a condition of permanent dilatation of one or more bronchi. When it occurs in the finer divisions it is sometimes described as bronchiolectasis.

**Ætiology.**—Bronchiectasis is invariably secondary, and may result from disease of the bronchi, the lung parenchyma or the pleura. Even the rare congenital cases are probably consequent on malformation, atelectasis or intra-uterine disease.

1. The bronchial conditions which may progress to dilatation are bronchitis, and any affection leading to partial bronchial obstruction, such as plugs of mucus, an inhaled foreign body, a tumour (simple or malignant), stenosis from cicatrization and external pressure from new-growth or aneurysm, or enlarged bronchial glands from any cause but more especially from tuberculosis. Localised pulmonary collapse thus induced seems to be the commonest antecedent condition. In children, measles and whooping-cough are not uncommon causes, especially when they follow one another in rapid succession, although either alone, if severe, may lead to it.

2. Conditions of the lung parenchyma which may cause bronchiectasis are unresolved pneumonia, broncho-pneumonia, collapse, syphilis and tuberculosis. Syphilis is rare and usually acts by leading to bronchial obstruction or stenosis. Fibroid tuberculosis is a common cause, but the clinical manifestations are, as a rule, masked by the primary condition. The pulmonary complications of influenza are not infrequently followed by bronchiectasis. A diffuse type of bronchiectasis is sometimes found in long-standing cases of asthma.

3. The pleural conditions which are followed by bronchiectasis are those which lead to pleural adhesion and those which are associated with pulmonary fibrosis, notably chronic pleural thickening, or empyema leading to prolonged or permanent collapse of the lung.

In a lesion with such diverse antecedents the age relations are necessarily indefinite. It may occur at any age, but is commonest in the third and fourth decades. It frequently commences in childhood, although the characteristic clinical manifestations may not develop until adult life.

**Sex.**—In most recorded statistics there is a striking preponderance in the male.

**Pathology.**—Four factors in the pathogenesis of bronchial dilatation have to be

considered. (1) The most important is the localised collapse which leads to secondary bronchial dilatation. (2) Weakening of the bronchial walls. Most of the conditions preceding bronchiectasis tend to induce severe bronchitis and peribronchitis, and thus render the walls more yielding. Where stagnation of secretion occurs, septic and putrefactive organisms develop, producing tryptic ferments which may act injuriously upon the lining membrane. (3) Increased pressure on the walls thus weakened is the determining factor. This is generally expiratory in origin and due to the strain of cough. The actual pressure of secretion accumulating behind an obstruction may promote yielding of the bronchial walls. In cases of bronchiectasis following on collapse of the lung the force of inspiration has been regarded as contributory, but this is doubtful and in any case is less important than the expiratory strain of cough. (4) The fourth possibility is the traction exerted upon the walls of the bronchi by contracting connective tissue in the surrounding fibroid lung. This obviously postulates the existence of pleural adhesion, which is not invariably present. While this must be admitted as a possible contributory factor, its importance is certainly less than that of the preceding ones.

Congenital bronchiectasis is a pathological rarity and may be confused with congenital cystic disease of the lung (see p. 1044). It is usually unilateral, and the bronchi involved are of small size, although in some cases the lung may show a large central cavity, with smaller spaces around it. Bronchiolectasis is also more of pathological than of clinical interest. It occurs chiefly in children, as the result of acute broncho-pneumonic processes. It is said sometimes to follow influenza and possibly tuberculosis. The lung has a peculiar spongy appearance, to which the name "honey-comb" has been applied.

Bronchiectasis of the larger tubes may be either cylindrical or saccular. In the former condition several of the bronchi are more or less uniformly dilated, and when opened out they appear like the fingers of a glove. Sometimes the dilatations are fusiform, at others they show a beaded arrangement, described as moniliform. These forms of dilatation are usually associated with emphysema and chronic bronchitis. Saccular bronchiectasis is generally localised and may be found in any part of the lung, but is most common in the lower lobes and near the base. This is partly due to the fact that the antecedent processes fall with special stress on the bases of the lung, and partly to the influence of gravity in leading to retention of secretions in these parts. Although it may be unilateral in origin, it often spreads and may involve both bases or even all the lobes. There may be one large irregular cavity, or a series of smaller globular dilatations involving the whole or part of the walls of one or more bronchi. The cavities are usually filled with the fetid secretion, to be described under expectoration. When this is washed away the walls are found to be thin, smooth and formed of thinned-out mucous membrane. In places this may have ulcerated, owing to the tryptic action of the secretion, and the lung tissue is thus exposed. An abscess may then form, and an aneurysm sometimes develops, as in a tuberculous cavity. The openings of the smaller bronchi, derived from the dilated bronchus, can often be recognised in its walls. In doubtful cases the histological demonstration of cartilage and muscle in the walls establishes the bronchial origin of a cavity. The surrounding lung tissue is usually airless and fibroid, and sometimes is almost of leathery consistence. Occasionally, however, it is emphysematous, congested or pneumonic. In the great majority of cases there is a dense pleural adhesion over the area of lung involved.

Other morbid conditions found post mortem include lardaceous disease, gangrene of the lung, empyema, pyo-pneumothorax, suppurative pericarditis and cerebral or spinal cord abscess. Owing to the obstruction of the pulmonary circulation which may result, engorgement and dilatation of the right side of the heart, tricuspid regurgitation and the results of systemic venous stasis are often found.

**Symptoms.**—The onset is usually insidious, the symptoms developing during

the course, or as a sequel, of one of the acute or chronic affections mentioned above. In some few cases, however, they develop rapidly in patients previously in good health. This is particularly the case where bronchiectasis results from an inhaled foreign body or after general anæsthesia, and a rapid onset should lead to the suspicion of this. The cough in well-developed cases is somewhat characteristic and occurs in paroxysms. These are frequently induced by change of posture—for example, bending forward or lying down. They occur with special frequency on rising, and are usually associated with the expectoration of large quantities of sputum, due to the overflow of the secretion, accumulated in the cavities during the night, into a sensitive or relatively healthy bronchus, which excites cough reflexly. They also occur on retiring to bed and at long intervals during the day. The sputum frequently amounts to as much as 20 or 30 oz. in the 24 hours. It is generally extremely fetid, although in the earlier stages this is not invariable. The patient's breath is often also malodorous, and the stench may pervade the room or even the house in which he lives, although it is not persistent. The patient is himself much distressed by the unpleasant character of the sputum, of which he is, as a rule, acutely conscious. On standing in a glass vessel it can be seen to settle into three layers—a surface scum of light frothy mucus, an intermediate stratum of thin, turbid, greenish fluid, and a deep layer of brownish colour consisting of muco-pus, bacteria, anaerobes, spirochætes and putrefactive products, including foul-smelling organic acids. Fetid yellow bodies called Dittrich's plugs can usually be found in the deep layer. Elastic tissue is only present when erosion of the wall has occurred. Hæmoptysis is not infrequent, and may occasionally be fatal. It may be the first and only symptom in some cases, which are referred to as dry or silent bronchiectasis. Dyspnoea is not, as a rule, apparent unless the condition is widespread, or unless the pulmonary or cardiac complications are present. The general condition of the patient is at first but little affected, and there may be no fever for long periods. As the disease progresses, lassitude, anorexia and some wasting slowly develop, while bouts of fever occur, due to retained secretions or to some complication.

Physical signs vary with the extent and degree of dilatation, and also with the amount of secretion present. In the early stages there is at most slight dullness at one base, with diminished air entry, peculiar sticky, "leathery" râles, and diminished vocal resonance. When bronchiectasis is well developed the signs are almost characteristic. The patient may appear well nourished and of good colour, although on cold days, especially in children, duskiness or cyanosis is often noticeable. There is well-marked clubbing of the fingers, generally of drum-stick character, and pulmonary osteo-arthritis, involving many joints, sometimes develops. There may be localised flattening or retraction of the chest wall over the affected area, with diminished movement, and the heart is drawn over to this side. The remaining signs vary with the state of the cavity. If this is full, there is diminished vocal fremitus, dullness and weak or absent breath-sounds and voice-sounds. If the cavity is empty or partly empty, the vocal fremitus is increased, the percussion note is boxy or dull, while the breath-sounds are bronchial or cavernous. Adventitious sounds are then generally audible, the most characteristic being sharp metallic or "leathery" râles. Bronchophony and pectoriloquy are marked, and occasionally the "veiled puff" of Skoda can be heard. Signs of bronchitis are often apparent in the adjacent lung tissues; compensatory emphysema may be demonstrable in the unaffected parts of the lung, and on the opposite side. Radiographic examination before and after the injection of lipiodol serves to define the extent of the disease and the degree of fibrosis. Tomography may also be useful.

**Complications and Sequelæ.**—The chief pulmonary complications are septic broncho-pneumonia, gangrene and abscess. The pleura may become involved, giving rise to dry pleurisy, which sometimes progresses to empyema and rarely to pyopneumothorax, while in other cases pleural adhesion and contraction result. Septic

pericarditis may develop and prove fatal. Septicæmia and pyæmia sometimes occur as terminal results. Cerebral abscess constitutes a serious and somewhat common complication in heavily infected cases, and may be found in the frontal, parietal or temporal regions, or suppuration may occur in the cerebellum or cord. Occasionally multiple abscesses form. Lardaceous disease sometimes develops, especially in the liver, kidneys and intestines. Multiple infective arthritis is an occasional complication.

**Diagnosis.**—In well-developed basic cases this is, as a rule, easy. The history of cough, influenced by posture and associated with copious sputum, is suggestive, especially when variable physical signs are observed. The development of the characteristic sputum with these signs renders the diagnosis almost certain, and the radiograph usually serves to confirm. Radiological investigation after an intra-tracheal injection of 10 to 20 ml. of lipiodol, through the crico-thyroid membrane or between two rings of the trachea, under local anæsthesia, or with care directly between the vocal cords, has greatly facilitated the diagnosis of bronchiectasis. Franklin has recommended the nasal route for the introduction of the lipiodol. One nostril, the oro-pharynx and the larynx are anæsthetised, then a gum elastic catheter is passed along the floor of the nose into the larynx. Procaine or other local anæsthetic is injected down the catheter and the lipiodol follows. Tilting and turning the patient in appropriate directions is done in order that the lipiodol should pass into the diseased portions of the bronchial tree. The injection should be carried out in the radiographic room and the patient instructed to restrain cough if possible until the films have been taken. The pictures obtained are strikingly characteristic and of great value. In cases with less characteristic symptoms and signs the distinction has to be made from chronic bronchitis, especially the fetid variety, pulmonary tuberculosis, gangrene or abscess of the lung, and fetid empyema. The distinction from chronic bronchitis may be difficult, especially in the early stages when the sputum is not fetid, but the paroxysmal cough, the copious expectoration with signs including bronchial breathing and sticky râles at the base, may be strongly suggestive. In fetid bronchitis the fetid sputum is not constant, and the cough and sputum may occur only during exacerbations of the bronchitis. Pulmonary tuberculosis may give rise to difficulty, particularly in cases of apical bronchiectasis. Repeated examinations for tubercle bacilli and also for elastic tissue in the sputum should be made. The history, the mode of spread and radiographic examination may all assist. It should be remembered that the two conditions may coexist and this may be suspected in some cases of fibroid tuberculosis with basic excavation. Abscess and gangrene of the lung have a more acute onset and course, but the chronic cavities left by these conditions may give rise to difficulty. In such cases the history may be an important aid in diagnosis. In fetid empyema rupturing through the lung, particularly when of interlobar origin, the patient is generally acutely ill, there may be a history of pleurisy at the onset and possibly some evidence of mediastinal pressure or cardiac displacement. The rare condition of congenital cystic disease of the lung may give rise to some difficulty (see p. 1044).

**Course.**—This depends on the extent of the bronchial involvement and the degree of infection. Probably only a small percentage of cases of bronchiectasis are clinically diagnosed. Those that are, are usually both extensive and heavily infected. Without treatment the condition tends to be progressive and leads to complications, many of which are lethal.

**Prognosis.**—Surgeons and physicians tend to have different ideas about the prognosis of bronchiectasis: the former are often of the opinion that without surgical treatment the prognosis is hopeless and the expectation of life short. The latter are not quite so pessimistic. The reason for this difference of opinion is that the surgeon tends to see a rather special selection of the worst cases; the physicians see these and also many cases which are little or at all progressive.



Given morbid anatomical bronchiectasis the prognosis is uncertain, but severely infected cases, with much foul sputum, repeated hæmoptyses and pyrexial episodes, are progressive with a short expectation of life failing adequate treatment, but there are exceptions even to this.

**Treatment.**—The medical treatment of bronchiectasis consists of efforts to secure efficient emptying and drainage of the affected part of the lung, to lessen or control the infective processes occurring in the lung and to promote the general health and well-being of the patient. Bronchograms of the affected lobe or lobes indicate the desirable position for evacuation of the lung. In bronchiectasis of the lower lobes the patient either bends over or his feet are raised so that the bifurcation of the trachea is below the level of the affected lung. If the anterior bronchi are affected, he lies on his back and if the posterior bronchi are affected he lies on his face. He should also be tilted on his side so that the affected side is uppermost. The best position for drainage can usually be found by a process of trial and error. The longer the appropriate position is maintained the more effective the result. In any case it should be maintained for not less than 30 minutes at a time. The initial instruction is best given by a qualified masseuse and the treatment must be maintained for life if the lobe is not going to be removed surgically. The Nelson bed, hinged in the middle, is helpful in maintaining the correct posture long enough for drainage to occur.

The sputum should be cultivated and the organisms identified and their drug sensitivity tested. The quantity and degree of infection can be altered by the appropriate use of antibiotic preparations, although the development of drug resistance reduces their effectiveness. They are especially valuable during pyrexial periods of exacerbation of infection due to defective drainage. Penicillin inhalations have some limited effect but no drug is really effective if the drainage from the affected bronchi is poor.

Creosote given by inhalation or in capsules of 3 minims was much used in the past and it has value in helping to disguise the fætor of the breath, which is one of the most distressing features of these cases. Bronchoscopic aspirations have been found effective in some cases, especially those where bronchostenosis or bronchial œdema prevents effective drainage.

The possibility of treatment by surgical segmental resection, by lobectomy or pneumonectomy should be considered. Surgeons have no doubt about the value of prophylactic surgery and may advise resection for anatomical bronchiectasis without symptoms. Many physicians are not so convinced of the necessity of these resections. Differences of opinion represent a different idea of the prognosis. There is unanimity about the desirability of resection for the infected cases with much sputum daily, with repeated pulmonary hæmorrhages or with a history of recurrent attacks of "pneumonia" or pyrexial episodes. Thoracic surgery has had no more dramatic successes than in these cases. Unfortunately in many of the worst cases the disease is too extensive for removal to be possible. In these cases medical treatment palliates and prolongs life.

## INJURY

External trauma applied to the chest-wall may cause rupture of a main bronchus. This is especially liable to occur after severe crushing accidents. One or other of the main bronchi may be completely severed from the trachea. The chief clinical feature presented in such a case is emphysema of the neck and upper portion of the chest-wall. Death usually ensues in 2 to 3 days.

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## DISEASES OF THE LUNGS

## HYPERÆMIA AND ŒDEMA

Hyperæmia of the lungs may be either active or passive. In the former there is an increased supply of arterial blood through the pulmonary and bronchial arterioles. In passive hyperæmia there is engorgement of the pulmonary venous radicles and capillaries. With both forms there is frequently œdema, due to the exudation of serous fluid into the lung alveoli. The term "congestion" is sometimes employed as an alternative to hyperæmia, but owing to its erroneous popular use it is best avoided.

## (a) ACTIVE HYPERÆMIA

**Ætiology.**—This may occur in association with any acute inflammatory process affecting the bronchi, lungs or pleura. It sometimes results from the inhalation of pulmonary or bronchial irritants, such as poisonous gases or heated air. Severe muscular exertion and exposure to extreme cold are described as causes, but the former at least is doubtful. An important variety is that known as *collateral or fluxionary hyperæmia*, which occurs when there is obstruction to the circulation in the whole or part of one lung, from conditions such as a large or rapidly developing pleural effusion, an extensive and spreading pneumonia, or in association with pneumothorax. This may develop in the sound lung, or in the unaffected parts of that diseased. A primary form of acute hyperæmia, the "*maladie de Woillez*", has been recognised by French authors, but this is generally regarded as a mild or abortive pneumonia.

The clinical manifestations of acute hyperæmia are merged in those of the processes with which it is associated, and therefore do not need separate description.

## (b) PASSIVE HYPERÆMIA

**Ætiology.**—Passive hyperæmia may be produced by conditions impeding the venous return from the lungs. The commonest causes of impeded return are left-sided heart lesions causing overfilling of, and increased pressure in, the left auricle. In mitral stenosis it may occur early and sometimes almost acutely, but aortic and myocardial lesions also lead to it, when the left ventricle fails and the mitral valve yields. Direct obstruction of the pulmonary veins sometimes results from external pressure by aneurysm, mediastinal tumour or enlarged bronchial glands, or from obstruction of the lumen by thrombosis.

Passive hyperæmia is obviously in the main dependent on mechanical factors; it is not surprising, therefore, that gravity seems to play a part in the localisation of its effects, which are usually most marked in the bases or most dependent parts of the lungs. In bedridden, enfeebled or old patients, particularly if myocardial weakness or degeneration coexists, this factor becomes of great importance. Not infrequently some degree of œdema of the bases develops, and the condition is then called hypostatic congestion. If such an area becomes infected the resulting process is known as hypostatic pneumonia. Basal hyperæmia and œdema of the hypostatic type also result from toxæmia due to diseases such as enteric fever, from poisoning by drugs such as morphine, and as a terminal event in many cerebral lesions causing increased intracranial pressure.

**Pathology.**—The pulmonary veins and capillaries are engorged, with the result that the lung is darker in colour and heavier, while the alveolar walls and septa are swollen. If the condition persists for some time, pigment derived from the hæmoglobin of red corpuscles escaping by diapedesis is deposited in the epithelium of the

alveoli and in the fibroblasts in the inter-alveolar septa. In long-standing cases the lung is firmer than normal and brownish red in colour, a condition described as *brown induration*. If any degree of œdema is present, serous fluid is found in the alveoli on post-mortem examination, and on section of the lung frothy serous fluid exudes, which may contain some of the pigmented alveolar cells, constituting what are called "cardiac cells". Although congested and œdematous lung is heavier than normal, it usually floats in water.

**Symptoms.**—In slight degrees of hyperæmia these may be absent or negligible. In more advanced cases, they are those resulting from the impeded circulation through the lungs and the deficient aeration which this entails. Dyspnoea is the most prominent symptom, and it is generally a measure of the degree of hyperæmia. It is markedly increased by exertion of any kind, and in extreme degrees it is distressing and eventually alarming. It may be inspiratory or expiratory in type, and in the latter case it is sometimes described as cardiac asthma. In severe cases there is usually orthopnoea. Cough is almost invariably present, and there is usually some expectoration of frothy fluid, which may be blood-stained. The pigmented cells referred to above as "cardiac cells" may be found in it. Cyanosis is common and indicates the degree of anoxæmia. This may be associated with distension of the jugular veins, and there is often obvious distress. As in other forms of cyanosis there is usually some increase in the number of red corpuscles. The vocal fremitus at the bases may be diminished, the percussion note impaired, the breath-sounds weak and accompanied by rhonchi, crepitations or bubbling râles, although these signs are for the most part due to the associated œdema. In addition, the signs of the primary condition in the heart will be apparent.

**Complications.**—Pulmonary œdema and infarction are the chief complications.

**Diagnosis.**—This condition has to be distinguished from (1) chronic bronchitis, in which case there may be some rise of temperature and the physical signs are more variable and more disseminated; (2) infarction, in which pain and hæmoptysis of sudden onset are the rule.

**Course.**—If the venous engorgement cannot be removed, it tends to become progressively worse, whereas when it results from temporary cardiac embarrassment, recovery is usually complete as soon as the heart function is restored.

**Prognosis.**—This is so entirely dependent upon the nature and degree of the condition responsible for the engorgement that no general rule can be formulated.

**Treatment.**—The treatment is that of heart failure, with digitalis, salt restriction and mercurial diuretics. In elderly patients, or those likely to be confined to bed for long periods, attention should be directed to the decubitus. This should be changed frequently, and if possible the patient should be permitted to sit up or to get into a chair, and encouraged to take a few deep breaths several times during the day.

### (c) ACUTE OR HYPERACUTE PULMONARY ŒDEMA

In this condition flooding of the alveoli with the serous exudate from the pulmonary capillaries occurs with great rapidity.

**Ætiology.**—The most important cause of pulmonary œdema is left heart failure, whether from hypertension, disease of the aortic or mitral valves, or coronary thrombosis. Pulmonary œdema may also occur in acute cor pulmonale from pulmonary infarction. It may complicate exposure to lung irritant gases, or disease of the nervous system, such as tumour, vascular accident or trauma, or intravenous transfusion, or disturbance of the fluid balance in treatment with deoxycortone acetate (D.O.C.A.), cortisone or stilbæstrol. Sometimes paracentesis of large effusions is followed by pulmonary œdema.

**Pathology.**—The alveoli are found to be flooded with a thin serous exudate. The lungs are heavier than normal, sodden, and on squeezing exude large quantities

of greyish-yellow or pinkish fluid. Frothy fluid of similar character is found in the bronchi and even in the trachea and naso-pharynx in hyperacute cases.

**Symptoms.**—The onset is sudden, and generally occurs when the patient is lying down, hence being most frequently observed at night. The patient awakes with intense dyspnoea, and a sense of suffocation, then frequently rolls or rushes about in the endeavour to breathe, even clutching at the throat. Cyanosis is present, and the aspect is one of anxiety and alarm. Frothy fluid, often pink in colour, may soon stream from mouth and nose, or be brought up in great gulps. The chest movements are hurried, and the accessory respiratory muscles are in violent action. Vocal fremitus is diminished over the lower lobes. The percussion note soon becomes impaired over the lungs, commencing at the bases. The breath-sounds are at first vesicular or harsh with prolonged expiration, then become faint and may be obscured by bubbling râles or crepitations, audible all over the chest. Voice conduction is diminished.

**Complications and Sequelæ.**—Owing to its acute and rapid course, complications do not occur. Bronchitis may result as a sequela.

**Diagnosis.**—The affection is usually so characteristic that the diagnosis is obvious. In the more protracted cases the dyspnoea and the physical signs are not unlike those of acute suppurative bronchitis or suffocative catarrh and broncho-pneumonia; but in both of these there is some degree of fever and the expectoration is less copious, and when it occurs is usually of purulent or muco-purulent character. The nocturnal onset of œdema may suggest asthma; but the physical signs and the late and scanty expectoration in the latter suffice to distinguish it.

**Course.**—The malady usually lasts only minutes or hours. Unless it remits, or treatment affords relief, the patient rapidly becomes unconscious and death follows, the heart continuing to beat after respirations have ceased.

**Prognosis.**—The prognosis is always very grave; but prompt treatment has saved some cases. Death may occur in less than 10 minutes, or be delayed for 24 or 48 hours.

**Treatment.**—The most successful treatment is the immediate subcutaneous injection of morphine gr.  $\frac{1}{4}$ . Good results have also followed the injection of atropine sulphate, gr.  $\frac{1}{100}$  to  $\frac{1}{50}$  hypodermically. Intravenous injection of aminophylline has been recommended. The dose is 0.25 g. in 10 ml. of distilled water. Oxygen inhalation by nasal catheter or the B.L.B. mask or oxygen tent is of value in some cases; others derive no benefit from it. Prompt venesection has been recommended.

#### (d) CHRONIC PULMONARY ŒDEMA

This is usually the sequel of chronic passive hyperæmia, and the causes and symptoms are those of that condition. It may also occur in chronic renal disease. *In marked degrees of œdema, however, the signs may closely simulate those of pleural effusion, save for the displacement of the cardiac impulse.* It is important to remember that some degree of hydrothorax may occur as a complication, and increase the difficulty in diagnosis.

### INFARCTION OF THE LUNGS

Infarction of the lungs or "pulmonary apoplexy" results when a branch of the pulmonary artery becomes occluded by embolism or thrombosis.

**Ætiology.**—*Embotic forms.*—The obstructing plug may originate in any part of the systemic venous system, in the right side of the heart or on its valves or in the pulmonary artery itself. The commonest peripheral cause of embolism is detachment of a thrombus in cases of thrombo-phlebitis. This may occur in the veins of

the lower extremity, or in those of the uterus after childbirth. Thrombosis with embolic detachment may also develop in prolonged or wasting diseases, such as enteric fever, tuberculosis and cancer; in acute processes, such as influenza, septicæmia and pyæmia; and in localised septic lesions, such as otitis. Pulmonary embolism is not infrequently observed after abdominal or pelvic operations, and after the radical cure of hernia or hæmorrhoids.

Intracardiac thrombi from the right auricle or ventricle, becoming detached, lead to embolism, and this occurs especially in cases of right-sided heart failure secondary to left-sided valve lesions. Vegetations forming on the tricuspid or pulmonary valves in septic endocarditis on detachment produce pulmonary infarction. Rarer causes are fat embolism after injury to bone or to a fatty liver, the entry of pieces of new-growth or hydatid daughter-cysts into systemic veins, and even air embolism, occurring sometimes as a complication of pneumoperitoneum. It may also occur during blood transfusion if the pressure in the bottle is raised unduly by a Higginson's syringe while the filter is partially blocked. Air embolism has followed insufflation of the vagina with silver picrate powder in the treatment of vaginitis and trichomonas infections.

*Thrombotic forms.*—Thrombosis occurs as a secondary process around pulmonary emboli; but it is probable that some cases of infarction are due to a primary thrombosis. This condition may be produced by some acute or chronic pulmonary disease, such as gangrene, tuberculosis and fibrosis, and by atheroma of the pulmonary artery. Any process leading to chronic venous hyperæmia may also cause it. A rare cause is thrombo-phlebitis migrans.

*Pathology.*—Although the pulmonary arteries are not strictly speaking end arteries, since there is some degree of anastomosis between them and the bronchial arterioles, yet the result of their obstruction is to produce infarcts comparable with those in other organs. The origin of the blood in the obstructed area has been much discussed. Cohnheim regarded it as the result of regurgitation from the veins, a view subsequently disproved, since the infarct is hæmorrhagic even when the veins are also obstructed. It is now regarded as due to influx from the anastomosing bronchial capillaries into the pulmonary capillaries, and the escape of this blood from the latter owing to their altered nutrition. It is generally accepted that embolism is much more common than thrombosis. If a large embolus has caused sudden death, it will be found arrested at the bifurcation of a large branch of the pulmonary artery, or even in one of the main divisions of that vessel. In such cases there has not been time for pulmonary changes to occur, and the chief post-mortem condition found is engorgement of the right side of the heart.

In post-mortem examination of cases where smaller emboli have led to infarction, the infarcts are usually found in the lower lobes, more commonly in the right lung. They extend to the surface in the majority of cases, and can be seen before section as slightly raised, dark-red areas, with the overlying pleura a little roughened from inflammatory exudate. They feel hard and firm, and on section are typically wedge-shaped, with the base on the surface and the apex centrally placed. In the rare deep-seated infarcts a spheroidal form is the rule. When recent, an infarct is dark red in colour, and suggests hæmorrhage with clot formation, hence the term "pulmonary apoplexy". In some cases infarcts have a purplish hue, and are said to resemble the colour of damson cheese; later they change to brownish red. Infarcted areas sink in water. There may be a single large infarct almost occupying one lobe, sometimes only a small one, or several of varying size and age scattered throughout the lungs. In some cases a fortunate section may reveal the embolus with its ensheathing thrombus, but sometimes a thrombus only is found. Microscopically, the alveoli and finer bronchioles are filled with red blood corpuscles, and there is a sharp delimitation from the healthy lung. If the embolus is infective, suppuration occurs, and abscess or empyema ensues.

**Symptoms.**—If a large embolus blocks one of the main divisions of the pulmonary artery, there is sudden intense dyspnoea, pain in the chest, distress, cyanosis and rapid unconsciousness, death resulting in a few minutes from asphyxia. In other cases the patient gives a short cry, and falls unconscious, death occurring almost immediately from syncope. In some cases unconsciousness develops so rapidly, and the respiratory symptoms are so little apparent, that a cerebral vascular lesion may be suspected. On the other hand, life may be maintained for several minutes or even hours, the patient being unconscious or in acute distress and anxiety with urgent dyspnoea, lividity and cyanosis. Respiration is deep and laboured, but fails to give relief to the sense of suffocation. In such cases also, death may result eventually from asphyxia or syncope, or the patient may slowly recover. In less severe forms, such as occur in cardiac and in some post-operative cases, there is sudden pain with difficulty in breathing, followed in a few hours or in a day or two by cough with hæmoptysis or by the expectoration of deeply blood-stained mucus persisting for some days, and slowly clearing up. If the embolus is infective, fever, often of hectic type, results, sometimes delayed for a day or more.

In the severe cases there is cyanosis, distension of the veins of the neck, acute anxiety with exophthalmos and cold, clammy skin. The only physical signs apparent are the deep, laboured breathing, the harsh breath-sounds, and the evidence of cardiac embarrassment with feeble, failing pulse.

In less severe cases the signs are also not characteristic. There are evidences of cyanosis and distress of less urgent character, possibly some limitation of movement on the affected side, increase of vocal fremitus, localised dullness, with weak or absent breath-sounds and sometimes a pleural rub. In some cases definite bronchial or tubular breath-sounds may be audible. A few fine râles are sometimes present in the adjacent lung areas.

**Complications and Sequelæ.**—Localised dry pleurisy is almost invariably present. With infective emboli, abscess or gangrene, and later empyema may result. In organisation an infarct leads to a localised area of fibrosis.

**Diagnosis.**—The dramatic onset, the history and the associated lesions of the veins or heart render diagnosis easy, as a rule; but it may be necessary to eliminate other causes of hæmoptysis, notably pulmonary tuberculosis and chronic venous hyperæmia.

**Radiological appearance.**—It is possible to have an extensive infarction without any visible radiological change, and in fact it is usually the smaller lesions which can be seen in the form of small peripheral areas of opacity not very clearly defined and occasionally associated with pleural effusion. The diaphragm may be raised.

**Course.**—As already described, death may occur from asphyxia or syncope in the course of a few minutes or hours, although recovery occurs in some very severe cases. In the less severe forms, after the initial urgent symptoms have passed off, recovery is often rapid and uneventful, save for pain, cough and blood-stained expectoration.

**Prognosis.**—This depends largely upon the initial shock. The prognosis is very grave when the patient rapidly becomes unconscious. As there is less likelihood of sepsis in cases due to cardiac lesions than in those due to localised venous thrombosis, the prognosis is rather better in the former; but, on the other hand, organisation of a clot in a vein may completely remove the source of the emboli, while the source often persists when they are derived from the heart.

**Treatment.**—Morphine, pethidine or papaverine should be given to allay the anxiety of the patient. Atropine gr.  $\frac{1}{100}$  or  $\frac{1}{80}$  is often given but is of doubtful value. Anti-coagulant therapy should be given to prevent further spread and formation of clot. Heparin should be given intravenously in doses of 5000 units 4-hourly for 24 hours. One of the dicoumarol derivatives, such as ethyl-biscoumacetate (Tromexan) or phenylindanedione (Dindevan) should be started at the same time.

Tromexan, 0.3 g., is given three times during the first day and after that three times a day in a dose controlled by prothrombin estimation. Dindevan, 0.1 g., is given morning and evening for the first day and subsequently twice daily in doses controlled by daily prothrombin estimations. After the prothrombin time has been brought to between 20 and 30 per cent. of normal, heparin is discontinued and Tromexan or Dindevan is continued in controlled doses. The danger of spontaneous hæmorrhages must be borne in mind. Pulmonary embolectomy has been successfully performed, but unless the services of a surgeon with special knowledge of cardiovascular surgery are available, the patient is more likely to survive if recovery is left to nature.

The danger of too great immobilisation of patients, especially elderly ones, must be borne in mind and whenever possible patients should be allowed to get out of bed for toilet purposes or allowed to sit in a suitable chair at intervals or limb exercises should be regularly performed under supervision.

## COLLAPSE OF THE LUNGS

In collapse of the lungs the alveoli are completely or partly devoid of air. The condition may be congenital, and due to non-expansion of the lung, when it is referred to as atelectasis. On the other hand, collapse may be the result of removal of the air from lung tissue previously expanded, when it is called apneumatoses or acquired collapse. The three terms—collapse, atelectasis and apneumatoses—are, however, used as synonyms by many writers.

### ATELECTASIS OR CONGENITAL COLLAPSE

**Ætiology.**—This condition occurs in still-born and in premature infants, and probably persists to some degree for weeks or even months in weakly children. It may result from immaturity or from weakness of the inspiratory muscles, and from obstruction of the air passages by mucus and meconium. It may be a consequence of disease, such as congenital syphilis or lesions and developmental defects of the nervous system.

**Pathology.**—Atelectasis is due to failure of the respiratory mechanism to draw air into the alveoli and expand them, as occurs normally with the first few inspiratory efforts of the newborn infant.

Atelectatic lungs are solid, airless and small. They are usually described as presenting appearances similar to those of adult liver as regards colour and consistence. In partial atelectasis the lung appears mottled, and small expanded areas of pinkish colour may project from the surface. The condition is chiefly of medico-legal and pathological interest.

### APNEUMATOSIS OR ACQUIRED COLLAPSE

There are two types of acquired collapse. That due to obstruction of some part of the bronchial tree and that due to external pressure by fluid, air or diaphragmatic abnormalities. These two conditions have previously been described as active and passive collapse respectively, but Pasteur, who described collapse in a Bradshaw Lecture in 1908, used these terms in quite a different sense since he described as "active", collapse which he thought was due to diaphragmatic paralysis and he used the term "passive" to describe lobular collapse due to bronchial obstruction. The terms are best avoided. This latter type of collapse is sometimes known as absorption collapse as opposed to relaxation or compressive collapse where the primary cause of the collapse is outside the bronchial tree.

The general consensus of opinion now is that collapse is due to bronchial obstruction produced by plugs of mucus, foreign bodies or by swelling of the mucous membrane, bronchial spasm or external pressure. Paralysis of the diaphragm, to which Pasteur gave the premier rôle, does not of itself produce massive collapse, although immobility or elevation of the diaphragm favours the formation of obstructive plugs on the one hand, and on the other may be the result of the obstruction and consequent collapse.

**Synonyms.**—Active Lobar Collapse; Massive Collapse.

**Ætiology.**—The causes are many and various. Foreign bodies in the bronchial tree, neoplasms of the bronchus, granulomata usually tuberculous, stenosis of the bronchus as a result of tuberculosis, syphilis or bronchiectasis form an endobronchial group. Compression of a bronchus by mediastinal tumours, aneurysms or pericardial effusions form another.

Then there is the much larger group of post-operative and post-traumatic cases and those occurring in *whooping cough*, *bronchitis*, *asthma*, *pneumonia* and *bronchiectasis*. In all these cases the probable common factor is obstruction by retained secretions.

Barium included in post-operative feeds and lipiodol inserted into the mouth during dental operations has shown that pulmonary aspiration is much commoner after operations than is generally realised.

Collapse due to fluid in the bronchial tubes, blood, lipiodol, liquid paraffin and sea water are specially mentioned because they tend to be forgotten.

Collapse of the lung which frequently follows the division of adhesions in artificial pneumothorax is probably due to the trapping of retained secretion, to bronchial stenosis or ulceration or a combination of these factors.

**Pathology.**—At post-mortem examination the whole of the lung, or a lobe or portion of a lobe may be deflated and retracted towards the hilum. The collapsed area is bluish red, firm, does not crepitate and sinks in water. There are often pneumonic and pleuritic changes but these may be either primary or secondary.

In massive collapse the heart and mediastinum are displaced towards the affected side and the unaffected lobes are distended with air.

**Symptoms.**—The abruptness of onset depends on the causation and the extent of collapse. Massive collapse of the whole lung and of a whole lower lobe following operation usually has a sudden onset with pain in the lower part of the thorax and behind the sternum. Severe dyspnoea quickly follows and the patient appears dusky, cyanosed and alarmingly ill. There may be a cough but it is often unproductive. The pulse and respiration rate are rapid and the temperature often rises abruptly. Occasionally, especially in old people, the onset is more surreptitious.

The physical signs of massive collapse are usually dramatic. There is immobility of the affected side, often with sucking-in of the ribs. The apex beat is displaced towards the affected side. *There is dullness to percussion on the affected side with hyper-resonance on the unaffected.* The vocal fremitus is diminished or absent, and the breath-sounds are diminished or absent. Occasionally conduction is increased with bronchial breathing and only the displacement of the apex beat and trachea gives a clue to the true diagnosis, but if the obstruction is in a main bronchus these physical signs are unlikely. Hilar or lobular collapse will give proportionately less physical indications.

**Radiological appearances.**—The radiological appearances are characteristic, but vary with the extent and duration of the collapse. There will be a homogeneous opacity varying in shape with the lobes involved, accompanied by focal and general compensatory emphysema, deviation of the trachea and heart to the side of the lesion and elevation of the diaphragm. Lateral or oblique views are essential.

**Complications and Sequelæ.**—These depend on the cause of the obstruction and vary from broncho-pneumonia and pulmonary abscess to pleurisy and empyema.



Post-operative cases which survive the abrupt onset usually make a complete recovery when the obstructing mucus is coughed up.

**Diagnosis.**—The most important conditions from which this malady has to be distinguished are lobar pneumonia, pulmonary embolism, pneumothorax and pleural effusion. The position of the cardiac impulse is often the deciding factor; in collapse it is displaced towards the lung involved, in pleural effusion and pneumothorax it moves away from the affected side, whereas in lobar pneumonia there is usually no cardiac displacement, although there may be dilatation. Labial herpes and blood-stained expectoration are more frequently seen in pneumonia than in collapse. When in right-sided collapse there is marked distension of the left lung with obliteration of the normal cardiac dullness, the signs superficially resemble those of a left-sided pneumothorax; but with careful examination no such error should be made. The distinction from pulmonary embolism may be difficult at first, but the localisation of the signs, and the blood-stained expectoration, may give useful indications.

**Course.**—The course of the affection in post-operative cases or cases associated with bronchitis, asthma or lobar pneumonia is rapid. After periods extending from 2 to 5 days the temperature falls to normal, the symptoms disappear, the lung quickly re-expands, the heart returns to its normal position and there is complete recovery.

**Treatment.**—Prophylactic treatment prevents the onset of post-operative collapse. Planned operations should not be carried out on patients with acute respiratory infections or with untreated suppurative conditions of the naso-pharynx. Patients should be encouraged to sit up and move as soon as possible after operation. Those found to have poor pulmonary ventilation before operation should be taught breathing exercises which will be of service both before and after operation. Once the collapse has occurred the object of treatment is to produce cough and expectoration and restore ventilation to the collapsed lung. Tight abdominal binders or strapping should be loosened, the patient laid flat on his back and gently rolled from side to side twelve times. This often results in cough, with expectoration of the obstructing mucus, and the lung rapidly re-expands. This treatment (*Sante manœuvre*) should be repeated every 4 hours if it is not successful at the first attempt. It is surprising how rapidly relief can be obtained by this simple manœuvre even in cases in which the collapse has been present for 2 or 3 days. Stimulant expectorants should be given subsequently for a few days. Postural drainage should be used and tapotage over the affected lung sometimes helps to dislodge the mucus and promote effective coughing. Inhalation of oxygen with 7 per cent. of carbon dioxide promotes deep respiration. Accurate measurements of the daily sputum should be kept. A diminution without clinical improvement is suggestive of recurrence of the obstruction. Bronchoscopic aspiration has been recommended in cases of post-operative massive collapse. Usually no plugs of mucus are seen obstructing the collapsed bronchus.

**COLLAPSE DUE TO EXTERNAL PRESSURE.**—Pleural effusions, pneumothorax and diaphragmatic displacement also produce collapse of the lung. The latter operates by alveolar compression. The first two operate by separating the two layers of the pleura and allowing the lung to retract. This first stage is known as relaxation collapse. Large effusions or pressure pneumothoraces cause compression collapse which is more complete. High-tension pneumothoraces in patients with a mobile mediastinum sometimes cause collapse of the peripheral portion of the contralateral lung. This form of collapse is described with the conditions which cause it.

## COMPLETE CONGENITAL ABSENCE OF A LUNG

Complete congenital absence of a lung is a rare condition, but can be diagnosed by radiographic examination. It is not compatible with a normal expectation of life.

## HÆMOPTYSIS

It should be recognised that hæmoptysis is a symptom, not a disease. It is here considered separately because the accurate diagnosis of its origin is essential to its treatment, which differs widely in different conditions.

**Definition.**—The term hæmoptysis is arbitrarily restricted to the expectoration of blood entering the air passages from structural below the larynx or from the larynx itself. When the blood is derived from the naso-pharynx or mouth it is sometimes described as spurious hæmoptysis.

**Ætiology.**—1. Pulmonary tuberculosis is the commonest cause, the blood being derived from an aneurysm in a pulmonary cavity, or from ulceration of a small vessel, or congestive processes around the early lesions.

2. Chronic venous congestion, particularly in mitral stenosis.

3. Bronchiectasis as a result of bleeding from granulation tissue or from ulceration of the bronchiectatic walls. Latent bronchiectasis without sputum may cause recurrent hæmoptysis (*forme hémoptoïque sèche*); this is more common in upper lobe bronchiectasis.

4. Inflammatory and destructive diseases of the lungs, air passages or pleura, such as pneumonia, broncho-pneumonia, especially the influenzal variety, abscess and gangrene. Pneumoconiosis, streptotrichosis and ulceration of the larynx, trachea or bronchi from tuberculosis, gumma or new-growth may also be associated with hæmoptysis. Breaking down of a caseous or calcareous bronchial gland is a rare cause, as also is rupture of an empyema through a bronchus.

5. Infarction of the lung from embolic or thrombotic obstruction.

6. New-growths of the lung, bronchi or mediastinal glands.

7. An aortic aneurysm may cause hæmoptysis by "weeping" through an eroded bronchus, or by direct rupture, the latter being, of course, immediately fatal.

8. Traumatic causes.—Injury may cause hæmoptysis, by fractured ribs wounding the lung, by contusion and by breaking down of healed tuberculous lesions. Hæmoptysis occurs frequently in wounds of the chest, both penetrating and non-penetrating. A foreign body, such as a piece of shrapnel, may lie dormant for years, and then cause recurrent hæmoptysis.

9. Certain abnormal blood conditions, chiefly leukæmia, purpura, hæmophilia, scurvy, minor degrees of vitamin C deficiency and occasionally pernicious anæmia. Hæmoptysis occasionally occurs in the malignant specific fevers, especially small-pox and measles.

10. Parasitic causes, such as pulmonary distomatosis and spirochætosis, are common in Asia but rare in Europe. Hydatid disease of the lung may cause repeated slight hæmorrhages.

11. Vicarious menstruation.—Some cases in women have been regarded as vicarious menstruation, and this view dates back to Hippocrates. It is probable, however, that most cases are to be explained as due to leakage from obscure pulmonary lesions.

12. Hæmoptysis occasionally occurs in apparently healthy persons. In some, with high systemic arterial tension, it is probable that the pulmonary arterial pressure is also raised, and the condition may be regarded as analogous to the epistaxis which occurs more commonly in such patients. Sometimes the hæmoptysis is due to leaking from an old arrested tuberculous lesion.

13. Rupture of an hepatic abscess or hydatid cyst through the diaphragm into a bronchus is an occasional cause.

14. Polyarteritis nodosa is a rare cause of pulmonary hæmorrhage.

Spurious hæmoptysis is usually due to staining of the saliva or the pharyngeal secretion with blood, generally derived from the gums, which are spongy and congested, often from early pyorrhæa. The condition is common in anæmic girls, and

is, as a rule, observed in the morning. Hæmorrhage from an enlarged pharyngeal vein is often suggested as a cause, but is rarely seen. Hæmorrhage after tooth extraction, and staining of the mucus expectorated after epistaxis, are other causes of spurious hæmoptysis.

**Pathology.**—From the list of causes it might be inferred that the origin of the blood differs in different cases. It may come from the pulmonary or bronchial vessels in pulmonary tuberculosis and other lung or bronchial conditions, and also in chronic venous congestion or infarction. It may come from the thoracic aorta direct, or from some of its branches, in aneurysm and mediastinal new-growth, and from the hepatic vessels in abscess of the liver. In cases due to disease of the trachea and larynx it comes direct from the vessels supplying them.

Post mortem, the larynx, trachea and bronchi may contain clots, or blood-stained froth and mucus, and their walls may be stained in places. Dark-reddish areas of lobular distribution, due to inhaled blood, may be seen in various parts of the lungs, particularly at the bases. Sometimes this may induce bronchitic changes, described as hæmoptoic bronchitis. Careful search in cases of profuse hæmoptysis will usually reveal the source of the hæmorrhage, and in pulmonary tuberculosis this is generally a ruptured aneurysmal dilatation in a cavity or an ulcerated vessel. The aneurysm may be small and escape notice unless many cuts are made into the lung.

**Symptoms.**—In hæmoptysis, the patient often experiences a tickling in the throat, followed by a gush into the mouth with a salt taste, and on expectoration notices blood. The alarm and anxiety this occasions lead to restlessness and rapid action of the heart. If the bleeding is profuse, cough is frequent, and large clots, together with liquid alkaline blood, may be expectorated to the extent of 20 or 30 oz. in a few hours. The bleeding may cease temporarily, to recur at intervals for several days, until the patient becomes blanched, weak and syncopal, with rapid, weak pulse. In any profuse hæmoptysis, death may occur in a few minutes, either from asphyxia or syncope. In the former case, the blood, at first bright and arterial, is soon dark and frothed, while the patient becomes cyanosed and livid. In slighter degrees of hæmoptysis there may be only streaks, small clots or liquid blood mixed with ordinary sputum. After the actual bleeding has ceased, the sputum may be blood-stained for some days, owing to the expectoration of blood inhaled into other parts of the lungs. This can be recognised by its colour, which varies from dark red to brown, owing to the changes undergone by the blood pigment.

**Diagnosis.**—This involves two problems—first the differentiation from hæmatemesis and spurious hæmoptysis, and secondly the recognition of the cause of the hæmorrhage. If the patient is seen at the time of the bleeding the first of these is easy. The nature of the blood, and its association with cough and possibly with pulmonary or cardiac signs, are conclusive. When the diagnosis has to be made upon the history given by the patient or by friends it may be difficult, especially in the absence of physical signs.

In hæmatemesis there is frequently gastric pain and faintness before the vomiting, the blood is acid in reaction, dark in colour, even brown from acid hæmation, and is sometimes mixed with food. The fact that in hæmoptysis blood may be swallowed and subsequently vomited increases the difficulty. Patients often give very dubious answers to questions as to whether the blood was coughed or vomited up. They should then be questioned as to whether sputum was brought up on the following day, and, if so, whether it was blood-stained. In cases of doubt the investigation of the pulmonary and abdominal physical signs, when the patient's condition permits, may decide the diagnosis.

The utmost caution should be exercised to exclude tuberculosis before making a diagnosis of "spurious hæmoptysis". Only when there are no pulmonary symptoms, signs or radiographic indications, and when some obvious cause, such as anæmia or pyorrhæa, is found, is it safe to do so.

While distinguishing between the various causes of hæmoptysis it is well to regard and to treat it as due to pulmonary tuberculosis until some other cause is conclusively established. The sputum should be examined for tubercle bacilli on several occasions, the temperature recorded and the physical signs including radiographic appearances most carefully watched.

The presence of a valvular lesion, especially mitral stenosis with signs of pulmonary engorgement, may render the cause of hæmoptysis clear. When tuberculosis and cardiac disease can be excluded, a careful study of the history, the symptoms and signs, may throw light on the diagnosis or suggest some investigation which will serve to establish it, e.g. examination of the sputum for parasites and hydatid hooklets, the cytological examination of the blood and radiographic examination.

In other cases, as in bronchiectasis, abscess or gangrene, the history, the physical signs and the nature of the sputum are often characteristic.

In the latent or silent form of bronchiectasis (*forme sèche*), the condition may be revealed only by lipiodol injection.

Bronchoscopy may be of great value in revealing the presence of adenoma or carcinoma. Patients who have had a hæmoptysis which has eluded diagnosis must be kept under observation with radiographic control.

**Prognosis.**—Apart from hæmoptysis due to aneurysm, which is rapidly fatal, or pulmonary tuberculosis, the immediate prognosis in cases of pulmonary hæmorrhage is not unfavourable, even when it continues for days. The ultimate prognosis depends upon the cause.

**Treatment.**—This is so entirely dependent upon the cause and origin of the bleeding that reference should be made to the corresponding diseases.

## EMPHYSEMA OF THE LUNGS

Emphysema of the lungs, or alveolar-ectasis, is a condition of distension of the alveoli; it is usually progressive and is associated with definite changes in the inter-alveolar walls. The following varieties are generally recognised—(1) large-lunged or hypertrophic; (2) small-lunged or atrophic; (3) compensatory; (4) acute vesicular; and (5) acute interstitial emphysema. The last-named condition has no relation to true emphysema except in name, but will be described in this group for convenience.

### 1. LARGE-LUNGED OR HYPERTROPHIC EMPHYSEMA (SUBSTANTIVE OR IDIOPATHIC EMPHYSEMA)

This is a chronic affection and is usually bilateral.

**Ætiology.**—*Predisposing causes.*—It may occur at any age, even in childhood, but is most frequently seen in middle and late adult life. It is commoner in men than in women, probably because they are more exposed to the conditions inducing it. Although not strictly hereditary, it often shows a familial incidence. Certain occupations are credited with being concerned in its production, notably those involving violent or prolonged muscular effort with closed or partially closed glottis, such as blowing wind instruments and lifting heavy weights. Dusty occupations also favour its onset by leading to bronchitis and cough.

The common *exciting cause* seems to be the strain of prolonged and repeated cough, induced by chronic bronchitis, bronchiectasis, asthma, whooping-cough, cigarette smoke inhaling and other causes of irritation of the upper air passages.

**Pathology.**—The pathogenesis of emphysema has been much debated and various explanations have been offered. (1) Primary degeneration theory. Villemin suggested that the essential lesion was a fatty degeneration of the alveolar walls, while Cohnheim believed that there was a congenital defect of the elastic tissue of the lung.

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**Pathology.**—From the list of causes it might be inferred that the origin of the blood differs in different cases. It may come from the pulmonary or bronchial vessels in pulmonary tuberculosis and other lung or bronchial conditions, and also in chronic venous congestion or infarction. It may come from the thoracic aorta direct, or from some of its branches, in aneurysm and mediastinal new-growth, and from the hepatic vessels in abscess of the liver. In cases due to disease of the trachea and larynx it comes direct from the vessels supplying them.

Post mortem, the larynx, trachea and bronchi may contain clots, or blood-stained froth and mucus, and their walls may be stained in places. Dark-reddish areas of lobular distribution, due to inhaled blood, may be seen in various parts of the lungs, particularly at the bases. Sometimes this may induce bronchitic changes, described as hæmoptoic bronchitis. Careful search in cases of profuse hæmoptysis will usually reveal the source of the hæmorrhage, and in pulmonary tuberculosis this is generally a ruptured aneurysmal dilatation in a cavity or an ulcerated vessel. The aneurysm may be small and escape notice unless many cuts are made into the lung.

**Symptoms.**—In hæmoptysis, the patient often experiences a tickling in the throat, followed by a gush into the mouth with a salt taste, and on expectoration notices blood. The alarm and anxiety this occasions lead to restlessness and rapid action of the heart. If the bleeding is profuse, cough is frequent, and large clots, together with liquid alkaline blood, may be expectorated to the extent of 20 or 30 oz. in a few hours. The bleeding may cease temporarily, to recur at intervals for several days, until the patient becomes blanched, weak and syncopal, with rapid, weak pulse. In any profuse hæmoptysis, death may occur in a few minutes, either from asphyxia or syncope. In the former case, the blood, at first bright and arterial, is soon dark and frothed, while the patient becomes cyanosed and livid. In slighter degrees of hæmoptysis there may be only streaks, small clots or liquid blood mixed with ordinary sputum. After the actual bleeding has ceased, the sputum may be blood-stained for some days, owing to the expectoration of blood inhaled into other parts of the lungs. This can be recognised by its colour, which varies from dark red to brown, owing to the changes undergone by the blood pigment.

**Diagnosis.**—This involves two problems—first the differentiation from hæmatemesis and spurious hæmoptysis, and secondly the recognition of the cause of the hæmorrhage. If the patient is seen at the time of the bleeding the first of these is easy. The nature of the blood, and its association with cough and possibly with pulmonary or cardiac signs, are conclusive. When the diagnosis has to be made upon the history given by the patient or by friends it may be difficult, especially in the absence of physical signs.

In hæmatemesis there is frequently gastric pain and faintness before the vomiting, the blood is acid in reaction, dark in colour, even brown from acid hæmatin, and is sometimes mixed with food. The fact that in hæmoptysis blood may be swallowed and subsequently vomited increases the difficulty. Patients often give very dubious answers to questions as to whether the blood was coughed or vomited up. They should then be questioned as to whether sputum was brought up on the following day, and, if so, whether it was blood-stained. In cases of doubt the investigation of the pulmonary and abdominal physical signs, when the patient's condition permits, may decide the diagnosis.

The utmost caution should be exercised to exclude tuberculosis before making a diagnosis of "spurious hæmoptysis". Only when there are no pulmonary symptoms, signs or radiographic indications, and when some obvious cause, such as anæmia or pyorrhæa, is found, is it safe to do so.

is common, and is to some extent a measure of the degree of emphysema. Varying degrees of polycythæmia may be observed. The patient may walk about with a more extreme degree of cyanosis than in any other condition except congenital heart disease. Clubbing of the fingers of moderate degree is common. Cough is usually due to the associated bronchitis, and is worse in the winter and in foggy weather. It is frequent, noisy and often hacking and paroxysmal. Expectoration is also the result of the bronchial catarrh, and varies from a few grey mucoid pellets to copious muco-pus.

The chest is enlarged, particularly in the antero-posterior diameter, the upper thoracic spine is rounded and kyphotic, the sternum protrudes forward, and the angle of Louis is prominent, the general effect being the so-called barrel-shaped chest. The ribs run forward more horizontally and the intercostal spaces are wider than normal, the chest being as a whole in the inspiratory position. The respiratory movements are much restricted, the patient elevating the rigid thorax with little expansion on taking a deep breath, so that the inspiratory increase at the level of the nipples may be only  $\frac{1}{2}$  to 1 inch instead of the normal  $2\frac{1}{2}$  to 3 for an adult. There is often filling and even bulging of the supra-clavicular hollow, while the neck appears short, the sternomastoids stand out, and the jugular veins are full. A zone of dilated venules, the "emphysematous girdle", is often present along the line of the costal attachment of the diaphragm, but is not pathognomonic. The cardiac impulse is not visible, as a rule, and may only be felt with difficulty, but epigastric pulsation is usually apparent. Vocal fremitus is diminished, and the percussion note is hyper-resonant. The superficial cardiac dullness is greatly diminished or even absent, and the lower limit of pulmonary resonance may extend to the costal margin, back and front, the hepatic dullness being encroached on or obliterated.

It is said that in bullous emphysema the breath-sounds are harsh over the outer part of the upper lobes in front, and weak at the bases. In general emphysema the breath-sounds are weak everywhere, inspiration is short and expiration is greatly prolonged. A loud rumbling, from contraction of the thoracic muscles, may entirely obscure the breath-sounds. A few fine bubbling râles may be heard at the bases or at the sternal margins. If bronchitis is present, scattered rhonchi may be audible. Vocal resonance is generally slightly diminished. The heart-sounds are weak and distant, and in late stages a tricuspid systolic murmur may develop. The "vital capacity" of the lungs, measured by a spirometer, is often reduced to one-half or less. Radiographic examination shows increased extent, and undue translucency of the lung tissue. It shows the diaphragm lower in position and flattened, and the costophrenic angle widened. The liver is sometimes palpable, possibly from downward displacement by the bulky lung. The spleen may also be depressed and palpable.

**Complications.**—Bronchitis is the commonest, and often causes a vicious circle. Asthmatic attacks, so-called "bronchial asthma", are common in later stages; on the other hand, spasmodic asthma may be the cause of the emphysema. Pneumothorax and interstitial emphysema may occur from rupture of the bullæ, although these accidents are relatively rare or perhaps relatively rarely diagnosed since the difficulties of diagnosis in these cases are obvious. Pneumothorax is a common complication of the severe emphysema of advanced pneumoconiosis. Pulmonary tuberculosis is an occasional complication of emphysema, which, contrary to popular opinion, is not antagonistic to it, although it may mask and obscure the early stages. Right-sided cardiac failure, with its train of consecutive changes, is a late and often terminal complication.

**Diagnosis.**—This is never difficult in advanced cases. The slighter degrees may be more difficult, and the diagnosis is then largely a matter of inference from the association of chronic cough and dyspnoea, with physical signs of hyper-resonance and prolonged expiration.

Confusion may occasionally arise with pneumothorax and pulmonary tuberculosis.

(2) The inspiratory theory, first suggested by Laennec and developed by Gairdner postulates the force of inspiration as the distending agent. (3) The expiratory theory, first enunciated by Mendelssohn, was independently brought forward and established by Jenner. The distension of the alveoli is regarded as due to the effect of forced expiration and cough. Jenner pointed out the special and early involvement of the apices, the anterior and lower margins of the lungs; in other words, the parts least supported by the thoracic cage. (4) Freund regarded the changes in the lungs as secondary to calcification of the costal cartilages, the chest becoming fixed in the inspiratory position and the lung permanently expanded in consequence. Christie in an analysis of these and other theories concludes that there are probably three factors of importance: inflation of the lungs caused by obstruction to expiration; loss of elasticity due to the stress and strain of coughing in asthma; lowered resistance of the lung to wear-and-tear varying from person to person and becoming progressively lower with advancing age.

The characteristic conformation of the chest is usually apparent (see Symptoms), the costal cartilages are often calcified, and on opening the thorax post mortem, the lungs bulge instead of retracting, so that the pericardium may be almost completely obscured. They are pale in colour, even in town-dwellers, a condition called albinism of the lung by Virchow. They are soft and pit on pressure, and, as described by Laennec, give the sensation of a down pillow. The surface of the lung under the pleura shows a finely vesicular appearance, due to the distension of the alveoli, the vesicles often being nearly as large as pins' heads. Not infrequently large bullæ or blister-like protuberances, varying in size from a pea to a Spanish olive, occasionally much larger, may be seen projecting from the surface, particularly at the apices and margins. These bullæ when incised show fine fibrous bands crossing them, the remains of inter-alveolar walls and of atrophied blood vessels. It was formerly customary to refer to such cases as bullous or marginal emphysema and to describe those in which the dilatation is less obvious but more widely diffused as general emphysema; but the conditions are so commonly associated together in varying degrees that little is gained by so doing. On section the lungs are pale and dry, except at the bases, where there is frequently some œdema in advanced cases. The bronchi may show some general dilatation. When bronchitis coexists, mucopus can be squeezed from the cross-sections of these tubes. As pointed out by Fowler, pleural adhesion is relatively uncommon. The infundibula and alveoli are dilated, and the inter-alveolar walls are thin and atrophic, even disappearing wholly or in part. The distension and coalescence of adjacent alveoli result in the formation of bullæ. The calibre of the pulmonary capillaries is diminished by stretching of the alveolar walls, and where atrophy of the inter-alveolar septa occurs the capillaries are destroyed. These two processes result in a considerable diminution in the total aerating surface, and cause the dyspnoea and cyanosis characteristic of the disease. Moreover, the normal anastomoses between the terminal bronchial and pulmonary capillaries increase considerably, and some of the blood in the latter may therefore fail to reach the alveoli and so escape aeration. Atrophic changes in the elastic tissue have been described. In order to maintain the circulation through the diminished capillary area, the right ventricle hypertrophies and the resultant raised blood pressure sometimes induces atheroma of the pulmonary artery. Emphysema being a progressive lesion, and the defective aeration of the blood perhaps interfering with the nutrition of the heart muscle, cardiac failure eventually ensues, causing tricuspid regurgitation, engorgement of the right auricle, and the visceral effects of venous engorgement, such as "nutmeg" liver.

**Symptoms.**—Dyspnoea of varying degree is the most characteristic symptom. In uncomplicated cases of moderate extent it is only present on exertion, unless bronchitis coexists. In advanced emphysema, dyspnoea is marked and becomes extreme in the bronchitic or "asthmatic" attacks and in foggy weather. Cyanosis

is common, and is to some extent a measure of the degree of emphysema. Varying degrees of polycythæmia may be observed. The patient may walk about with a more extreme degree of cyanosis than in any other condition except congenital heart disease. Clubbing of the fingers of moderate degree is common. Cough is usually due to the associated bronchitis, and is worse in the winter and in foggy weather. It is frequent, noisy and often hacking and paroxysmal. Expectoration is also the result of the bronchial catarrh, and varies from a few grey mucoid pellets to copious mucopus.

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**Diagnosis.**—This is never difficult in advanced cases. The slighter degrees may be more difficult, and the diagnosis is then largely a matter of inference from the association of chronic cough and dyspnoea, with physical signs of hyper-resonance and prolonged expiration.

Confusion may occasionally arise with pneumothorax and pulmonary tuberculosis.



Careful record of the symptoms and signs and the investigation of the sputum generally suffice to distinguish these conditions. In doubtful cases radiography will assist.

**Course.**—Emphysema is progressive, unless the cause is removed or the effects of the disease are mitigated by residence in a warm, dry climate, especially in the winter. Conversely, residence in unsuitable districts, persistence in detrimental employment, and repeated attacks of bronchitis accelerate its course.

**Prognosis.**—This depends upon the degree of emphysema and the circumstances of the patient. If progressive, it exerts an increasingly crippling effect, and it certainly shortens life under urban conditions. A "vital capacity" of less than 50 per cent. of the normal is of serious import. The advent of severe bronchitis or of cardiac complications may affect the prognosis gravely.

**Treatment.**—Emphysema may be arrested but cannot be cured. Attention must be directed to prevention of the causes of chronic cough and increased intra-alveolar tension. In any person with hereditary tendency to emphysema or to winter cough, the questions of occupation and place of residence should be carefully considered. When the disease is established, the patient, if in a position to afford it, should spend the winter in a warm, more equable climate, either abroad or at the south-west coast of England.

Various attempts have been made to increase the respiratory ventilation of the lungs by deflation. The most generally used method is by the use of a well-fitting abdominal belt to raise the diaphragm. Efforts in the same direction have been made by pneumoperitoneum and even pneumothorax. Their justification is doubtful.

Expiration breathing exercises are of general application and quite impressive results can be obtained by their use provided the chest wall is not completely rigid. Even in these cases diaphragmatic movement can be increased.

The diet should be simple and easily digestible, especially in the later stages. If there is spasmodic dyspnoea or asthma, no late meal should be permitted. Clothing should be warm, but the excess of under-garments, often worn in fear of chill, is harmful. Patients should avoid those who have colds and should themselves stay in bed at the first sign of such an infection in themselves.

In other respects treatment is largely symptomatic. In acute bronchitic attacks the measures to be adopted are in no way different from those in bronchitis uncomplicated by emphysema. In the more chronic bronchitis so commonly present in the winter, iodides with alkalis and balsamic expectorants seem beneficial. When asthma or paroxysmal dyspnoea occurs, antispasmodic drugs and measures similar to those used in spasmodic asthma may be employed. When cardiac failure supervenes, the appropriate treatment must be vigorously applied. If there is marked cyanosis and venous engorgement, oxygen administration and diuretic drugs may be employed, and digitalis administered; any associated pulmonary infection, even bronchitis, requires energetic treatment with the appropriate antibiotic; bronchospasm should be treated with antispasmodics.

## 2. SMALL-LUNGED EMPHYSEMA (ATROPHIC OR SENILE EMPHYSEMA)

**Ætiology.**—This condition occurs in old age and forms part of the general atrophy of the tissues.

**Pathology.**—The alveolar walls become thinned and disappear, so that adjacent alveoli coalesce. The condition is primarily atrophic, and therefore differs from true emphysema, although the result is to produce a diminished area for aeration. Post mortem the lungs are small and do not bulge or obscure the pericardium. They are often deeply pigmented, and are more spongy than normal, but although bullæ occur they are small. On section the lung tissue is bloodless and friable. The bronchi may be slightly dilated and show catarrhal changes.

**Symptoms.**—These are slight and are masked by the enfeeblement due to the

general atrophy and debility. There is shortness of breath only on exertion, or on exacerbation of the chronic bronchitis which is frequently present. The chest is small, flat and thinly covered, the movements are poor and there is elevation of the chest as a whole, with poor expansion. Kountz and Alexander maintain that there is very little diminution in vital capacity, that the movements of the diaphragm are increased and that the intervertebral disks are abnormal. There is little cyanosis, and no clubbing. The vocal fremitus is unaltered or slightly diminished. The percussion note is hyper-resonant, but there is no encroachment on the cardiac and hepatic areas of dullness. Breath-sounds are weak, and there is but little prolongation of expiration. Rhonchi and râles may be heard, especially if bronchitis is present, or if the heart is failing.

**Diagnosis.**—The condition is generally so obvious that no difficulty arises.

**Treatment.**—This is chiefly a matter of careful regimen and diet, with treatment of co-existing bronchitis or cardiac failure.

### 3. COMPENSATORY EMPHYSEMA (LOCALISED OR SECONDARY EMPHYSEMA)

**Ætiology.**—Localised emphysema is a sequel to some process inducing collapse, contraction or destruction of areas of lung tissue. It may be lobular in distribution in bronchitis, broncho-pneumonia, tuberculosis and diphtheria. It may affect one or more lobes, or the whole of one lung, especially in cases of fibrosis following tuberculosis, pneumonia, chronic pleural effusion and empyema.

**Pathology.**—It is generally conceded that the inspiratory theory of Laennec and Gairdner satisfactorily explains the genesis of this condition. When shrinkage of an area of lung occurs, the chest wall may fall in if there is pleural adhesion, but otherwise inspiration tends to expand the normal parts of the lungs. None the less, it must be admitted that the expiratory strain of cough may assist in its production.

Although it may be compensatory and physiological at its inception, it is doubtful whether a true hypertrophy takes place after adolescence. In any case it soon leads to atrophy of the alveolar walls, as in true emphysema, and thus becomes pathological and harmful. Post mortem the condition may be found in an upper lobe around contracted scarred lung tissue, or in a lower lobe when the upper lobe is contracted or disorganised. In cases where one lung is fibroid and contracted, compensatory emphysema may be found throughout the sound lung. The resulting adaptations caused by enlargement of one part and shrinking of another may produce some striking displacements, the lower lobe extending upwards nearly to the clavicle, or the anterior margin of the sound lung crossing the mid-line. The general appearances are closely similar to those of ordinary emphysema, except that bullæ do not occur, at any rate until the process is advanced and definitely pathological.

**Symptoms.**—This condition does not produce symptoms that can be differentiated from those of the primary disease. When it affects a lobe or the whole of one lung, there is hyper-resonance over the area involved, which often contrasts strikingly with the dullness due to the primary lesion. The hyper-resonance may extend across the sternum and even for an inch or more beyond it. The heart is displaced towards the side where fibrosis is in progress. Vocal fremitus and vocal resonance are little altered, but may be increased at first and subsequently diminished. In the early stages, when there is alveolar dilatation without degenerative mural changes, the breath-sounds are exaggerated, harsh or puerile, but when such processes develop, they become weak and there are indications of dyspnoea and cyanosis on exertion.

**Diagnosis.**—This is easy, owing to the difference between the diseased and "compensatory" areas, and to the indications of contraction and displacement.

**Treatment.**—No special treatment apart from that of the primary condition is required.

## 4. ACUTE VESICULAR EMPHYSEMA

Although custom has included this condition with emphysema, it is in reality only a temporary acute distension of the alveoli resulting from any condition causing widespread obstruction of the smaller bronchi. It is sometimes observed after death in cases of acute bronchitis, whooping-cough or asphyxia and in anaphylactic shock, and its existence may be inferred in severe asthma. Post mortem the lungs are bulky and the alveoli distended.

The symptoms are dependent upon the primary condition, although dyspnoea is invariably present. The chest is found to be fully expanded, the vocal fremitus is diminished, the percussion note is hyper-resonant, and the breath-sounds vary with the condition inducing it. In cases due to asthma, the injection of a few minims of 1:1000 adrenaline often produces visible deflation and helps to differentiate it from hypertrophic emphysema.

## 5. ACUTE INTERSTITIAL EMPHYSEMA

In acute interstitial emphysema air is present in the stroma of the lungs, and in the subpleural connective tissues. It may follow external trauma, such as fractured ribs, or wounds penetrating the lungs. The alveoli may rupture with violent expiratory efforts, as occur in whooping-cough or influenzal broncho-pneumonia. It may occur in diphtheria. The air sometimes tracks along the pulmonary roots to the mediastinum, and appearing in the neck or on the chest-wall gives rise to surgical emphysema.

Post mortem, subpleural bullæ may be seen containing air, and on section of the lung minute air bubbles may be found in the inter-alveolar connective tissue. A diagnosis cannot be made unless the physical signs of surgical emphysema are present. The air is usually completely absorbed, and a perfect recovery takes place. No special treatment is required beyond keeping the patient at rest, and giving sedative drugs to allay cough.

## ABSCESS OF THE LUNG

**Definition.**—Abscess of the lung includes any circumscribed collection of pus formed in the lung tissue, but softened tuberculous areas and bronchiectatic accumulations are usually excluded.

**Ætiology.**—*Predisposing causes.*—These include any diseases producing general cachexia or malnutrition, notably diabetes and chronic alcoholism, also any conditions leading to diminished resistance locally in the lung, such as injury, disease or exposure.

*Exciting causes.*—These are pyogenic organisms, which reach the lung by inhalation, by extension from adjacent suppurative processes, or by the blood-stream, either directly or in septic emboli. The common organisms found are streptococci, staphylococci, the pneumococcus, Friedlander's pneumo-bacillus, *Cl. welchii* and *Bact. coli*—sometimes acting in conjunction with putrefactive bacteria. Spirochaetes, *F. fusiformis* and other anaerobic organisms are often present, especially after rupture has occurred. Pulmonary abscess may form under the following conditions:

(1) After inhalation of foreign material into a bronchus. This may be a foreign body, or may occur in association with septic conditions in the nose, naso-pharynx and larynx, or during and after operations in these regions. These are referred to as inhalation abscesses, though some post-operative cases are regarded as due to embolism and not to inhalation. (2) As a result of lobar or lobular pneumonia, especially after the deglutition and aspiration varieties of the latter. Such abscesses are sometimes called meta-pneumonic. (3) Embolic causes—in pyæmia, or following on septic pulmonary emboli due to right-sided septic endocarditis, or derived from distant

septic processes, such as otitis media, and infective thrombo-phlebitis. Amœbic abscess occurs occasionally after dysentery, and pulmonary abscess may be found as a rare complication of enteric fever. (4) From infection of the lung tissue due to spread from adjacent disease. This may occur in bronchiectasis, in ulcerating new growths of the lung, bronchi, œsophagus or mediastinal glands, in caries of the vertebræ or ribs, and in suppurating mediastinal glands. Rupture of an empyema, of a subphrenic abscess, of a liver abscess, or of infected hydatid cysts of the lung or liver may also lead to pulmonary suppuration. Ten per cent. of cases of abscess are due to new growths. (5) As a sequel of perforating chest wounds, or of fractured ribs piercing the lung.

**Pathology.**—Abscess of the lung is generally single and basic when consequent on pneumonia, whereas embolic abscesses are often small and multiple and may be found in any part of the lung. Abscesses due to extension from adjacent disease are generally solitary, and are often large and irregular. The walls of acute abscesses are generally formed of congested and œdematous lung tissue, or of a zone of unresolved pneumonia. Since acute abscesses commonly rupture quickly into a bronchus, a fibrous capsule is unusual, but in chronic abscess there is often considerable fibroid change in the neighbouring lung tissue. The pleura may become involved over superficial abscesses, leading to empyema, or to pyo-pneumothorax if rupture follows.

**Symptoms.**—Abscess may develop insidiously, with comparatively slight symptoms. More commonly they are an intensification of those due to the primary or antecedent condition. The patient often appears seriously ill, the fever becomes of septic type, remittent or intermittent in character, and of a high range. Rigors and sweating are common. Clubbed fingers are a characteristic and early sign. The pulmonary symptoms at first may be only slight cough with scanty muco-purulent expectoration. Dyspnoea may be present and pain of acute character develops if the pleura is involved. Hæmoptysis occurs in 70 per cent. of cases of abscess. A considerable leucocytosis, up to 20,000 or 30,000 may be found, and occasionally the breath may be offensive, even before rupture into a bronchus occurs, followed by the sudden expectoration of a large quantity of pus. The pus is sometimes unpleasant or offensive-smelling, but has not the extreme fetor of gangrene. Microscopical investigation will demonstrate the presence of pulmonary debris, especially elastic tissue, together with pus cells and micro-organisms. After the expectoration of the pus, the temperature usually falls and the general condition of the patient is much improved, though cough and expectoration persist. In chronic cases after rupture the temperature may become irregular and periodic, a few days of normal temperature being followed by a period of fever and later by increased expectoration. The physical signs in a deep-seated or small abscess are often inconspicuous, and comprise slight dullness over a small area, weak breath-sounds and possibly a few râles in the surrounding infiltrated or œdematous lung tissue. With a large or a superficial abscess, the signs before rupture may be those of consolidated or collapsed lung. After evacuation occurs, the characteristic signs of excavation usually develop at once. In multiple embolic abscesses the signs are usually those of disseminated broncho-pneumonia, and in multiple abscesses due to staphylococcal infection widespread diffuse opacities may be apparent on radiographic examination. These rapidly develop into cavities either empty or with a fluid level. They may be mistaken for lung cysts owing to their thin walls.

**Complications and Sequelæ.**—The commonest complication is dry pleurisy. This may progress to empyema, or to pyo-pneumothorax, if rupture into the pleura occurs. In some cases mediastinitis or pericarditis may develop. Gangrene is described, but is a rare sequel. Metastatic abscesses may be produced in other parts of the body, especially in the brain, and meningitis is a rare and serious complication. The most important sequelæ are fibrosis of the lung, with bronchiectasis, pleural adhesion and rarely indurative mediastinitis.

**Diagnosis.**—This is difficult before rupture into a bronchus, but abscess may be suspected from the gravity of the symptoms in relation to the history and signs, especially if leucocytosis and fetor of the breath are present. Radiographic examination may be helpful, by demonstrating a localised shadow before rupture, and excavation afterwards, and also by establishing the situation of the abscess. A fluid level can often be seen in films taken in the erect position, although a fluid level may sometimes be more obvious if the patient is radiographed lying on one or other side or tilted to one side. The sudden expectoration of pus, followed by retrogression of symptoms and signs of excavation is very suggestive of abscess. After rupture has occurred the differential diagnosis has to be considered from:

1. *Interlobar empyema.*—This may be very difficult or even impossible. In this condition the signs are generally most marked in the region of an interlobar septum, there may be some cardiac displacement, and the sputum, though purulent, does not contain elastic tissue.

2. *Bronchiectasis.*—The history, the characteristic cough and sputum, and the variation of the physical signs with the state of the cavity usually suffice to distinguish this condition. A lipiodol or Neo-Hydriol bronchogram will distinguish in doubtful cases, since the oil does not, as a rule, enter abscess cavities and the appearances in bronchiectasis are characteristic.

3. *Gangrene of the lung.*—This is a distinction with little difference except that gangrene is a suppuration of the lung that has not localised. The extreme gravity of the patient's general condition and the horrible fetor of the breath and sputum are the most characteristic features of gangrene.

4. *Tuberculous excavation.*—The history, the distribution of the signs and the characters of the sputum, including the presence of tubercle bacilli, are the distinguishing indications.

5. *Purulent bronchitis.*—The history, the widespread physical signs and the absence of elastic tissue from the sputum usually serve to establish the diagnosis, and lipiodol or Neo-Hydriol investigations may be helpful.

In multiple or pyæmic abscesses, it is often impossible to recognise the condition, though it may be suspected from the severity of the symptoms and signs. In any doubtful case radiographic examination or tomography should be carried out, if the condition of the patient permits. The possibility of malignant growth as a cause of abscess should be borne in mind and, when necessary, bronchoscopy as well as lipiodol investigation carried out. Exploratory puncture as a means of diagnosis is dangerous and should be avoided.

**Prognosis.**—The prognosis though grave in many cases is better than might be anticipated and has been much improved by modern treatment. Pyæmic abscesses have a more serious prognosis except when staphylococcal, which sometimes improved spontaneously even before the days of antibiotics.

**Treatment.**—Penicillin should be given in doses of 1 to 2 million units daily as soon as the diagnosis is made. When sputum from the abscess is available the sensitivity of the various organisms should be tested in case any of them are penicillin resistant but are sensitive to streptomycin, chloramphenicol, chlortetracycline or other antibiotics. A careful record of the daily amount of sputum must be started and the patient given postural drainage in the position appropriate to the site of the abscess.

The posturing must be kept up for as prolonged periods as possible. Special beds on frames make prolonged postural drainage more effective and more comfortable. Tapotage over the abscess in the correct postural position helps drainage of the abscess and breathing exercises should be combined with the postural drainage. Once the abscess has started to discharge, diminution in the measured amount of sputum should be accompanied by improvement in the clinical condition. If it is not, the drainage is imperfect. Improvement must be correlated with radiological changes.

In a considerable number of cases recovery takes place with penicillin and postural drainage alone.

If in spite of postural drainage and the use of suitable antibiotics, there is no steady progress of improvement from week to week, surgical intervention is called for. The operation of choice in these cases used to be external drainage after the sealing off of the pleura. Resection, however, is more effective when the localisation of the abscess renders the procedure possible.

Bronchoscopic drainage has its advocates and its successes, but it has little advantage if any over postural drainage, except that it is sometimes successful by making the patient cough. Artificial pneumothorax is never advisable in these cases owing to the imminent danger of pyo-pneumothorax.

## GANGRENE OF THE LUNG

In this condition localised or diffuse areas of lung tissue undergo putrefactive necrosis.

**Ætiology.**—*Predisposing causes.*—These include old age, over-indulgence in alcohol, general debility, diabetes and insanity. In certain rare cases, especially after broncho-pneumonia complicating measles, gangrene of the lung is met with in children.

*Exciting causes and associated conditions.*—These are, in the main, identical with those of pulmonary abscess (sec p. 1002). In addition, the pressure of aneurysm or of new-growth on branches of the pulmonary artery may lead to gangrene. The causal organisms are also very similar to those found in abscess of the lung, and include staphylococci, streptococci, sarcinæ, the *Micrococcus tetragenus*, *Bact. coli*, *Ps. pyocyanea*, *F. fusiformis* with its associated spirochæte, and various anaerobes. Some of these organisms yield putrefactive products, with the liberation of phenol, indole and skatole compounds.

**Pathology.**—It is not quite clear what are the factors determining whether abscess or gangrene occurs in an infected area of lung. Doubtless the general resistance of the body, the degree of local vascular disturbance and the virulence of the infecting organisms all play their part. Laennec first described the two varieties of gangrene, the circumscribed and the spreading or diffuse. Around the former there are indications of a line of demarcation, formed by congested lung tissue, which may present the appearance of red hepatisation. The surrounding lung tissue is invariably somewhat œdematous. The gangrenous area is soft and pulpy, and its colour varies from reddish brown to greenish black. As the necrosis advances, putrefactive liquefaction occurs, with the formation of a horribly reeking fluid, containing shreds and masses of necrotic lung tissue. When this is discharged, excavation results, and isolated vessels may be seen running across the resulting cavity, the walls of which are rough and covered with fetid pus. The diffuse variety of gangrene is less common; there is no attempt at a zone of demarcation, and the whole of a lobe or of one lung may be affected. In both forms, the overlying pleura is intensely inflamed, and empyema or pyo-pneumothorax may be produced.

**Symptoms.**—These are similar to those occurring in abscess of the lung, but are more acute. The patient is desperately ill, rigors are more common and sweating is more profuse. The breath has a peculiar fetor, which, on account of the presence of the skatole group of putrefactive products in the gangrenous lung, has an almost faecal odour. The sputum is intensely offensive, and on standing separates into three layers, similar to those of the expectoration in cases of bronchiectasis. Elastic tissue is usually present. Hæmoptysis is not infrequent and may prove fatal. In rare cases gangrene is not accompanied by fetid expectoration, especially when developing in the insane, in young children, and in diabetics, or after pulmonary embolism.

The physical signs closely resemble those present in cases of pulmonary abscess, and are those of consolidation before liquefaction occurs, and of excavation afterwards. The signs of the antecedent condition such as bronchiectasis, aneurysm or malignant disease may also be present.

**Complications and Sequelæ.**—These are similar to those met with in pulmonary abscess, but owing to the rapid course and greater fatality of gangrene, they are not so common. Cerebral abscess may occur.

**Diagnosis.**—The differential diagnosis is as for pulmonary abscess, the distinguishing features being the extremely critical condition of the patient and the revolting fetor of the breath and expectoration. Radiographic examination may give great assistance if the patient's condition permits it to be made.

**Course.**—The course is usually rapid, unless the diseased area is small and circumscribed. In rare cases of localised gangrene of small extent, resolution and subsequent fibrosis occur.

**Prognosis.**—This is always extremely grave, though a few cases of localised gangrene recover spontaneously. The prognosis is improved by early operation in suitable cases. The outlook is said to be worse if the condition is apical, and diffuse gangrene is invariably fatal.

**Treatment.**—Operation is indicated when the general condition of the patient permits, if the gangrenous area can be localised by physical signs or radiographic examination. Exploratory puncture should not be carried out. The other operative procedures are similar to those for abscess of the lung. Operation is contraindicated in cases of diffuse gangrene. The medical treatment is in all respects similar to that for pulmonary abscess. Injections of neo-arsphenamine, in doses of 0.3 g., have given good results, especially in cases due to fuso-spirochaetosis. The sensitivity of the organisms in the sputum to the various antibiotics should be determined, and the appropriate antibiotic given.

## PULMONARY FIBROSIS

**Synonyms.**—Fibroid Disease of the Lung; Chronic Interstitial Pneumonia; Cirrhosis of the Lung.

**Definition.**—Pulmonary fibrosis is a late sequel of many acute and chronic inflammatory or irritative processes affecting the bronchi, lungs and pleuræ. It is therefore rather of pathological than of clinical interest, and in no sense constitutes a separate disease, although the end-results are remarkably similar in different forms. It is described here partly in deference to tradition, and partly to point out the methods of diagnosis between the various causes producing such strikingly similar effects.

**Ætiology.**—(1) The commonest cause is pulmonary tuberculosis, particularly the fibroid and fibro-caseous varieties. (2) The group of pneumoconioses contributes a considerable number of cases, and possibly some varieties of gas poisoning may induce fibroid changes. (3) Broncho-pneumonic processes, particularly the forms associated with measles and whooping-cough, may be followed by widespread fibrosis, especially in children. (4) Although fibroid induration is commonly described as a sequel of lobar pneumonia, this disease is one of the rarer causes. (5) Localised fibrosis may occur around any circumscribed pulmonary or bronchial lesion, such as that produced by syphilis, leprosy, glanders or actinomycosis. Similarly it occurs about infarcts, pulmonary abscesses and parasitic cysts. (6) Chronic venous congestion, if prolonged, leads to fibroid change, which is referred to as "brown induration". This is usually of moderate degree and does not affect the clinical manifestations. (7) Chronic pleural affections, particularly those leading to adhesions or causing pulmonary collapse, may induce fibroid changes within the lung, and these forms are described as "pleurogenous cirrhosis". (8) Any condition causing obstruction

of a bronchus and leading either to collapse or to bronchiectasis may, if long continued, cause fibrosis of the corresponding lung area. Among such may be mentioned inhaled foreign body, new-growth, cicatricial contraction and thoracic aneurysm.

**Pathology.**—The fibroid overgrowth may be: (1) Massive or lobar; (2) localised or insular; (3) peri-bronchial and (4) reticular.

Any part of the connective tissue framework of the lungs and bronchi may contribute to the fibrosis. In the massive form, which generally affects the whole or the major part of a lobe or even of one lung, the appearances in cases due to tuberculosis differ from those due to other causes. In the tuberculous variety the primary distribution is usually apical, and evidence of other tuberculous processes may be apparent in the form of large or small dried-up cavities, inspissated caseous material or calcareous masses enclosed in fibrous strands. In non-tuberculous processes, the early localisation is commonly basal, and although the primary cause may be obvious in the form of bronchial obstruction or some pleural condition, this is not always the case. On the other hand, non-tuberculous processes may involve the upper lobe primarily and fibroid tuberculosis may fall with special stress upon the lower lobe. In both forms of fibrosis, bronchiectasis may result, although this is more common in the non-tuberculous cases. Apart from the special tuberculous lesions, the end-results are very similar in both forms. The affected area of the lung is shrunken and often devoid of air except for that in the bronchi and in the cavities. It is dark in colour, very firm and hard. On section it presents a mottled appearance owing to the strands of blue-grey fibrous tissue traversing it, contrasting with the pigmented, condensed, airless lung tissue. The fibroid area may be honeycombed by cavities or may present one large excavation, due either to tuberculous cavitation or to bronchiectatic dilatation. There is nearly always thickening and adhesion of the pleura. The contraction of the abnormal fibrous tissue leads to marked displacement of the heart and mediastinum.

The localised form is commonly due to healed tuberculous processes at an apex. There may be simple puckering with or without pleural thickening and adhesion, or a dense mass enclosing dried-up caseous matter or calcareous spicules. In bronchitic or broncho-pneumonic processes a patchy fibrosis may occur, described as insular fibrosis by Fowler.

Reticular fibrosis is a rare condition in which the fibrous tissue in the interlobular septa seems to become increased as well as that around the bronchi. It is at present only of pathological interest.

**Symptoms.**—The symptoms of pulmonary fibrosis are, in the main, expectoration and dyspnoea together with those of the primary affection. In the non-tuberculous cases, bronchiectasis is so frequently associated that the symptoms and signs found are practically those of this condition. Even in tuberculous cases, some degree of bronchial dilatation is the rule, although the sputum is rarely offensive. The cough is generally periodic and associated with change of posture. The expectoration is abundant, and if bronchiectasis is present, it has the usual characteristic features. The dyspnoea is proportional to the extent of lung involved. It may be extreme in the later stages, when the heart becomes embarrassed and begins to fail. Fever is usually absent, except when complications occur.

The patients are generally spare, although nutrition may sometimes be well maintained until late. They may show signs of deficient aeration in duskiness, cyanosis and congested cheeks. Polycythemia sometimes occurs. Clubbing of the fingers is almost constant. Evidence of contraction is generally forthcoming in the flattening and retraction of the affected side, with the dropped shoulder and compensatory spinal curvature. Movement is greatly restricted, contrasting with the increased expansion of the other side. The cardiac impulse is sometimes much displaced, especially in left-sided cases, when it may be in the left posterior axillary line or even under the angle of the scapula. In right-sided cases, it is drawn to the right of the



sternum, even sometimes under or outside the right nipple. Vocal fremitus is either increased or diminished, depending on the patency of the bronchus, and percussion gives dullness of varying degree over the fibroid area, while the unaffected parts may be hyper-resonant from "compensatory" emphysema. The diaphragm may be drawn up, and the liver or stomach correspondingly displaced. The breath-sounds may be weak or inaudible but often when a deep breath is taken bronchial breathing can be heard especially if there is underlying bronchiectasis. If there is cavitation the breathing will be cavernous or amphoric. The presence of whispering pectoriloquy is an important indication that bronchial breathing will probably be heard. Vocal resonance will be increased where the breath-sounds are bronchial or diminished if the bronchi are not patent. Adventitious sounds may be entirely absent, and when present vary from rhonchi and bubbling râles to coarse metallic râles, according to the presence or absence of excavation. Radiographic examination gives useful confirmation showing contraction of the rib spaces, scoliosis of the spine to the opposite side, displacement of the trachea and heart to the side of the opacity in which translucent areas of cavitation may be seen occasionally.

**Diagnosis.**—The diagnosis is usually easy. The evidence of contraction and of mediastinal displacement towards the affected side, especially if signs of cavitation are also present, is highly suggestive. In the absence of the cavitation some difficulty may arise in regard to chronic pleural effusion or empyema. In the earlier stages the contra-lateral displacement of the cardiac impulse should prevent any mistake, but where partial absorption has occurred, this may be very slight or absent. In such cases an exploratory puncture or a radiographic examination may be helpful.

When the diagnosis of pulmonary fibrosis has been made, the differentiation of the cause is an essential to prognosis and treatment. If the condition is apical, there is a presumption in favour of tuberculosis; if basal, some other cause is more probable. Repeated examinations of the sputum should be made for tubercle bacilli, and if these prove negative, radiographic examination may reveal some cause such as new-growth, aneurysm or even foreign body. In some cases a careful consideration of the history may afford a clue to the diagnosis.

**Course.**—The course is invariably chronic, and may not shorten the natural span of years.

**Prognosis and Treatment.**—These depend upon the primary condition, but in most cases the latter is mainly symptomatic.

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## THE PNEUMOCONIOSES

**Definition.**—A group of lung diseases which result from the inhalation of dust in various trades. Strictly they should be called *Pneumonokonioses*.

**Classification.**—The pneumoconioses can be considered under headings according to the nature of the dust involved.

1. Silica.
2. Coal.
3. Fibrous silicates.
4. Non-fibrous silicates.
5. Non-pathogenic inorganic dusts.
6. Pathogenic inorganic dusts.
7. Vegetable dusts.
8. Animal dusts.

**Nature of dusts.**—Dusts consist of particles or aggregates of particles suspended in air and measuring from 150 microns to 0.5 microns in diameter. The sand of deserts, the dust of streets and the pollens of plants are of such large particle size that they become trapped in the nose and upper respiratory passages and never reach the lungs. Industrial dusts result from vigorous mechanical attrition, blasting, grinding, drilling, rubbing, crushing, hammering and sawing. Particles 5 microns or less in diameter can reach the alveoli of the lungs; in the ashed lung specimens of men who have died of silicosis the most representative particle measures 1 micron in diameter.

**Reaction of lung tissue to dusts.**—Of the dusts which do reach the alveoli silica and fibrous silicates set up different types of fibrous reaction in the lungs and the process is usually progressive. But the dusts of some of the non-fibrous silicates and of the compounds of certain metals, among them calcium, iron, tin and barium seem to be inert when inhaled. They are capable of lying in the lungs for years without inducing any deposition of fibrous tissue or other reaction, but because they are relatively radio-opaque they may produce changes in the X-ray film which must then be distinguished from those of silicosis. The resulting conditions are sometimes referred to as *benign pneumoconioses*. The inhalation of vegetable and animal dusts may cause asthma and bronchitis indistinguishable from these diseases of non-occupational origin.

## 1. SILICOSIS

**Synonyms.**—Dust Consumption, Ganister Disease, Grinders' Asthma, Grinders' Consumption, Grinders' Rot, Grit Consumption, Masons' Disease, Miners' Asthma, Miners' Phthisis, Potters' Rot, Rock Tuberculosis, Stone Hewers' Phthisis and Stonemasons' Disease.

**Definition.**—A disease due to the inhalation of uncombined silica (silicon dioxide). Silicosis and pneumoconiosis must not be used as synonymous terms. Logically, one could classify the pneumoconioses as pneumoconiosis due to silica, pneumoconiosis due to asbestos, pneumoconiosis of coal miners and so on, but such a method would be too cumbersome. Legal considerations make it important that the term silicosis be reserved for that condition caused by the inhalation of uncombined silica, the special characters of which render it capable of being identified when it occurs in typical form. Dusts other than uncombined silica produce pneumoconioses, but these do not present the characters which are possessed by silicosis in its typical form.

**Ætiology.**—The industries of sandstone quarrying, mining and dressing are the most widespread of all silicosis-producing industries in Great Britain. In various parts of the world the granite industry, the mining of gold, hematite iron ore, tin and coal, sandblasting and the manufacture of refractory materials produce cases of silicosis. The severity of the disease depends on such factors as duration and intensity of exposure, dust particle size and, to a large extent, on individual susceptibility. The *solubility theory* of its causation supposes that the fine particles of stone dust which get into the lungs are pathogenic, not because they produce microscopic trauma but because a toxic substance dissolves from their surfaces. This is thought to be silicic acid. It has also been suggested that the rôle of silicic acid in silicotic tissue depends on its degree of polymerisation and that only highly polymerised silicic acids are capable of producing fibrosis.

**Pathology.**—Round nodules of fibrous tissue, 2 to 5 mm. in diameter, are scattered throughout the lungs. Several may be aggregated together to form large composite nodules or they may be united in a massive fibrosis. Individual nodules may be thrown into sharp relief by emphysema of the surrounding lung, and their centres sometimes undergo calcareous change. Histologically the silicotic nodule is a mass of concentrically laminated dense fibrous tissue, and similar changes are found in

the tracheo-bronchial lymph glands. Tuberculosis often complicates silicosis and the pathological appearances of the one may obscure those of the other.

**Symptoms.**—There is usually a history of exposure to silica dust of about 30 years' duration, but the latent interval is extremely variable, varying from 6 months to 60 years, and the patient has on occasion left the industry for some years before beginning to complain.

Silicosis is generally divided into first, second and third stages, or slight, moderate and severe degrees. The first stage, the so-called simple silicosis, supervenes in a workman who has been employed in an industrial process involving exposure to siliceous dusts for a period of many years. The onset of symptoms is marked by dyspnoea on exertion, slight at first, and later increasing in severity. Throughout the illness dyspnoea remains the most important symptom. Slight cough may be present from the first. It is usually unproductive or with scanty sputum. The general condition of the patient is unimpaired. Physical signs in the chest are slight. Diminished expansion is scarcely, if at all, present. Dullness can rarely be demonstrated, and in older subjects there may be areas of hyperresonance due to emphysema. There is no alteration of the breath sounds, and there are no added sounds. In this early stage the radiograph shows the presence of discrete nodular shadows, circular and at the most 2 mm. in diameter. They may be partially distributed throughout the films, more widespread, or even generalised, but they remain discrete. In this stage, impairment of working capacity may be slight or absent.

In the second stage dyspnoea and cough become established and further physical signs appear. There is diminished expansion of the chest, patchy dullness, sometimes with bronchial breath sounds and scattered rhonchi, especially at the bases. The radiograph shows the whole of both lung fields occupied by shadows, indicative of nodulation, and there is some coalescence to form more or less dense opacities. There is always some degree of impairment of working capacity. In the third stage dyspnoea leads to total incapacity. The radiographs indicate areas of massive consolidation. Right heart hypertrophy and then failure may supervene. Pulmonary tuberculosis may be present in any stage of silicosis. It may alter the symptoms, physical signs, radiographic appearances and the whole course of the disease. It is the most frequent accompaniment of silicosis. Since tuberculosis of the lungs may simulate silicosis in radiographs, no diagnosis should ever be made exclusively on radiographic appearances.

**Treatment.**—Silicosis is a man-made disease and should be prevented. In mining operations ample dilution of the air in the mine with fresh air is the simplest method of reducing the dust concentration. Various forms of ventilation are in use. Drilling with pneumatic hammer-drills is responsible for much dust, but usually wet drilling can be employed. The method used consists of hollow drill-steels through which a continuous spray of water passes. After shot-firing a mist projector is used to allay dust. It is really an atomiser using compressed air and spraying a mixture of water containing 0.5 per cent. of castor oil. In order to avoid the hazard of dust inhalation no man is allowed to return to the rock face until 8 hours after the blasting charges have been fired.

In the grinding trades sandstone wheels should be abolished and replaced by wheels made of harmless synthetic abrasives such as carborundum (silicon carbide) and corundum (aluminium oxide). Where sandstone wheels are still used, the operations of rodding and hacking as well as the actual grinding of metals must be carried out under a continuous stream of water which is drawn away from a trough at the base of the rotating grindstone.

In foundries steel and other metals are poured in the molten state into sand moulds, and it follows that the final castings are partly covered with sand and therefore can produce silica dust when treated with particular tools. Fettleing (steel-dressing) implies the use of a compressed air chisel to clean up a casting. Locally applied

exhaust ventilation must be used in such an occupation. Where castings and other metal objects are cleaned by sandblasting, the man wears a special dress, so arranged that he breathes pure air from outside the sandblasting cabinet. It is better to use shot-blasting in which crushed ball-bearings replace sand. The steel powder resulting is harmless. The hydro-blast is the safest apparatus used to clean castings. A high velocity jet of sand and water is projected on to castings, thereby removing moulding material, cores and scale. The velocity of the water as it leaves the hydro-blast gun is in excess of 3 miles per minute. In all these trades where it is found impossible to control the dust completely the worker must wear either a dust mask or an air-line breathing apparatus.

Pre-employment clinical and radiographic examinations of the chest are essential. Periodical radiographic examinations enable silicosis to be detected at an early stage. They therefore help to get men out of a dusty industry before damage to the lungs has gone too far. They are also a means of discovering men with pulmonary tuberculosis who not only expose themselves to additional risk by remaining in the dusty occupation but are possible sources of infection to their fellow-workers.

## 2. PNEUMOCONIOSIS OF COAL MINERS

**Synonyms.**—Pneumoconiosis of Coal Workers, Coal Miners' Asthma.

**Definition.**—A dust disease of coal workers slowly disabling and quite different from classical silicosis. The rise in its incidence, particularly in South Wales since 1925, can be related to the great increase in the amount of dust which has followed the mechanisation of the industry.

**Ætiology.**—The bulk of cases occurs in colliers working at the coal face, and to a less extent among other underground workers. That the disease is also found in surface workers on the screens and in coal trimmers at the docks strongly suggests that the causative agent is coal dust and not silica. Classical silicosis occurs in only the small percentage of coal miners who are exposed to silica dust in the occupations of ripping, brushing, driving a hard heading and driving a cross measure drift, but both coal pneumoconiosis and silicosis are often indistinguishably combined. The highest incidence of the disease is found in the mining of high rank coal or anthracite; it is less common in medium rank or steam coal mines, and least common in low rank or bituminous coal mines.

**Pathology.**—Throughout the lungs coal dust collects in foci around the small bronchioles and their accompanying arteries, and a diffuse network of reticulin fibres is laid down around these foci. In certain cases the air spaces around the coal foci become dilated, an appearance described as *focal emphysema*; these emphysematous spaces may enlarge and become confluent, although bullæ projecting from the surface of the lung do not occur. In other cases a progressive coalescent collagenous fibrosis occurs, leading to the formation of nodules and later to a massive fibrosis. This fibrosis may be due to a sporadic factor such as silica, with possibly a complicating tuberculosis infection. In some cases the changes of tuberculosis predominate.

**Symptoms.**—The clinical course of the illness may cover many years, and routine radiographic examinations usually show changes in the lungs before the onset of symptoms. Dyspnoea and cough productive of coal black sputum are the most prominent, the chest becomes emphysematous and there may be clubbing of the fingers. The earliest radiographic change is a fine network of pinhead shadows, sometimes sharp and lace-like but much more often blurred. Such shadows are variously known as *reticulation* or *pinhead mottling*. They are followed by the stage of *nodulation* where the nodules are 2 to 5 mm. in diameter. The next stage is one of *coalescent nodulation*, and in more advanced cases there are multiple less well-defined fluffy shadows. Large well-defined, dense massive shadows are seen in advanced cases of *progressive massive fibrosis*. Focal emphysema cannot be diagnosed in life but its

presence may be suspected when there is intense dyspnoea leading to death from respiratory or right heart failure. Where the changes are those of massive fibrosis, progression is less rapid unless active pulmonary tuberculosis, unresponsive to treatment, supervenes. The course of pulmonary tuberculosis is generally modified by coal pneumoconiosis and often its presence cannot be identified confidently in life. This is in contrast with the severe type of infection which occurs in patients with silicosis. Thus in coal pneumoconiosis the miner is more breathless than ill and dies of *miners' asthma*, whereas in silico-tuberculosis he is ill as well as breathless and dies of *miners' phthisis*.

**Treatment.**—As in the case of silicosis treatment is entirely symptomatic. Young men with quite advanced simple pneumoconiosis are usually not seriously disabled, whereas men with progressive massive fibrosis are much disabled and their disability increases both with age and with deterioration in radiographic appearances. It has been shown that simple pneumoconiosis does not progress in the absence of further exposure to coal dust, whereas massive fibrosis is nearly always progressive whether or not dust exposure ceases. This is a strong argument in favour of periodic radiographic examinations. Measures directed towards dust suppression are wet cutting, wet drilling, water infusion of the coal face and hand spraying of the coal face before the coal is pulled down. Adequate ventilation is, of course, essential in reducing dust concentration.

### 3. FIBROUS SILICATES

The fibrous silicates include asbestos, talc, sillimanite and sericite.

#### (a) ASBESTOSIS

**Ætiology.**—Asbestos is the name given to a series of minerals composed of the silicates of magnesium and iron crystallised in silky and fibrous form. Canada produces 65 per cent. of the world's asbestos. It is mined both in open pits and by underground methods. In Great Britain the main processes involved in the asbestos industry include the crushing and disintegration of the raw material, carding and card cleaning and finally the spinning of the yarn and weaving of the cloth. Besides being woven, asbestos is ground and mixed with cement and plastics to make insulating slabs and many other articles. Asbestosis can follow employment in any of these processes but the risk is greatest in the crushing, disintegrating, carding and card cleaning processes, where there is most dust. It seems that the fibrosis is caused by mechanical irritation from the asbestos fibres during the movements of respiration, and that this peculiarity is related to the flexibility of the fibres not possessed by other foreign bodies.

**Pathology.**—Large areas of the lung are tough owing to the presence of fibrous tissue; emphysema, although extensive, is usually localised to the lower and apical parts of the lungs, and there are many pleural adhesions. On histological examination the alveolar walls are diffusely thickened, there is generalised fibrosis and throughout the lung tissue are seen fibres of asbestos and asbestosis bodies.

**Symptoms.**—The average length of exposure before the onset of symptoms is 7 years. Dyspnoea is the most conspicuous symptom and it may be out of proportion to the signs found in the chest. There is often a non-productive cough with pain between or under the shoulders, and behind the sternum, but hæmoptysis does not occur except in the presence of pulmonary tuberculosis. Clubbing of the fingers is not uncommon; examination of the chest shows limitation of respiratory excursion, sometimes with medium crepitations of a metallic tone in both bases. Asbestos bodies are found in the sputum. These are golden-yellow structures of beadlike form, elongated and often with bulbous ends and varying in length from 20 to over 200 microns. An asbestos fibre forms the central core in the body.

The radiograph shows a diffuse ground-glass or fine cobweb appearance, mainly at the lung bases. It changes later into a fine punctate stippling and extends to involve the middle and upper zones, although the extreme apices usually remain unaffected. The interlobar pleura is thickened and there is a shaggy appearance to the heart outline.

**Prognosis.**—Fibrosis develops more rapidly than in the case of silicosis and death may occur within 5 years of the onset of symptoms. The incidence of associated pulmonary tuberculosis although not as high as in silicosis, is significant. Bronchial carcinoma supervenes in more than 10 per cent. of cases.

**Treatment.**—Treatment is symptomatic only. In asbestos mining wet-rock drilling is imperative. In factories and textile mills the principle of locally applied exhaust ventilation must be enforced to prevent the escape of asbestos dust into the air of any room in which work is done. Suppression of dust in the cleaning of carding machines is best ensured by the use of a revolving brush fitted with a cover and connected to a portable vacuum cleaner. By the use of closed-in machines handling should be reduced to a minimum. Dust washes must be used where necessary. In Great Britain legislation has been so effective in controlling the disease that, with few exceptions, cases now diagnosed have industrial histories going back before 1931.

#### (b) TALCOSIS

Talc is a hydrated magnesium silicate. It is used as a toilet powder, as a dusting agent for rubber tyres and gloves, in ceramics and in the manufacture of paper. Talc pneumoconiosis has occurred mostly in the mining and milling industry. Disability is less than might be suggested by the radiographic appearance of nodular shadows distributed diffusely over both lung fields. There is, however, an increased susceptibility to pulmonary tuberculosis.

#### (c) SILLIMANITE PNEUMOCONIOSIS

The sillimanite group of minerals are all aluminium silicates and are used in the manufacture of high-grade refractories. Radiographic and histological changes have been found in workers exposed to the dust, although there is no disability.

#### (d) SERICITE PNEUMOCONIOSIS

Sericite, which is a fibrous variety of muscovite, has, without justification, been suggested as a cause of pulmonary disease. The fibre particles are too small to produce the sort of reaction which is found in asbestosis; they are, however, often present in the lungs of miners with silicosis because of the association of sericite with quartz.

### 4. NON-FIBROUS SILICATES

The minerals in this group are complex aluminium silicates combined with potassium, magnesium or iron. When inhaled as dusts, they cause no disability but are capable of producing the radiographic changes of pneumoconiosis.

#### (a) MICA

Mica is transparent and heat resistant, and is therefore used for the chimneys of oil lamps and for peep-holes in furnaces and stoves. Because of its high resistance

to the passage of electricity it is one of the essential minerals in the electrical industry. Radiographs of workers exposed to mica dust have shown diffuse shadows in the middle zones of the lungs, sometimes with fibrosis of the peribronchial type.

#### (b) FULLER'S EARTH

Fuller's Earth is an absorbent of grease and is used for the filtration of mineral oils, and as an ingredient of soap, wall papers and toilet requisites. Fine punctate mottling with some coalescence has been described in the radiographs of men exposed to the dust. The necropsy appearance is that of a soft, patchy pneumoconiosis unlike the hard nodular appearance of silicosis.

#### (c) KAOLIN

Kaolin or china clay is used in the manufacture of paper, in ceramics, as a filler in the rubber industry, for paints, for wall plasters and white Portland cement. Extremely fine mottling or reticulation has been described in the radiographs of a number of workers exposed to the dust.

### 5. NON-PATHOGENIC INORGANIC DUSTS

The dusts of the salts of calcium, iron, tin and barium are inert when inhaled, and give rise to the *benign pneumoconioses* (see p. 1009). Particles small enough to enter the alveoli are engulfed in phagocytes which are either coughed up or deposited in the aggregations of lymphoid tissue at the bifurcations of the bronchioles. Radiographic shadows may be produced, the density of which varies directly with the atomic weight of the element in the compound concerned. Calcium (atomic weight, 40), inhaled as the dust of limestone, marble, lime or cement, may give rise to non-progressive, arborescent shadows. Iron (atomic weight, 56) can cause reticulation or nodulation. The radiographic appearances in the chest of an electric arc welder may be identical with those of silicosis but *welders' siderosis* can be distinguished from silicosis by the complete absence of disability. *Stannosis*, a condition which results from the inhalation of salts of tin (atomic weight, 118) gives rise to scattered dense punctate shadows with no associated symptoms or abnormal physical signs. In *baritosis* or barium pneumoconiosis (atomic weight, 137) there is no disability, but in radiographs there are small sharply circumscribed nodules evenly distributed throughout the lung fields.

### 6. PATHOGENIC INORGANIC DUSTS

Aluminium is capable of producing fibrotic pulmonary lesions, and manganese, cadmium and vanadium give rise to chemical pneumonitis. Both types of reaction can follow the inhalation of beryllium and its compounds (see p. 385).

#### (a) ALUMINOSIS

Exposure to the inhalation of aluminium dust in Germany during the War of 1939-1945 gave rise to a condition known as *aluminosis* or *aluminium lung*. The development of the illness was rapid and appeared to bear no relation to the length of exposure to the dust. A dry cough with pain on breathing, shortness of breath, anorexia and gnawing abdominal pain were the main symptoms. Radiographs showed focal shadows in the apices with a reticular appearance in the upper and middle zones, later becoming confluent. Spontaneous pneumothorax occurred in a few of the cases.

**(b) PNEUMOCONIOSIS IN BAUXITE SMELTERS (SHAVER'S DISEASE)**

Between 1941 and 1943 *aluminosis* occurred at Niagara in men exposed to fume in the manufacture of the abrasive corundum ( $\text{Al}_2\text{O}_3$ ), a form of artificial emery. They heated bauxite, an ore containing 80 per cent.  $\text{Al}_2\text{O}_3$  and up to 7 per cent.  $\text{SiO}_2$ , with iron and coke in the electric ore at  $2000^\circ\text{C}$ . Some of the bin men, furnace feeders and overhead crane men developed diffuse fibrosis of the lungs with emphysematous bullae but without silicotic nodules. There were 13 deaths from pneumothorax. One man had 8 pneumothoraces and he is the only man seriously affected who still lives. Meanwhile tuberculosis has not developed in the lungs of the survivors.

**7. VEGETABLE DUSTS**

Chronic lung disease sometimes results from the prolonged inhalation of the dusts of bagasse, cotton, derris, flax, flour, gum arabic, grain, hay, hemp, jute, linseed, malt, nuts, paprika, sisal, straw, tea and wood. It usually takes the form of chronic bronchitis, indistinguishable from non-occupational bronchitis, and it is not accompanied by any characteristic radiographic appearance.

**(a) COTTON**

Four conditions affecting the respiratory system are described in workers exposed to cotton dust in different parts of the world. These are mill fever, byssinosis, weavers' cough and an acute illness occurring among people who handle low-grade stained cotton.

(1) *Mill fever*.—Almost all workers suffer from *mill fever* or *cotton cold* when they begin to work in the cotton mills, and a similar illness occurs on first exposure to the dusts of flax, grain and malt. Tolerance is established usually within a few days, though symptoms may reappear following an absence from work for a time as short as 2 to 4 weeks. *Mill fever* begins within 12 hours of exposure to the dust. The temperature may rise as high as  $103^\circ\text{F}$ . but returns to normal over night. Headache, malaise and exhaustion accompany the fever, and occasionally nose-bleeding, nausea and vomiting occur. Symptoms may reappear each night for the first few days, or even weeks of exposure but most workers become acclimatised within the first month.

(2) *Byssinosis*.—

**Synonyms.**—Strippers' Asthma, Grinders' Asthma, Cotton Card Room Asthma.

**Ætiology.**—The illness begins suddenly after many years of exposure to dust in the cleaning and carding of cotton, especially in men who strip and grind the carding machines.

**Symptoms.**—Three stages are recognised in its development. In the first stage, the worker complains of an irritating cough with tightness in the chest and breathlessness usually on Monday, hence the name *Monday fever*, and he remains well for the rest of the week. In the second stage the symptoms extend over more days in the week and finally become permanent. In the third stage the byssinosis is disabling; tightness of the chest and dyspnoea due to chronic bronchitis and emphysema are so distressing that the worker has to leave the cotton industry.

**Treatment.**—The condition is reversible only in the early stages and for recovery to take place there must be complete withdrawal from exposure to cotton dust. The treatment of chronic bronchitis and emphysema is discussed on p. 1000.

(3) *Weavers' cough*.—This is an acute illness confined to workers employed in cotton weaving sheds. Outbreaks have always been associated with the handling of mildewed yarn, which suggests that the causal agent is a fungus. Tightness of the chest, retrosternal pain, dyspnoea and cough productive of purulent sputum are the



isolated conform to the bovine variety. In tuberculosis of bones and joints up to the same age, 29 per cent. of the cases are of bovine origin.

The bacilli may gain access to the body by inhalation, by alimentary ingestion, through the tonsils, through the skin, or possibly, in rare instances, by hereditary transmission. It is probable that in the majority of cases of pulmonary tuberculosis in adults, the organisms are carried direct to the lungs in the inspired air, and Ghon showed that in children, who had died of tuberculosis of the lungs, a primary focus was present in the lungs in 92.4 per cent. Calmette and others have demonstrated that the bacilli may gain access to the bronchial glands from the alimentary tract through the thoracic duct, or from the tonsils through the cervical and mediastinal glands but this is now considered to be an exceptional path of infection. Cases have been recorded in which primary cutaneous infections have been followed later by active pulmonary tuberculosis. Direct intra-uterine transmission of the tubercle bacillus if it occurs at all, must be so rare that it is a factor of negligible importance.

The incubation period of tuberculosis is uncertain owing to the difficulty of determining when infection takes place. It is believed by many authorities that the majority of individuals in a semi-rural or semi-urban country like Great Britain are originally infected in infancy, early childhood or youth by the inhalation of bacilli in infected spray droplets or dried dust, or else by ingestion of bovine or occasionally human bacilli. The inhaled bacilli produce a lesion in the tissue known as a primary lesion which has special characteristics.

The focal lesion is relatively slight but the reaction in the regional glands is much more obvious and characteristic. Three possible things may happen as a result of the tuberculous lesion. The lesion may disappear, leaving little or no trace, the focal lesion and the regional glands may become fibrous and then calcified as described by Ghon; or the focal lesion or the glands may break down and infection may spread locally or generally through the blood-stream.

What happens in an individual infection depends on the dose of infection, the age and general condition of the infected person and possibly the degree of inherited resistance to tuberculous infection. The earlier the age at which infection takes place, the more serious the result.

Following infection, acquired resistance develops to a greater or lesser extent and is probably permanent. The acquired resistance modifies the effect of any subsequent infection so that in post-primary tuberculosis there is a much more severe focal reaction than in the primary infection and little or no regional glandular reaction. It has been held that reinfection does not take place but that all tuberculosis subsequent to the primary infection is a reactivation or a spread from the original focus just as tertiary gummata in syphilis are not evidence of reinfection but of spread from an original primary chancre. This theory would tend to discount the danger of contact infection in later life, but, in fact, there is a great deal of evidence to show that reinfection is the common cause of post-primary tuberculosis.

**Pathology.**—The earliest lesion in the lung is the formation of tubercles whose structure is described in the general article on tuberculosis. Whereas pulmonary primary lesions may appear anywhere in the lung, post-primary lesions for some reason not understood generally appear first at one or other apex. Each lesion often appears radiologically as an area of localised opacity in the subclavicular area. This lesion was described first of all by Assmann, although the lesion he described was from 1 to 2 in. in diameter and probably consists of a tuberculous lobular collapse. When the lesions are small they are described as minimal lesions. Both these lesions may and often do develop into progressive tuberculous infiltration.

**SECONDARY CHANGES.**—1. *Caseation.*—The tubercle is avascular, and owing to this, and possibly also to the action of tubercle toxins, coagulation necrosis and fatty degeneration frequently ensue. This combined process is known as caseation and

results in the formation of a structureless, cheesy mass. Further changes may now occur, either softening, with the development of a "cold abscess" filled with tuberculous "pus", or calcification, with the subsequent formation of gritty masses known as "pneumoliths".

2. *Cavitation*.—Cavities result from the liquefaction of caseous areas, and the expectoration of the resulting debris. They may be no larger than a pea, or may occupy the whole of one or more lobes. A recent cavity has an irregular outline, with rough, shaggy walls and a vascular line of demarcation. It is often traversed by trabeculae, formed by bronchi and vessels which may be partly or completely obliterated, while sometimes the trabeculae consist of condensed lung tissue which originally separated adjacent cavities. In chronic cases, the cavity is surrounded by fibrosed lung tissue forming a pseudo-capsule, and its interior becomes lined by a thin, smooth, false membrane. Small aneurysms may be found, arising either from vessels running in the walls or in the trabeculae of the cavity, the former being the more common. In some cases, where hæmoptysis has occurred, rupture of such an aneurysm is the cause.

3. *Fibrosis*.—Reactive changes in the lung stroma lead to the formation of fibrous tissue. This may occur early or after caseation has taken place.

In the majority of deaths from all causes, old tuberculous lesions are found post mortem near the apex of one lung. These consist of small nodules of arrested disease, with thickening and dimpling of the adjacent pleura.

*DISSEMINATION IN THE LUNGS*.—The disease may spread from the primary peri-bronchial deposit—(a) by direct infiltration; (b) by the peri-bronchial lymphatics and capillaries, leading to a racemose appearance or to peri-bronchial fibrosis; (c) by the subpleural and interstitial lymphatics, with localised miliary dissemination; (d) by inhalation into a bronchus of tuberculous material, which is then carried to other parts of the same or to the opposite lung—this not infrequently happens after hæmoptysis and in cavitation; (e) by the blood vessels, e.g. generalised miliary tuberculosis may result from erosion of a caseous tubercle into a vein.

The pathology of the clinically distinguishable forms of pulmonary tuberculosis will now be described.

1. *ACUTE MILIARY TUBERCULOSIS*.—A primary caseous focus may be discovered at the apex of one lung, in the bronchial glands, or at some distant spot in the body. Local erosion of a vein may be found, accounting for the dissemination of the disease. The lungs are usually studded with minute grey tubercles, the smaller ones requiring a hand lens for their recognition. In very acute cases death occurs before any secondary broncho-pneumonic changes take place. Miliary tuberculosis may develop as a terminal event in chronic fibro-caseous or fibroid tuberculosis. The tubercles are then found in large numbers around the old foci of disease, but to a less extent in the more remote portions of the lung.

2. *CHRONIC MILIARY TUBERCULOSIS*.—Reports of cases of this condition were commoner before the recognition of sarcoidosis and many cases were probably erroneously diagnosed. It is questionable whether real chronic miliary tuberculosis exists, although even before the use of streptomycin there were great divergences in the rapidity of development of miliary cases and some might almost have been termed subacute although their fatal termination was the same.

3. *ACUTE CASEOUS TUBERCULOSIS*.—Large areas of consolidation form rapidly, which differ histologically from the common chronic tuberculous broncho-pneumonia in that the alveolar exudate is more definitely inflammatory and contains fibrin. In the rare lobar cases, the rapid caseation and the presence of tubercle bacilli show that the caseous pneumonia is a specific process. Firm yellowish patches, which may be confluent, are seen, usually scattered throughout both lungs. The affected areas are airless and sink in water. Softening is generally present in varying forms up to actual cavity formation, which may be extensive, involving even a whole lobe.

4. **FIBRO-CASEOUS TUBERCULOSIS.**—This is the commonest variety of the disease; the appearances of the lung vary with the relative preponderance of the caseous and fibrotic changes. The early lesions are miliary or broncho-pneumonic, but areas of caseation in varying stages, including cavitation, are almost always present. The older lesions show considerable fibrosis, the strands of sclerotic tissue being pigmented and glistening. The earliest lesion is usually near the apex of the upper lobe at the back, more rarely a little lower and towards the front. From this focus disease may spread directly or through the lymphatic, bronchial or the vascular system to adjacent or distant parts of the lung. An open cavity from which infected sputum can overflow and pass or be aspirated through the bronchial tree to lower parts of either lung is to be regarded as particularly dangerous. Pleural adhesions are usually present over the oldest lesions and in the interlobar fissures.

5. **FIBROID TUBERCULOSIS.**—Fibrosis may be localised around a small arrested lesion, or may spread throughout a lung in which caseation or excavation has occurred. One lobe or the whole lung is then contracted and firm. In the interstices of the fibrous tissue, which is usually pigmented, inspissated caseous material, calcareous patches, or cavities are seen. The shrinkage may lead to bronchiectasis, especially in the lower lobes. The overlying pleura is much thickened and adherent, and the mediastinum is drawn over towards the affected side. The opposite lung, or the sound portions of the fibrosed one, may show compensatory emphysema.

*The bronchial glands.*—The tracheo-bronchial glands are affected in all forms of pulmonary tuberculosis. In post-primary disease the glandular lesions are insignificant as a rule, whereas in primary disease, depending on the stage of the disease, they show considerable enlargement, caseation or fibrosis with deep pigmentation and calcification. Occasionally in apical tuberculosis the cervical glands on the affected side are involved.

*The pleura.*—This, too, is almost constantly affected. The commonest changes are an early dry pleurisy, and a later thickening with adhesions which may completely unite the visceral with the parietal layers. In acute disease or active spread, the pleura may be studded with miliary tubercles, leading to a large serous effusion.

The post-mortem appearances of the lesions situated in the other organs, found as complications of pulmonary tuberculosis, are described in the respective sections dealing with them, and include tuberculous meningitis, peritonitis, enteritis, genito-urinary tuberculosis and osseous tuberculosis. There is usually atrophy of the skeletal muscles, sometimes lardaceous and fatty degeneration of the liver, and hypoplasia with fatty degeneration of the heart.

**Symptoms.**—The symptoms fall into three groups (Pottenger)—(1) pulmonary, such as catarrh, expectoration, hæmoptysis and pleurisy; (2) reflex, such as pain, cough and laryngeal irritability; (3) toxæmic, including malaise, tachycardia, pyrexia and loss of weight.

**ONSET.**—The mode of onset is very variable, but certain forms can be recognised.

(a) The diagnosis is made by a routine radiological examination and the patient has no symptoms whatever. This does not unfortunately mean that the lesion can be ignored, it may be the golden moment for treatment.

(b) *Insidious.*—The early symptoms may be malaise, anæmia, amenorrhœa, cardiac irritability, progressive loss of weight and slight rise of temperature, generally towards evening. Cough and expectoration often appear only when the signs in the chest are quite apparent.

(c) *Catarrhal.*—Colds which appear to persist with fatigue and persistent cough should be regarded with suspicion.

(d) *Hæmoptysis.*—Hæmoptysis may first draw attention to the lungs. It may be slight, and is then due to early inflammation around the focus of infection. If it is more marked, it may afford dramatic evidence of extensive disease which had not been recognised previously, or arise from an old unsuspected cavity.

(e) *Laryngeal*.—Hoarseness or aphonia may be the first symptom, but laryngeal tuberculosis is almost invariably secondary to pulmonary disease, although the latter may have been unsuspected.

(f) *Gastro-intestinal*.—Anorexia and flatulence often occur early. When they are accompanied by slight loss of weight and pyrexia, the possibility of pulmonary tuberculosis should be suspected.

(g) *Pleural*.—Dry pleurisy is a frequent manifestation of latent pulmonary tuberculosis. When a serous effusion develops, its tuberculous character can be determined by laboratory investigations. Pneumothorax, developing in a previously healthy individual is a rare but often serious clinical mode of onset.

(h) *Pneumonic*.—"Galloping" consumption often begins with *pneumonic* manifestations, especially in the young.

(i) *Associated with other diseases*.—Tuberculosis may follow immediately on an attack of measles, influenza or whooping-cough, especially if complicated by broncho-pneumonia. In some cases it develops at a later period after the acute disease.

(j) *Senile*.—In old people an insidious onset is common. The disease may be of bronchitic type, and the signs are often masked by emphysema. There may be little or no rise of temperature. Sometimes *pneumonic* or *broncho-pneumonic* tuberculosis of the type more familiar in infants is found. Sometimes the differential diagnosis is from bronchial neoplasm.

THE CHIEF SYMPTOMS of pulmonary tuberculosis are—

*Cough*.—This varies considerably in different types of disease. It may be very slight or absent in generalised miliary tuberculosis, or in any form in the insane. It is sometimes dry, persistent and ineffective, especially in miliary extension in the lungs from an old focus of disease, in bronchial gland tuberculosis, or in pleurisy. When there is associated bronchitis or caseation, the cough is usually accompanied by expectoration, which, if very tenacious, may lead to retching or even to vomiting, particularly in the morning. In laryngeal tuberculosis the cough is husky and frequently painful.

*Expectoration*.—In early disease there is usually no sputum, and in some cases, more especially in the fibroid type, widespread lesions may be present with practically no expectoration. When caseation is in progress, or when there is secondary infection with bronchitis, the sputum may be abundant and amount to as much as 20 or more ounces in the 24 hours. It may be clear or mucoid, or thick tenacious mucopus. If mucoid, it often contains small particles, the size of a pin's head or larger, of yellow caseous material. Nummular sputum may be met with in active caseous disease, especially with excavation. This consists of flat rounded masses of mucopus, with a somewhat distant resemblance to coins. In tuberculosis the sputum is usually inoffensive. If bronchiectasis or gangrene occurs as a complication, the expectoration becomes typically malodorous. Pulmonary calculi or pneumoliths, composed chiefly of calcium carbonate or phosphate, are sometimes expectorated. They vary in size from a pin's head to a pea, are irregular in outline and sometimes branched, being derived generally from the walls of a cavity. Although the occurrence of these does not necessarily indicate fresh activity in the lungs, yet such a possibility should always be suspected, and a careful watch maintained on the temperature during the next few days. In some cases larger pneumoliths, as big as a cherry, may be coughed up, and those are frequently derived from calcified tracheo-bronchial glands. They may give rise to alarming symptoms at once, and be the forerunner of fresh activity in the lungs.

*Microscopical examination*.—The presence of tubercle bacilli in the sputum is the most decisive test of the existence of this disease. The small yellowish caseous particles should be selected from the sputum, and appropriately stained. If no tubercle bacilli are found, samples from the whole sputum of the 24 hours, concentrated by the antiformin method, can be examined. Droplets collected on a laryngeal

mirror by cough induced by it may be examined for the presence of tubercle bacilli, especially in children or in patients who habitually swallow sputum. In similar cases, tubercle bacilli may be found by gastric lavage.

**Sputum culture** by the Loewenstein or Dubos method may be of value when tubercle bacilli are not found in smears. The cells present are usually of the mononuclear type, either mononuclear leucocytes or altered alveolar epithelial cells. The presence of elastic tissue indicates that destructive pulmonary lesions are in progress. Secondary infecting organisms may be demonstrated by cultural methods. Failure to find tubercle bacilli in the sputum does not in any way exclude pulmonary tuberculosis, since their detection depends on chance and diligence as well as on the stage of the disease. Persistently negative sputum in patients with large quantities of purulent sputum should, however, suggest the possibility of alternative infections.

**Dyspnœa.**—Slight dyspnœa occurring early in the disease may be due to diminished movement of the diaphragm on the affected side. In more advanced cases the degree of dyspnœa is proportional to the amount of lung tissue involved. In addition, cough and pyrexia play a part in its production. Complications such as pleurisy, pleural effusion, pneumothorax and cardiac failure increase the shortness of breath. It is rare to find orthopnœa even in acute and rapidly spreading disease. In arrested cases the dyspnœa is proportional to the extent of fibrosis.

**Cyanosis.**—This is not an early symptom of tuberculosis. It is dependent upon the amount of lung tissue involved, but is increased by the coexistence of emphysema or cardiac failure. The "hectic flush" of tuberculosis is a vasomotor effect caused by toxæmia.

**Pain.**—Not every sufferer from tuberculosis experiences pain, even in the acute stages of the disease. The commonest cause of pain is dry pleurisy. When the diaphragmatic layer of the pleura is affected, pain may be referred to the epigastrium or to the corresponding shoulder. In chronic fibroid phthisis there is frequently a dull, aching pain in the chest. It may be caused by the contraction of the condensing fibrous tissue. Cutaneous tenderness of the chest-wall is met with in some cases of advanced disease, and is probably due to a cachectic neuritis. A "cold abscess" forming along one of the ribs or costal cartilages is a rare cause of localised pain in the chest-wall. Cough may be painful, especially when paroxysmal or frequent, the pain being referred to the costal attachments of the diaphragm and upper abdominal muscles. The sudden occurrence of pneumothorax may cause such severe pain as to induce collapse; but when of more gradual onset no severe discomfort may be experienced. Tuberculous laryngitis may be the cause of very great suffering.

**Night sweats.**—Although not pathognomonic, night sweats occur more frequently in tuberculosis than in other diseases. They are met with in all stages of active lesions, and may be of great severity.

**Loss of weight.**—This is often an early symptom. It is most marked in acute disease and in the late stages of chronic fibro-caseous tuberculosis.

**Fever.**—Pyrexia is one of the most important indications of activity at any stage of pulmonary tuberculosis, although it does not follow that the disease is arrested when there is no fever. During treatment the temperature should be recorded at certain definite hours in the day. (a) On waking. The normal mouth temperature at 7 or 8 a.m. is 97° or 98° F. in the mouth, and 97·2° to 99° F. in the rectum. This temperature should be taken in bed, before eating or drinking. (b) At 1 p.m., after the hour's recumbent rest. (c) At 6 p.m. (d) At 9 p.m., after retiring to bed. The maximum temperature is usually reached between 4 and 6 p.m., but may be delayed to 8 or 9 p.m. The temperature is dependent upon the extent and the activity of the disease, and upon the amount of exercise taken. Only 5-minute readings should be accepted.

(a) In acute miliary tuberculosis it may be continuous or remittent, and the "typus inversus" is not uncommon, the morning temperature being higher than the evening. This is generally regarded as a sign of grave prognosis.

(b) In acute caseous tuberculosis the high temperature at the onset is continuous, and the record resembles a pneumonic chart. When caseation occurs it becomes hectic or intermittent, with a daily swing of  $4^{\circ}$  or  $5^{\circ}$  F. This is probably due to the action of tubercle toxins, and not to the presence of a secondary infection.

(c) In chronic fibro-caseous tuberculosis there is no characteristic temperature record. There may be only a very slight rise occurring at intervals of a few days. On the other hand, the patient may be afebrile while resting, but febrile when ambulant. Further an afebrile ambulant patient may over-exert himself, and develop a sharp rise of temperature, which subsides in a few days with rest. The temperature chart is thus a guide to prognosis and to treatment, and if acute miliary tuberculosis or caseation occurs, a typical temperature variation ensues.

(d) In fibroid tuberculosis the temperature is usually normal, unless excessive auto-inoculation results from exercise, or the disease advances. The occurrence of hæmoptysis may have a very definite effect upon the temperature. In some cases it is not followed by pyrexia, but if the inhaled blood leads to a hæmoptoic bronchitis, there may be a slight degree of fever lasting for a few days. When a definite and persistent pyrexia follows, it usually indicates activity around an old focus of disease, or fresh spread by inhalation of blood containing tubercle bacilli to distant parts of the lung.

A premenstrual rise of temperature may occur; but as it is also met with in healthy women it is not pathognomonic.

*Hæmoptysis.*—Hæmoptysis occurs at some stage of pulmonary tuberculosis in about 50 per cent. of all cases. With early lesions the sputum is only streaked. This may result from the inflammation of tuberculous bronchitis, or from a small area of collapse or broncho-pneumonia. Profuse hæmoptysis generally occurs in chronic disease; but it is occasionally met with in acute caseous forms. Recovery may take place after coughing up 2 or 3 pints, or death may ensue rapidly from suffocation before any considerable quantity of blood has been expectorated. After the cessation of bleeding the sputum may be blood-stained for several days, the colour becoming darker. The source of profuse hæmoptysis is generally an aneurysm of a branch of the pulmonary artery lying in a cavity or in a fibroid lung, although occasionally ulceration without previous aneurysm formation may occur. In the majority of cases hæmoptysis begins while the patient is lying down or resting, so that exercise or work are not frequent exciting causes.

The patient notices a salt taste, feels a warm gush in the mouth and then expectorates the blood. He is usually greatly alarmed, flushed and sweating, with rapidly beating heart. The blood at first is, as a rule, bright and frothy but some clots may be present; later it is mixed with muco-purulent expectoration, in the form of clots or streaks.

*Circulatory system.*—The heart may be small, but the right side often hypertrophies in chronic fibroid cases. Tachycardia may be due to nervousness, but when constant it generally indicates active disease or over-exertion on the part of the patient. The blood pressure is usually low in the stages of activity, and a steady rise during treatment is a favourable sign.

*The blood.*—The red cells are usually normal in number, but there may be a slight anæmia. On the other hand, when there is much cyanosis, or after sanatorium treatment, the red cells may be increased. In the early stages the leucocytes may be slightly increased. A polymorphonuclear leucocytosis occurs in caseation and in early cavity formation, and at times with secondary infection of the lungs. In pyrexial cases the sedimentation rate is raised, as a rule. Although the rate is raised in active disease, a normal level cannot unfortunately be regarded as evidence of arrested

disease as the initial rate is not infrequently normal in spite of progressive disease.

*Alimentary system.*—The tongue is usually clean and the appetite good even in cases with marked fever. When tuberculosis of the larynx is present, there is frequently severe dysphagia. Dyspepsia may be complained of; anorexia, flatulence and distension with nausea are the commonest symptoms, pain being rarely noticed. There may be marked intolerance of fat in the diet. Atonic dilatation of the stomach may occur in some cases towards the end of the disease.

*Nervous system.*—The classical "*spes phthisica*" is rare, but when present is very striking by its contrast with the realities of the disease. It should be remembered that "the reality of the disease" is known only to the physician and not the patient, and it might be as reasonable to talk about "*spes carcinogenica*" in a patient who has no idea that he has a growth. *Spes phthisica* is sometimes a bold front put up by a patient and stands in sharp contrast with the depression and melancholia which often affects patients whose lesions are "slipping". Patients with chronic tuberculosis sometimes become emotional and self-centred but most of the psychological changes are the result of the long periods of treatment and frequent disappointments characteristic of the disease and are not caused by the disease itself. Insomnia may be due to cough, pyrexia, night sweats or pain, especially laryngitis. With marked cachexia, a definite peripheral neuritis may occur.

*Genito-urinary system.*—In the early stages there is often an increased sexual desire, and this may recur when arrest is taking place. This is probably in part due to the therapeutic régime, the rest, abundant food and lack of interesting occupation reacting upon the nervous system of young adults. In advanced disease, all sexual desire is lost. Menstruation ceases early, and occasionally the patient may seek advice for amenorrhœa, but this occurs more often in acute or advanced cases. Women remain fertile even in advanced disease. The urine is normal in the early stages, later a febrile albuminuria may occur, or in advanced cases an amyloid nephrosis with generalised œdema may develop.

**THE PHYSICAL SIGNS OF EARLY DISEASE.**—There are no physical signs in really early disease and the diagnosis is a radiological one. At a later stage diminished expansion of an apex may be found together with slight impairment of percussion note and slight increase of breath-sounds and voice conduction. An important physical sign is the presence of fine post-tussive crepitations at one or both apices. Many of the physical signs described in previous days as signs of early tuberculosis although they can be found by the skilled examiner are now really only of historical interest and none replace a radiological picture in accurate diagnosis.

**PHYSICAL SIGNS OF ACUTE MILIARY TUBERCULOSIS.**—If the condition develops acutely from breaking down of an infected bronchial gland or small lung focus, the physical signs are generally those of an acute generalised broncho-pneumonia, unless there is meningeal involvement as well, in which case the pulmonary symptoms and signs are masked or obscured by those of the cerebral involvement. When miliary tuberculosis occurs as a terminal event in a chronic case, marked dyspnoea, cyanosis and tachycardia are early symptoms. There may be crepitations or fine crepitant râles widely distributed over both lungs, and sometimes areas of tubular breath-sounds especially in the lower lobes. The original signs are often masked or less apparent. This is especially the case if meningeal involvement occurs also.

**THE PHYSICAL SIGNS OF CONSOLIDATION.**—Limitation of movement and flattening over the affected part of the lung, usually the apex, is now more noticeable.

The diminution of movement is confirmed on palpation, and vocal fremitus is found to be definitely increased.

The pulmonary resonance is diminished to definite dullness and the sense of resistance is correspondingly increased.

The breath-sounds are bronchial.

Adventitious sounds may be absent, but usually fine or medium crackling râles are heard with inspiration, especially after coughing. When active softening is in progress the râles frequently become coarse and crackling. The voice conduction is much increased, bronchophony and whispering pectoriloquy being audible.

**THE PHYSICAL SIGNS OF EXCAVATION.**—Flattening of the chest-wall and diminished movement over the cavity are now more marked; if the cavity is apical there is in addition notable dropping of the shoulder, and wasting of the shoulder-girdle muscles.

The diminution of movement is confirmed by palpation. Vocal fremitus is generally increased owing to the surrounding consolidation, but if the cavity is full or there is much pleural thickening, it is diminished.

The percussion note is dull when the cavity is small or filled with secretion. A peculiar boxy or "cracked-pot" note, the "*bruit de pot fêlé*", is obtained over large superficial cavities, especially when communicating with an open bronchus. This is best heard on percussing with the mouth open, and Wintrich showed that the note may be altered in pitch over such cavities when percussing with the mouth open or closed, apart from the actual presence of the cracked-pot sound.

The breath-sounds are bronchial, broncho-cavernous, cavernous or amphoric, according to the size of the cavity, and to the amount of its contents. When it is full the breath-sounds may be distant, weak or even absent, and this is especially noticeable in basal bronchiectasis.

With a dry cavity there may be no adventitious sounds. Usually râles are audible; they may be medium or large, and bubbling or crackling in character. Over a large cavity a metallic tinkle and amphoric echo may be heard. With a very large cavity, extending through the whole of one lung, a typical *bruit d'airain* is at times obtainable. Voice conduction is increased, bronchophony and whispering pectoriloquy are present, and in some instances post-tussive suction is heard. Some cavities are only revealed by radiographic examination or by tomography.

**THE PHYSICAL SIGNS OF FIBROSIS.**—The chest is asymmetrical, the affected side being flattened and moving little, while compensatory scoliosis or kypho-scoliosis is often present. The cardiac impulse is seen to be displaced towards the affected lung and may be higher or lower than normal. It may be drawn over to the right axilla, or on the left side as far back as to the posterior axillary line, or even to the angle of the scapula. The intercostal spaces may be retracted, and dilated venules are sometimes seen over the front of the chest as the result of obstruction, caused by displacement of the mediastinum and traction on the deeper veins.

Diminution of movement is confirmed by palpation, and the cardiac impulse can be more accurately localised. Vocal fremitus may be increased or diminished; the former occurs when the lung is consolidated and the large bronchi patent, the latter when there is much pleural thickening.

The percussion note over fibroid lung is dull and the sense of resistance increased, *unless cavities are present. The opposite lung may be hyper-resonant, and its resonance extend across the mid-sternal line.* The cardiac dullness is often continuous with that of the fibroid lung, and its area can only be determined by the cardiac pulsation.

The breath-sounds may be weak and distant or bronchial in character, depending on the patency of the bronchi and the presence of cavities.

Often there are no adventitious sounds, although fine or medium râles of a sticky or metallic nature may be heard. The voice conduction may be diminished, or there is pectoriloquy and bronchophony.

It must be borne in mind that in actual disease the lesions are not so clear cut and well defined. In a case of some duration different stages of disease can be found in the same individual, thus infiltration, consolidation with softening, excavation and fibrosis may be present in different lobes of the lungs, and thus it may be possible to determine the site of origin and path of spread of the disease.



Certain other signs are occasionally seen in pulmonary tuberculosis.

Myoidema is an undue irritability of the muscles to direct mechanical stimulation, revealing itself by a flickering fibrillary contraction on tapping with the finger, and may occur in tuberculosis at all stages. It is best seen over the pectoralis major on the affected side. It may be present quite early, but is not pathognomonic, as it may occur in any cachectic state.

Clubbing of the fingers is commonly seen in chronic cases, the nails are curved and present a parrot-beak appearance, the thumb, index and middle fingers being most affected. Drum-stick clubbing is only seen in fibroid lesions with bronchiectasis.

**EPITUBERCULOSIS.**—This term was applied by Eliasberg and Neuland in 1920 to a condition of consolidation in tuberculous infants, often affecting a whole lobe. In spite of definite physical signs and characteristic radiological appearances, there are few symptoms, and recovery is the rule, with fairly rapid clearing of the radiographic shadows, from the periphery inwards. It is probably due to atelectasis of a lobe in whole or part, due to bronchial obstruction from enlarged hilar glands.

**PULMONARY OSTEO-ARTHROPATHY.**—In cases with bronchiectasis the joints may be affected, swelling occurring especially in the wrists, ankles and knees, and rarely in the hips and shoulders. A serous effusion into the joints may be present. Pain is usually slight, but there is much deformity and functional impairment. Radiographic examination reveals productive periosteal changes, which may also affect the long bones and the spine (see p. 1171).

**RADIOGRAPHY OF THE CHEST.**—Careful study of serial radiographs is essential for the control of the treatment and progress of pulmonary tuberculosis. Examination of the chest with the fluorescent screen gives valuable information as to the movements of the diaphragm, the cardiac pulsation and the lighting up of the apex of the lungs with inspiration. Tomograms often show unsuspected cavities in the lung and are also valuable to show the extent of pulmonary infiltration. Close studies of serial pictures are necessary to determine the activity or otherwise of the radiological lesions. Opinions as to the activity of lesions on the basis of hardness or softness of the shadows are of little or no value.

**Complications and Sequelæ.**—Compensatory emphysema is common in chronic fibroid disease, but bronchiectasis occurs less frequently. Gangrene of the lung is not often observed. Colds and catarrhal affections of the respiratory passages are frequent in sufferers from tuberculosis, and lobar pneumonia may develop as a complication. Bronchitis often occurs, due either to spread of the tuberculous process or to a secondary infection. In some instances asthma appears for the first time after tuberculosis has become manifest. A tuberculous abscess occasionally forms about a rib or costal cartilage.

Small areas of dry pleurisy are present at some stage in nearly every case; a serous pleural effusion is common, and an empyema may develop as the result of a mixed infection, or from the tubercle bacillus alone. Pneumothorax may occur as an early complication, or late in the disease, generally from rupture of a caseous focus just under the pleura; this frequently progresses to the formation of a pyo-pneumothorax. The implantation of tubercle bacilli from the expired air or sputum may lead to secondary foci in the larynx, trachea and epiglottis, or more rarely in the pharynx, tonsils, base of the tongue or nose. Swallowing of sputum containing tubercle bacilli may give rise to gastro-intestinal complications in some cases. The most common site of tuberculous ulcers, is the terminal portion of the small intestine, but the appendix may be affected, and the connective tissue around the cæcum is sometimes matted and thickened to form a palpable mass (hypertrophic tuberculoma). Tuberculous peritonitis is not common in adults and is usually secondary to intestinal lesions. The stomach is very rarely ulcerated, but an atrophic gastritis may occur in advanced cases. Fistula-in-ano and ischio-rectal abscess are comparatively common complications and tubercle bacilli may be found in the discharges.

Fatty degeneration of the myocardium occurs as a result of toxæmia, and infection by direct spread along the lymphatics may lead to pericarditis. The peripheral circulation is not infrequently poor, chilblains are common and cachectic purpura may be seen. Lardaceous degeneration as a consequence of chronic tuberculosis is not so common nowadays as formerly, but when present may affect the liver, spleen, intestines, lymph glands and kidneys.

The genito-urinary complications include lesions in the kidneys, bladder, epididymis and prostate. If the suprarenal body is affected Addison's disease will usually develop. Spinal caries is occasionally observed. A peripheral neuritis may form part of the lesions occurring with marked cachexia. Generalised dissemination of the tubercle bacilli by the blood-stream is followed by tuberculous meningitis.

**Diagnosis.**—This is easy when definite signs are present in the lungs, and when tubercle bacilli are found in the sputum. On the other hand, the diagnosis of early cases may present one of the most difficult problems in clinical medicine. Tuberculosis may be suspected on account of symptoms, although the physical signs are indefinite. The conditions which most frequently lead to doubt are dyspepsia, neurasthenia, debility, tachycardia associated with early Graves' disease or heart disorders, affections of the nose and throat, and in children enlargement of the bronchial glands. The history and symptoms are of great importance in these cases, and a careful examination should be made of each system. A test meal, opaque meal or blood examination may be required before the correct diagnosis is established.

On the other hand, there may be definite signs of disease in the lungs which have to be differentiated from those produced by other conditions simulating tuberculosis. The cases included in this group embrace the majority of pulmonary lesions, especially chronic bronchitis, fibrosis, bronchiectasis, asthma, emphysema, apical collapse, pleurisy, new-growths and cysts. Diagnosis depends upon the history and course of the disease, together with a careful record of the physical signs in the chest, investigation of the sputum for infecting organisms, radiographic examination and, in some cases, the determination of the Wassermann reaction.

A condition of special difficulty is that of the variety of sarcoidosis known as Boeck's sarcoid. The lesion is a benign lymphogranuloma or reticulosis. It affects the lymph glands, lungs, bones especially those of the fingers, and the skin (see pp. 1045, 1245). The parotid and lachrymal glands are sometimes involved and iridocyclitis has been recorded in 10 per cent. of the cases. The intestines, spleen and liver may be affected. The chief diagnostic points are the character of the skin lesions and the chronicity and tendency to spontaneous arrest. Tubercle bacilli are not found and the Mantoux reaction is often negative. The radiological appearances in the lungs are those of a diffuse mottling—coarser than that of miliary tuberculosis. The hilar glands are often markedly enlarged.

When the diagnosis still remains doubtful the patient should be placed under observation, and a series of examinations carried out, the object of which is to determine whether or not active tuberculosis is present. The temperature should be observed with the patient in bed, a daily rise to 99° F. or a swing of 1.5° to 2° below normal being suspicious. The sputum should be examined repeatedly for tubercle bacilli by the ordinary method, and if not found the antiformin process should be carried out, and gastric washings should be examined and cultivated.

The sedimentation rate of the erythrocytes is affected in this disease. In active cases the sedimentation rate is increased, but this reaction is not specific. It is also increased in other conditions such as pregnancy, carcinoma, syphilis, rheumatism and acute infections. The test is therefore of little or no value in diagnosis, but it affords valuable indications of the degree of activity, and may assist in determining the form of treatment. A normal sedimentation rate unfortunately does not necessarily mean that the tuberculous disease is quiescent. As in radiology it is often the serial records that are most valuable.

Patients with resolute and persistent personality are more likely to persevere with treatment and to recover, than those of weaker moral fibre.

The prognosis is greatly affected by the type of the disease. Acute miliary tuberculosis used to be rapidly fatal in 100 per cent. of cases, whereas with the use of streptomycin the mortality is less than 50 per cent. and in acute caseous tuberculosis, although the prognosis is very grave, recovery may occur. In fibro-caseous tuberculosis the prognosis is most uncertain and difficult to forecast. Every factor must be carefully considered, and the response to treatment noted. The best outlook is in fibroid disease, which often undergoes complete and permanent arrest.

**SYMPTOMS IN THEIR RELATION TO PROGNOSIS.**—Persistent cough, by exhausting the patient and disturbing sleep, is often unfavourable.

The amount of sputum is usually dependent upon the type of disease and upon the presence of secondary infection, and may therefore be of value in prognosis.

*The significance of tubercle bacilli in the sputum.*—The figures obtained at the Midhurst Sanatorium, over a period of 8 years, in which the after-history of the patients was traced for the ensuing 6 years, show that the prognosis is best in "closed" cases; but that it is nearly as good in those cases in which the tubercle bacilli disappear from the sputum during the sanatorium treatment. Persistence of bacilli in the sputum is an unfavourable sign. The actual number of bacilli in the sputum and the presence of "beading" have no definite prognostic significance.

Cases commencing with hæmoptysis progress more satisfactorily than those with other modes of onset, chiefly because they are diagnosed earlier. Hæmoptysis occurring later may exert an unfavourable influence, either indirectly by spreading the disease into previously healthy portions of the lungs, or actually by the loss of blood.

If dyspnœa is not due to attacks of bronchial spasm, it has usually an unfavourable significance.

The temperature affords a clue to the type and activity of the disease, and is thus a valuable aid to prognosis. Profuse and persistent night sweats, or marked anorexia, especially when occurring early in the disease, are grave signs. Tachycardia due to toxæmia, signs of cardiac failure, œdema and albuminuria are of bad omen. The blood pressure is thought by some to be a useful guide, systolic figures below 100 mm. Hg being unfavourable, whereas a rise of pressure may be associated with amelioration of the disease. In fibroid lesions the pressure may be raised throughout.

**THE EXTENT OF PHYSICAL SIGNS.**—The activity of the disease rather than its extent is often the more important factor in determining prognosis, but both factors are of importance since the outlook is always more serious if both sides are affected especially if cavitation is present. The development of compensatory emphysema is of value only as an indication of fibrosis in the tuberculous portion of lung, and therefore of chronicity.

**THE INFLUENCE OF COMPLICATIONS ON PROGNOSIS.**—Generally speaking, the presence of complications increases the gravity of the disease. Involvement of the larynx is a serious complication, especially when accompanied by dysphagia; but complete recovery may take place if the pulmonary lesion is quiescent. In early cases spontaneous pneumothorax occasionally acts favourably; but when it develops in association with extensive tuberculosis, and especially if it progresses to pyopneumothorax, it is almost invariably fatal though, if the disease is unilateral, surgical measures may prove successful.

Pleural effusion often has a beneficial influence by diminishing the movements of a lung in which there is an early tuberculous focus.

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deleterious effect. Involvement of the genito-urinary system increases the severity of the disease, especially if the kidneys or bladder are affected. If the epididymis alone is involved the prognosis is not materially affected, as the lesion can be dealt with surgically, although the administration of a general anæsthetic may cause spread of the pulmonary disease. For this reason when operations are urgently needed on these patients, gas and oxygen, basal anæsthetics, local or spinal anæsthesia should be insisted on.

The rate of sedimentation of the erythrocytes (see p. 1023) has proved to be a valuable aid to prognosis. A persistently rapid rate is unfavourable.

**Treatment.—PROPHYLACTIC.**—The prophylaxis of tuberculosis involves a consideration of public health questions dealing with the purity of the milk supply, the inspection of meat, sanitation and housing, the early diagnosis of tuberculosis, the examination of contacts and the segregation of "open" cases. Inoculation with B.C.G. vaccine (attenuated living bovine bacilli) is being used increasingly in Great Britain for protective vaccination of children and especially of contacts. It is now generally advised for Mantoux-negative reactors on hospital staffs. All these questions are considered in the general article on Tuberculosis. Mass radiography, using miniature films, has been used for investigating the incidence of unsuspected tuberculosis in certain groups of the population, such as factory workers, and men in the forces. The average findings in this series shows that in about 0.5 per cent. of those examined shadows suggestive of tuberculosis are found, although the incidence of active disease is considerably lower. If these cases can be adequately treated it should tend to check the spread of infection.

The treatment of Mantoux-negative reactors working in sanatoria or hospitals has recently received attention. The Joint Tuberculosis Council advises that they should be weighed and have their blood sedimentation estimated monthly and their Mantoux reaction tested at least every 3 months, preferably every month. When the reaction becomes positive they should be examined radiologically and clinically. According to the degree of the signs and the radiological appearances they may either be allowed to work part-time and rest in bed when off duty, or taken off duty till it is clear that no progressive lesions are developing. Those showing definite symptoms must be treated as cases of active disease.

**CURATIVE.**—This varies with the type and stage of the disease. In all acute or febrile cases treatment should be commenced at home or in a nursing home or hospital, where the patient can be under careful observation in bed. The various forms of treatment which may be considered are—(1) sanatorium treatment; (2) home or institutional treatment; (3) dietetic treatment and personal hygiene; (4) climatic treatment; (5) graduated rest, exercise and labour; (6) medicinal treatment; (7) specific measures; (8) operative treatment; (9) symptomatic treatment.

**1. SANATORIUM TREATMENT.**—This constitutes the best mode of treatment for early and for certain types of chronic disease; but is totally unsuited for acute febrile or very active cases. The advantages obtained are: (a) the patient learns the most suitable mode of life, and the methods employed to check the spread of the disease; (b) the housing is specially designed and the climatic conditions are good; (c) the dietary is abundant and adapted to the patient's needs; (d) there is constant skilled medical supervision, and the daily routine is adapted to the actual physical condition of the patient.

On arrival a newcomer is kept in bed for a few days in order that his resting temperature may be observed, and the necessary examinations carried out. If there is pyrexia, rest in bed must be enforced until the temperature falls to normal. If the temperature rises above 99° F. when the patient is up, return to bed is usually necessary. The routine of sanatorium treatment varies in different institutions, the most important divergence being whether or not a system of "graduated exercise" is employed. In nearly all an hour's recumbent rest is enforced before lunch and dinner.

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Meningitis is still a very serious complication, but streptomycin has made a great difference to the prognosis. Tuberculous peritonitis or enteritis is a very grave complication, but fistula-in-ano often occurs in chronic cases, and exerts no marked

deleterious effect. Involvement of the genito-urinary system increases the severity of the disease, especially if the kidneys or bladder are affected. If the epididymis alone is involved the prognosis is not materially affected, as the lesion can be dealt with surgically, although the administration of a general anaesthetic may cause spread of the pulmonary disease. For this reason when operations are urgently needed on these patients, gas and oxygen, basal anaesthetics, local or spinal anaesthesia should be insisted on.

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After 3 months' stay it is usually possible to decide whether the patient is responding to treatment, and, if so, it should, if possible, be prolonged for at least another 3 months, or until the sputum is free from tubercle bacilli.

2. HOME AND INSTITUTIONAL TREATMENT.—Treatment at home, in nursing homes or in special hospitals, is essential in early cases with fever, and in cases in which it is necessary to establish the diagnosis. Home treatment is also usually necessary on return from sanatorium or climatic treatment, if arrest is incomplete. An endeavour should always be made to carry out the principles inculcated at the sanatorium, and the patient should be under regular medical supervision. Advanced cases are best looked after in special institutions.

3. DIETETIC TREATMENT AND PERSONAL HYGIENE.—It is desirable to graduate the diet in each case so that the patient is restored to the previous maximum weight; but, in order to accomplish this, the food should be slowly increased and all ideas of enforced overfeeding discountenanced. A total calorie value of 3000 to 3500 is usually ample; but, if the patient is performing heavy work, as much as 4000 may be necessary. Meat, fish, eggs and fats are usually well tolerated. It is not often necessary to give large quantities of milk when the patient is on a full dietary.

In all cases in which there is expectoration the patient should be clean-shaven. Great care must be taken in the disposal of sputum to ensure that it does not become dry, and that flies do not have access to it. All patients who are up should carry special sputum flasks, while those who are in bed should have sputum cups suitably covered and containing disinfectant. The sputum should be burnt, or, if this is impossible, it should be emptied into the water-closet after disinfection with carbolic acid or other simple or cheap disinfectant.

Smoking is best avoided in cases of active disease or laryngeal tuberculosis, and in no instance should inhaling be allowed. Sun-bathing and injudicious uncontrolled sun exposure are dangerous and often activate quiescent lesions. Patients should be strongly warned of this danger.

4. CLIMATIC TREATMENT.—Climate is not now considered to be so important as it used to be. Broadly speaking, bracing areas with cool dry air, porous soil and moderate height promote a feeling of well-being, stimulate the appetite and the mind and are more favourable than damp, low-lying "relaxing" sites. Countries with a high mean temperature and high humidity are unsuitable for tuberculous patients. With proper treatment patients are just as likely to recover in the sanatorium in their home area as by travelling far afield. There is no special virtue in Switzerland except that the mountains are an agreeable background to prolonged bed rest and the air and atmosphere are crisper and cleaner than in this country. In any case early treatment and control are best carried out in this country. Patients with diminished vital capacity due to fibrosis or emphysema should not be sent to sanatoria at over 2,000 ft.

5. GRADUATED REST AND EXERCISE.—Rest is an essential preliminary part of the treatment of active tuberculosis. Even apyrexial patients benefit from several weeks of bed rest. Pyrexial cases must be kept in bed until the temperature has remained normal for several weeks. It is an advantage to allow patients up for toilet purposes, but acute cases with a high initial temperature may require periods of absolute rest when no movement or activity on the part of the patient is allowed. Rest treatment should be controlled by careful temperature observations. Rectal temperatures or 5-minute mouth readings must be used and even minor variations should be regarded as significant.

The patient is allowed to get up by degrees starting with 1 hour daily, increasing to 6 or 8 hours. If still apyrexial the patient is allowed walking exercise of 1 or 2 miles daily. The system of "graduated exercise" which Paterson instituted at the Frimley Sanatorium caused a revolution in sanatorium treatment in that it introduced a progressive occupational therapy into the previously otiose and sterile stagnation of sanatorium life. Paterson had the theory that muscular exercise liberated tuber-

culous toxins and that if the exercise was carefully graduated a condition of increasing immunity through the use of autogenous tuberculin would arise. However, even if the theory has no certain foundation and excess effort is to be avoided, progressive occupational therapy is essential.

6. MEDICINAL TREATMENT.—There has been a long series of drugs used in the treatment of tuberculosis. One no longer used which had a long vogue and an extensive optimistic literature was *sanocrysin*. It took over 10 years before it fell into virtual disuse because the natural course of pulmonary tuberculosis is so uncertain that it takes a great many years and a great many cases before one can conclude anything from studying the results of treatment.

Streptomycin starts with the very great advantage that it is known to cure many cases of two diseases previously incurable: miliary tuberculosis and tuberculous meningitis. In pulmonary tuberculosis it is thought to be most effective where there is fresh infiltration and less so or ineffective in chronic fibrocaceous tuberculosis.

Streptomycin is usually given in doses of 1 g. daily. It may be given continuously over a period of 2 or 3 months at a time, but it is more usual to give two to four courses of injections each lasting 2 or 3 weeks with an interval of about 2 weeks between each course. The object of the interval is to diminish the likelihood of toxic reaction. One of these is giddiness due to labyrinthine damage. Another is nerve deafness which sometimes follows the prolonged dosage given in miliary tuberculosis or tuberculous meningitis. A less common toxic reaction is an urticarial or erythematous rash with or without pyrexia. The effectiveness of streptomycin is limited by the tendency for drug resistance to develop. The organisms rarely become resistant before a minimum period of 14 days but the number of resistant strains rapidly rises in proportion until after about 3 months it is maximal unless measures are taken to prevent it. It has been found that the simultaneous administration of other drugs, such as sodium aminosalicylate (P.A.S.) or isoniazid, diminishes or delays the appearance of strains resistant to streptomycin or to themselves.

Streptomycin in combination with one or other of the above drugs is given generally in cases of miliary tuberculosis or tuberculous meningitis. It is usually given in acute caseous pneumonia or broncho-pneumonia.

Physicians differ as to its use in other forms of the disease. Many oppose its use in fibrocaceous disease because it is not very effective, because the patient may spread streptomycin resistant disease and because, if the patient subsequently requires surgery, it would probably not be possible to get a maximal effect in the prevention of local spread of infection during surgical intervention. On the other hand, it may serve to prevent or limit the local spread of broncho-pneumonia which bring the patient's life progressively to an end. Some use it in tuberculous pleural effusion or in minimal tuberculous lesions in an attempt to arrest the disease in its incipient stage. They discount the possibility of losing the eventual protective effect of streptomycin by the hope that they will have rendered improbable the necessity of surgical intervention. Many use it in early infiltration with the same object. It is rarely given in primary tuberculosis, although it is probably wise to give it in very young children, or in the so-called progressive primary in which a massive primary lesion slips directly into a post-primary stage with incidental danger of miliary spread. It is generally used to prevent spread during resection or thoracoplasty.

It appears to be effective in the treatment of tuberculous laryngitis, tuberculosis of the bronchi, ulcers of the tongue and possibly of the intestines.

The permanent place of streptomycin in therapy will take many years to determine. Sodium aminosalicylate has a bacteriostatic effect *in vitro* but is not apparently bactericidal. It has been used by itself in treatment and good results have been claimed. Probably its only important use is in combination with streptomycin to delay the development of resistant strains of tubercle bacilli. The dosage recommended is 3 to 4 g. four times a day, making a total daily dosage of 14 to 18 g. Larger



doses have been used but they often produce gastric disturbances which may necessitate the abandonment of the treatment; and the doses given above are usually the largest that can be tolerated by the majority of patients. Small initial doses and the routine administration of the drug with meals often limit the gastro-intestinal disturbances. The drug may produce erythematous rashes with pyrexia in a small percentage of cases.

Isoniazid (isonicotinic acid hydrazide) is also used in the treatment of pulmonary tuberculosis, the usual dose being 100 mg. in the morning and 50 mg. in the evening; but it may be increased to a total of 200 mg. per day in divided doses. It is bactericidal *in vitro* and good results are obtained in treatment with this substance combined with streptomycin. Resistance to isoniazid develops rapidly but appears to be delayed when it is combined with streptomycin and there seems to be some probability that it delays the development of streptomycin resistance as effectively as does sodium aminosalicylate. Its status in the treatment of pulmonary tuberculosis cannot be finally estimated at the present moment.

The sulphones and thiosemicarbazones are of doubtful value, and liable to produce methæmoglobinæmia and anæmia in the first instance, and jaundice and possible liver damage in the second.

**7. COLLAPSE THERAPY.**—This form of treatment has the object of relaxing the affected lung and allowing it to contract towards the hilum. In this way it provides rest, allows cavities to collapse and therefore heal and probably prevents the spread of tuberculous disease in the collapsed lung and prevents the formation of cavities.

The following methods of collapse therapy are available—artificial pneumothorax, phrenic paralysis, pneumoperitoneum, extra-pleural pneumothorax and thoracoplasty.

(a) *Artificial pneumothorax.*—This treatment is the oldest method of collapse therapy, dating from Forlanini of Pavia in 1898. In suitable cases it is still the most effective method of collapse therapy.

If old and dense pleural adhesions are present, it is impracticable. If there is much emphysema or cardiac embarrassment, it involves risk. It is also of value in certain cases of repeated severe hæmoptysis. Tuberculous laryngitis or enteritis are not contraindications, providing that other conditions are suitable. Sterile air is introduced into the pleural cavity, and the lung allowed to collapse. The method of induction of artificial pneumothorax is as follows: A preliminary subcutaneous injection of gr.  $\frac{1}{2}$  of papaveretum (Omnopon) is given half an hour before the start. The patient lies on the sound side with the head low and supported on a pillow. A second pillow is placed under the chest to expand the intercostal spaces. The skin and the tissues down to the pleura are anæsthetised with 2 per cent. procaine hydrochloride solution after the application of iodine. The site usually chosen is in the sixth intercostal space in the mid-axillary region. The pneumothorax apparatus is carefully tested to make sure that it is in working order. A special pneumothorax needle is attached to the machine by a rubber tube which is pinched to show that the manometer oscillations are free and the needle is then pushed through the intercostal space until the pleural cavity is reached. The apparatus is then adjusted so that the intrapleural pressure can be observed. No air should be introduced until the manometer shows a normal negative pressure range with inspiration, of 5 to 10 or more cm. of water. This is the test of entry into the pleural space, and when this is established 200 to 300 c.cm. of sterile air may be allowed to enter the pleural cavity. The final pressures are then recorded and the needle is withdrawn. A refill is given next day and another after 2 more days, the quantities of air introduced being determined by the final pressures, which should be kept slightly negative. Subsequent refills are gradually spaced out to a week, then 10 days and later to 2, 3 and 4 weeks' intervals. The usual custom now is to maintain the collapse for 3 years or longer. If the condition of the patient is satisfactory, re-expansion may then be permitted cautiously. It should be remembered that after expansion pleural adhesion almost

invariably occurs and the treatment by artificial pneumothorax cannot be repeated. In some cases of bilateral disease, which is active but not very extensive in either lung, a cautious use of bilateral artificial pneumothorax has proved practicable and helpful, but very great care is necessary in adjusting the pressures.

There are certain dangers in the procedure. These are now rare, and they can usually be prevented by careful attention to the technique. Death has occurred from air embolism when the needle has accidentally been put into a blood vessel in the lung. It is for this reason that air should never be allowed to flow unless there is a clear negative swing of the manometer showing that the needle is in the pleural cavity. If the lung is adherent to the chest-wall, owing to pleural adhesions, or if the needle is pushed in too far, it may be inserted into the lung or into a pulmonary cavity; the manometer will then show a swing above and below the zero line instead of entirely below it. Under these circumstances, no air should be allowed to enter. The needle may be inserted into a blood vessel. In this case the manometer pressure will rise above zero, and blood may appear in the glass section inserted in the rubber tube leading from the manometer to the needle. The needle should be withdrawn immediately, lest air should enter the vessel.

If the pleura is found to be adherent at the site of the first puncture, another attempt may be made elsewhere, *e.g.* just below the inferior angle of the scapula. This spot may be selected for the initial puncture in left-sided cases where there is marked cardiac displacement. In cases in which localised band or cord adhesions prevent adequate collapse, it is often possible to cut them by electrocautery or diathermy through an operating thoracoscope, thus ensuring completely effective collapse. This is called internal pneumolysis. Provided that the lung is sufficiently relaxed to permit closure of cavities the persistence of adhesions does not necessarily make the treatment ineffective.

Over-collapse may lead to atelectasis of a lobe probably due to bronchial obstruction. It is not uncommon after adhesion section. Its persistence is a serious complication as it may lead to pleural effusion, empyema or bronchiectasis but often the lung re-expands as the excess air is absorbed. Pleural effusions sometimes occur during treatment. Small amounts of fluid in the costophrenic gutter occur at some time in the majority of cases. Large effusions sometimes occur requiring aspiration. They do not necessarily prevent continuation of treatment but are often followed by progressive obliteration of the pleural cavity and occasionally they become purulent.

Other rare complications are pressure pneumothorax following injury to the lung during induction or refill and very rarely secondary infection of the pleural cavity.

(b) *Phrenic paralysis*.—Crushing of the phrenic nerve results in a paralysis lasting from 8 to 18 months. The paralysed diaphragm is elevated at rest and rises during inspiration. The degree of collapse varies very much but occasionally very satisfactory lung relaxation occurs. It is rarely used as the only treatment but is usually combined nowadays with pneumoperitoneum.

The indications are the same as those for pneumothorax and it is used where pneumothorax has failed or is being postponed for some reason. Phrenic crush should not be used if thoracoplasty is likely to be necessary as the operation cannot be performed until the diaphragm recovers its mobility. Occasionally phrenic crush is followed by permanent paralysis.

(c) *Pneumoperitoneum*.—Air introduced into the peritoneal cavity raises the diaphragm and produces partial collapse of the bases of the lungs. As in an artificial pneumothorax, the injections of air must be repeated at intervals to compensate for absorption. In order to achieve the best results, the diaphragm on the affected side should be paralysed by crushing or evulsion of the phrenic nerve. In a favourable case, a pneumoperitoneum will raise the diaphragm by several inches, and this, together with the abolition of the diaphragmatic movement, relaxes and rests the lower part of the lung. The operation is indicated in cases of cavitating tuberculous

lesions in the lower lobe when an artificial pneumothorax has failed. It is particularly successful in the treatment of cavities in the apex of the lower lobe (dorsal segment). Care is necessary in the technique to avoid the risk of air embolism. This treatment is used where pneumothorax has failed or as a prelude to pneumothorax treatment when the activity of the tuberculous disease in the lung has subsided sufficiently to make pleural effusion less likely to follow artificial pneumothorax. It is less effective than pneumothorax treatment but quite effective in some cases.

(d) *Extra-pleural pneumothorax*.—This treatment was the logical development of pneumothorax treatment when it was impossible to collapse the lung by orthodox pneumothorax treatment on account of adhesions. Collapse is obtained by separating the pleura and the underlying lung from the chest-wall inside the endothoracic fascia and then by maintaining the separation by putting air in the space thus formed. It fell out of use because of the frequency of secondary infection and spread of disease to the extra-pleural space. The development of antibiotics has led to some revival of the operation.

(e) *Thoracoplasty*.—This operation was originally used in cases where artificial pneumothorax had been attempted and failed because of adhesions or because cavities remained patent in the partially collapsed lungs. It is, however, often used as a primary form of collapse. It is particularly used to collapse apical cavities. The operation involves division of a variable number of ribs sometimes combined with apicolysis to allow the lung to collapse by mobilisation of the chest-wall. It is a serious operation but good results are obtained. The more radical thoracoplasties are not so often done nowadays and resection is replacing many thoracoplasties.

(f) *Resection*.—All the surgical measures previously described are designed to put the diseased lung in a favourable state for natural healing to occur. Resection aims at eradicating the lesion itself. It is a less mutilating operation than thoracoplasty and more effective than thoracoplasty in dealing with cavities of the lower lobe. It is being increasingly used to remove apical cavities, tuberculomata and tuberculous bronchiectasis. Only time can show whether too optimistic a view is taken of its value by some enthusiasts. Its use is limited by the multiplicity of tuberculous lesions. Resection may very well replace many forms of collapse therapy but its least debatable value at present is in putting a full stop to disease already arrested by other methods. No form of surgical treatment is a substitute for general treatment.

8. **SYMPTOMATIC TREATMENT**.—When cough is ineffective it may be relieved by a sedative lozenge or linctus containing diamorphine or codeine, or by the well-known liquorice lozenge. If there is difficulty in bringing up the sputum, a simple saline mixture is of value, such as sodii bicarb. gr. 10, sodii chlorid. gr. 3, sp. chlorof. min. 10, and aq. anethi dest. ad fl. oz. 1.

*Night sweats*.—Free ventilation is the key to prevention. The windows should be widely open. The clothing and bedclothes should be as light as consistent with warmth. Feather or rubber mattresses should be avoided. In very severe cases a rush or thin cork mattress has been recommended.

*Fever*.—Rest in bed up to the extent of "absolute rest" is the best means of lowering the temperature.

*Hæmoptysis*.—In cases in which the sputum is only streaked no special treatment is required. Moderate hæmoptysis with expectoration of 3 or 4 oz. of blood requires more active measures. The patient should be put to bed and as there is usually anxiety, given a sedative, either chloral hydrate or morphine gr.  $\frac{1}{2}$ . In profuse or persistent hæmoptysis, the patient should be confined strictly to bed, and if it is known from which side the bleeding has occurred, he should be on the affected side to prevent the blood from being aspirated into the sound lung.

He should have one or two pillows and should not be kept too immobile as the blood may cause collapse of one or more lobes unless it is coughed up. Hæmoptysis

is rarely fatal except in advanced cases, but causes alarm out of proportion to the danger. Reassurances and sedatives help to allay fear, but sedatives should be adapted to circumstances and not overdone. If the bleeding is severe and continual, drip transfusion should be given.

Artificial pneumothorax has been used to stop hæmorrhage when the affected side is known, although it is rarely needed and indeed it is probably seldom that it could be performed. It has, however, been successfully employed on several occasions when all other measures had failed.

Congo red and other blood coagulants are of no value.

*Gastro-intestinal symptoms.*—Anorexia or dyspepsia are usually due to toxæmia, and improve with rest. Sometimes the milk diet, increased fat, cod-liver oil and so forth which these patients are often given are the cause of the dyspepsia. Alkalis are often helpful. Patients should be advised not to swallow their sputum and told why they should not, as otherwise they often ignore this advice.

If diarrhœa develops, a low residue diet with a high vitamin content should be given. Diarrhœa usually occurs in terminal cases, and tincture of opium will help to relieve it.

Insomnia is often a troublesome symptom, and every endeavour should be made to obtain a good night's rest by administration of mild hypnotics, and by relieving distressing cough and pain.

The treatment of the complications of pulmonary tuberculosis is described under their respective headings. The rehabilitation of patients discharged from sanatoria is an important subject, to which considerable attention is being devoted, and involves a consideration of the advisability of establishing training centres or industrial colonies for consumptives. These are proving of very great value.

## MINIMAL TUBERCULOSIS

As a result of mass radiography, the significance of minimal lesions requires especial study. There are various definitions of what constitutes a minimal lesion, but the exact definition is not important.

These are usually small nodular discrete lesions found in the upper part of either lung usually below the first or second or third ribs: there may be one or more than one: they do not give rise to any physical signs and their presence can only be detected by radiological examination. These are post-primary lesions and are not accompanied by glandular enlargement. Under observation these shadows may rarely recede and disappear or may become denser as they are replaced by fibrous tissue or calcification. They may, on the other hand, eventually cavitate or there may appear in the adjacent lung small areas of infiltration with progressive disease. These latter changes may occur months or more often years after their first detection.

Observation has now shown that at least 30 per cent. develop into progressive disease and the proportion may really be higher. At the present time, partly owing to shortage of hospital and sanatorium accommodation in many clinics, patients showing these radiological shadows are merely kept under observation without treatment, only receiving treatment when progressive disease has occurred. It is probable that most cases of progressive tuberculosis with sputum would at some time previous have shown these minimal lesions. These lesions should always, therefore, be treated seriously as they present a golden opportunity for treatment at an early stage. If successfully treated, progressive tuberculosis might become rare and the incidence of tuberculosis diminish.

It has already been stated that some of these lesions become calcified and give no further trouble, but there is at the present time no method of determining which lesions will remain static and which will progress. Patients showing these lesions

should be put to bed. Five-minute or rectal temperatures should be carefully charted and the sputum, if any, should be examined; if there is no sputum, laryngeal swabs or gastric washings should be examined and cultivated, although at this stage tubercle bacilli are rarely found. Observation of the temperature chart will often show minor yet important deviations from the normal, even in patients who have no symptoms. A raised sedimentation rate should be accepted as evidence of activity, but the sedimentation rate is rarely raised and a normal sedimentation rate does not exclude a progressive lesion. If all these observations are negative it may be considered safe to discharge the patient and keep him under observation. A wiser course, however, is probably to give these cases courses of streptomycin and isoniazid. Whether progressive disease can be prevented by this treatment it is not yet possible to say, but certainly it does not always prevent spread of the disease. Artificial pneumothorax does appear to prevent spread and cavitation, and should be induced in young patients or patients who show definite evidence of activity as shown by pyrexia, a positive sputum or radiological change in the lesion. In the United States of America these lesions are often excised, and incidentally it has been shown that they represent a localised broncho-pneumonia. Resection may well become the treatment of choice, but the difficulty of adopting drastic measures of treatment or even of admitting the patients for observation and assessment is that the patient has no symptoms whatever. The name "minimal lesion" is not a happy one, as it suggests an insignificant lesion, but once it is generally realised that these shadows, like the cloud no bigger than a man's hand, may be the presages of storms to come, they will receive the serious treatment which they deserve and the whole picture of pulmonary tuberculosis may be altered in our own time.

## THE PULMONARY MYCOSES (PNEUMONOMYCOSES)

A number of fungi produce pulmonary lesions. Considerable confusion exists in regard to their nomenclatures, and at the present time it is difficult to give accurate accounts of them. The pulmonary mycoses have one feature in common, in that they produce chronic pulmonary lesions practically indistinguishable clinically from those of the chronic forms of pulmonary tuberculosis.

Among the varieties of mycotic infection at present separated clinically may be mentioned—Actinomycosis; Sporotrichosis (see p. 196); Aspergillosis; Torulosis (see p. 197); North and South American Blastomycosis (see pp. 198, 199); Coccidioidosis (see p. 200); and Histoplasmosis (see Appendix i).

### PULMONARY ACTINOMYCOSIS

**Ætiology.**—The general characters of the streptothrix group of organisms are described in the section on Actinomycosis (see p. 193). A large proportion of cases show the first lesions in the head and neck regions, but primary pulmonary cases occur, and are probably more frequent than is generally recognised.

**Pathology.**—In the primary pulmonary cases the distribution of the lesions is at first very similar to that of tuberculosis, and the disease may extend in an identical manner. In the forms due to spread from other organs such as the liver, the base of the lung may be first involved, while in cases extending down from the neck the path of the infection is apparent.

Owing to the tendency of the lesions to spread by contiguity, subcutaneous abscesses may form and simulate caries of the ribs. Pleural adhesion is the rule, but occasionally empyema results. When a subcutaneous abscess ruptures or is opened, the characteristic "sulphur granules" may be found, although this is not invariable. The skin around the sinuses which result is often puckered in a somewhat characteristic fashion.

**Symptoms.**—These are in general identical with those of the chronic forms of pulmonary tuberculosis, such as cough, expectoration, which may be offensive, dyspnoea, fever and night sweats.

**Complications and Sequelæ.**—These are usually due to the other localisations of the organism; but, in addition, empyema and bronchiectasis may be mentioned.

**Diagnosis.**—This can only be established by the discovery and identification of the organism in the sputum and the discharge. The characteristic "sulphur grains" are not invariably present, and may escape notice unless looked for carefully. In any obscure case of pulmonary disease in which tubercle bacilli are not found after repeated search, the possibility of actinomycosis should be considered, and direct films should be specially examined.

**Course.**—This is progressive, and may lead to asthenia, emaciation and death.

**Prognosis.**—This is serious, although some cases respond well to treatment.

**Treatment.**—(See p. 196). Surgical treatment of local abscesses or of empyema may be required. Penicillin is often effective in doses of 1 million units daily for several weeks. Large doses of potassium iodide are traditional.

#### PULMONARY ASPERGILLOSIS

**Ætiology.**—Infection of the bronchi and lungs sometimes occurs by *Aspergillus fumigatus*, more rarely by *A. nidulans*. The disease has been most frequently observed in France. It occurs among pigeon breeders and hair sorters and combers. The former acquire the disease from the process of artificial feeding, from transferring grains in the mouth to the beak of the bird; the latter from the use of rye flour in cleaning the hair. Millers and farm labourers have also been the subjects of the disease.

**Pathology.**—The fungus induces nodular formations in the lung tissue somewhat resembling aggregated tubercles. Bronchitis, patchy lobular consolidation and fibrosis result. Emphysema, bronchiectasis and cavity formation may follow. A secondary aspergillosis may occur in chronic cases of bronchitis or lung disease, but is of little clinical importance.

**Symptoms.**—Primary aspergillosis produces symptoms similar to those of bronchitis, broncho-pneumonia or pulmonary tuberculosis, according to the localisation and degree of the lesions. The sputum may be blood-stained, or definite hæmoptysis may occur. There is generally wasting with irregular fever.

**Diagnosis.**—The condition has to be differentiated from pulmonary tuberculosis, and from other varieties of pneumonomycosis. It may be suspected when repeated examinations of purulent sputum do not show tubercle bacilli. It is, however, a rare disease and even if the fungi are found they may be secondary invaders or contaminants.

**Course.**—Acute broncho-pneumonic forms may be fatal in a few weeks or months. The chronic lesions may extend to years, and arrest with fibrosis is not uncommon.

**Treatment.**—This consists in avoiding further infection, and giving large doses of potassium iodide. Open-air measures and general tonic treatment are also to be recommended. All *Aspergilli* are completely resistant to penicillin.

#### FARMER'S LUNG (see p. 1015)

#### OTHER MYCOTIC INFECTIONS

Fungi of the genera *Blastomyces* (*Oidium*, *Coccidioides*) and *Sporotrichum* are well known to produce cutaneous affections simulating chronic gummatous or tuberculous lesions. They may also give rise to pulmonary disease producing symptoms like those of tuberculosis.

Castellani has described various broncho-pulmonary conditions due to species of the genus *Monilia* (*Candida*), including the "tea-tasters' cough" and "tea-factory cough". Another fungus, *Mucor mucedo*, has been found in the sputum, and is regarded as pathogenic to man.

All these moulds produce bronchitic symptoms and mild infections, while more severe forms simulate pulmonary tuberculosis. The diagnosis in each case depends upon the recognition of the fungus, and the treatment recommended is large doses of potassium iodide.

#### PULMONARY HISTOPLASMOSIS

This is described in the article on Histoplasmosis (see Appendix f).

#### TOXOPLASMOSIS

This is described in the article on Toxoplasmosis (see Appendix v).

### SYPHILIS OF THE LUNGS

**Ætiology.**—Clinically recognisable pulmonary syphilis is a rarity; but syphilitic lesions occur in the lungs in both the congenital and acquired forms of the disease.

**Pathology.**—Even post mortem it is often difficult to establish the syphilitic nature of the pulmonary lesions found in cases of syphilis, owing to the fact that they tend to the formation of scars presenting no characteristic features.

**Congenital syphilis.**—The essential changes are—(1) Round-celled infiltration with eventual fibrosis, starting round the bronchi and spreading to the inter-alveolar framework; (2) periarteritis of the smaller arteries and (3) desquamation and degeneration of the epithelium of the alveoli and bronchi. Gummata may be present, but are rare. Spirochætes can be demonstrated in the lesions by Levaditi's method. The microscopic appearances comprise the "white pneumonia" of Virchow, and an interstitial pneumonia which is commoner, although both conditions are frequently associated. White pneumonia is found in premature or still-born infants, and in those dying soon after birth. The condition may be widespread or localised. The affected areas are firm, consolidated, smooth and greyish-white in colour. There are no interstitial changes, and the consolidation is due to the filling of the alveoli with desquamated, degenerating epithelial cells.

In the commoner interstitial form the lung is firmer, harder and darker grey in colour, and the connective tissue is mainly involved. To this condition the term "pancreatisation of the lung" has been applied by Rogers.

**Acquired syphilis.**—Syphilitic lesions of the bronchi have already been described in the section on diseases of the bronchi. Gummata may occur in or around the intra-pulmonary bronchi or in the lung tissue. They may be single or multiple, and vary in size from that of miliary granules to a hen's egg. They are said to be more common in the deeper parts of the lung near the roots and in the lower lobe. They undergo changes similar to those occurring in gummata elsewhere, but tend more to fibrosis and contraction than to softening. Owing to these secondary changes, the following conditions may result: broncho-pneumonic processes, widespread fibrosis and contraction with pleural adhesion, bronchiectasis and occasionally excavation.

**Symptoms.**—Small gummata may be latent and give rise to no symptoms or signs. When fibrosis occurs, they are similar to those of pulmonary fibrosis from other causes. It is generally recognised that in rare cases a destructive process occurs, formerly called "syphilitic phthisis", and almost exactly similar in its clinical manifestations to those of caseous or fibro-caseous tuberculosis.

**Complications and Sequelæ.**—Syphilitic lesions in the larynx, trachea or

bronchi may complicate the course. Bronchiectasis has already been mentioned, and tuberculosis may occur as a complication.

**Diagnosis.**—This is often difficult and sometimes inconclusive. Obscure pulmonary signs in a syphilitic subject should arouse suspicion. The Wassermann reaction should be determined, and other indications of syphilis looked for in all fibrosing and destructive lung conditions when no tubercle bacilli are found in the sputum. These cases have never been common in modern memory and are becoming rarer. Other syphilitic lesions such as aortic regurgitation are usually present. The difficulty of diagnosis is increased by the association of syphilis and tuberculosis mentioned above.

**Course and Prognosis.**—Where the lesions are localised and can be recognised early, the course is favourable if anti-syphilitic treatment is applied. Where fibrotic changes occur, leading to bronchiectasis, the course is less favourable, and in the destructive form it is serious. An inter-current tuberculous infection increases the gravity of pulmonary syphilis.

**Treatment.**—When a diagnosis of pulmonary syphilis has been established, vigorous anti-syphilitic treatment should be carried out. Its beneficial effect is undoubtedly promoted by open-air treatment. In cases where tuberculosis coexists with syphilis, anti-syphilitic treatment is strongly recommended, especially by French physicians.

## NEW-GROWTHS IN THE LUNGS

Both benign and malignant tumours may occur in the lungs, the latter being the more common.

**Ætiology.**—Malignant tumours occur more frequently in the male sex in the ratio of 5 to 1; carcinoma is rare before the age of 40. The lung is now the commonest site of cancer in the male. Some of the apparent increase is due to more accurate diagnosis but there is probably a genuine increase. It has been observed that cancer of the lung is most commonly found in smokers, and Doll and Hill have produced suggestive figures showing that heavy cigarette smokers have a much greater incidence than non-smokers. Further studies are necessary to determine the importance of cigarettes as an ætiological factor.

**Pathology.**—Benign tumours found in the lungs usually arise in the bronchial mucous glands or in the bronchi. They include adenoma, fibroma, lipoma and chondroma (see p. 972).

Malignant tumours may be primary or secondary. The primary growths are carcinoma or sarcoma. It is probable that all varieties of bronchial carcinoma arise in the basal cells of the bronchial mucous membrane. Certain types are described, the squamous-celled carcinoma, the adeno- or columnar-celled carcinoma and the oat-celled tumour. The squamous-celled carcinomata form a clearly differentiated group, in which may be included columnar-celled growths with duct and acinar formation; the remainder are sometimes known as undifferentiated tumours, consisting of more primitive types of cells. These types, however, may be combined so that any one particular carcinoma may vary histologically in different areas. Sarcoma is extremely rare and most tumours thus described prior to 1928 were in fact anaplastic carcinomata. Metastatic carcinoma may arise from primary tumours in breast, stomach, intestines, liver, pancreas, prostate or kidney and metastatic sarcoma most often results from tumours of bone. Chorion-epithelioma also give rise to secondary deposits in the lungs.

Primary malignant tumours are usually unilateral; but secondary growths are often multiple. Dissemination in the lungs may occur by spread through the bronchi or vessels, and a condition of miliary carcinomatosis is at times produced. The pleura is often affected by direct extension. Infiltration of, or pressure upon, the mediastinal structures frequently occurs.



**Symptoms.**—Simple tumours except adenomata are pathological curiosities, and as a rule, only produce symptoms when they cause obstruction of a bronchus or press on mediastinal structures (see pp. 972, 1094).

The early symptoms of malignant growths are slight, and consist of malaise with, perhaps, cough and expectoration. Later, when the growth becomes more extensive and exerts pressure on, or involves the larger bronchi, mediastinum or pleura, they are more noticeable. Pain, dyspnoea and loss of weight with cachexia usually develop, and the cough and expectoration are more marked. The latter is often of the typical "currant jelly" or "prune juice" appearance due to altered blood. Microscopically, groups of large fatty cells, or irregular epithelial cells may be seen. Malignant cells may be found in 60 per cent. of cases by Dudgeon's wet method. There are usually no definite physical signs until the tumour causes pressure upon the bronchi, mediastinum or deep thoracic veins or nerves. The chest-wall may bulge locally, owing to the presence of a growth near the surface, or it may be retracted if a main bronchus is obstructed. An actual subcutaneous swelling caused by the tumour eroding through the chest-wall may be visible. Enlarged veins often run across the chest, and one or other arm may be swollen or cedematous if there is mediastinal obstruction. Vocal fremitus is often unaffected, but is increased when the growth is near the surface, and diminished if pleural effusion has occurred. The percussion note over a moderate-sized tumour is impaired and may be extremely dull; more often the dullness is due to collapse of the lung. The breath-sounds vary with the size and position of the growth, and with the displacement or pressure effects produced. They may be weak, or loud and stridorous. The stridor is usually unilateral. Adventitious sounds depend upon the presence of complications such as bronchitis. Some degree of fever often occurs. The supra-clavicular and axillary glands are not infrequently enlarged, and evidence of malignant disease may be present in other parts of the body such as the abdomen.

One special variety of apical carcinoma is the superior pulmonary sulcus or Pancoast tumour, which gives rise to a somewhat characteristic or suggestive clinical picture. The chief symptoms are pain in the shoulder, inner side of the arm and forearm together with weakness and wasting of the small muscles of the hand. Paralysis of the cervical sympathetic on the same side develops. There is usually localised dullness at the extreme apex. Radiological investigation reveals a sharply defined apical shadow with destruction of the posterior part of the first three ribs and sometimes localised vertebral erosion. Pancoast suggested that these tumours may arise from remnants of the fifth branchial cleft.

**Complications and Sequelæ.**—Bronchitis is nearly always present in some degree. Pulmonary collapse, fibrosis, bronchiectasis, emphysema, gangrene, hæmoptysis, pleural effusion, abscess and empyema are sometimes observed. The effusion is frequently bloodstained. In cases of primary malignant disease of the lungs, secondary deposits may occur in other parts of the body such as glands, brain, suprarenals, heart and bones. Cardiac arrhythmia, such as auricular fibrillation, may result from direct invasion of the pericardium or myocardium.

Carcinoma of the lung may be accompanied by neurological syndromes which are not due to secondary deposits, and which may cause symptoms before the carcinoma. Four types of neuropathy are recognised: subacute cerebellar degeneration, sensory neuropathy, polyneuritis and motor neuropathy. The clinical manifestations are not always clear-cut and there may be evidence of multiple lesions in the nervous system. The characteristic picture of subacute cerebellar degeneration is of a rapidly progressive ataxia and dysarthria; diplopia, euphoria and dementia are common, and there may be pyramidal and sensory changes. In sensory neuropathy the presenting symptoms are pain and paræsthesiæ in the limbs, and ataxia; there is peripheral sensory impairment and ataxia, absent tendon reflexes and only slight muscular weakness. In polyneuritis there are motor and sensory changes. In motor neuro-

pathy there is a progressive atrophic paresis predominantly affecting the limb girdles; bulbar palsy, diplopia and ptosis may occur; the tendon jerks are diminished or absent; there are often subjective sensory manifestations such as pain, cramps or paræsthesiæ, but objective sensory changes are rare.

**Diagnosis.**—This is difficult in early cases, and not easy in some advanced ones. It not infrequently happens that metastases, especially in brain or bone, afford the earliest manifestations to be recognised. Difficulties may arise in connection with pulmonary tuberculosis, fibrosis and gumma of lung, aneurysm, pericardial and pleural effusion and enlargement of the mediastinal glands due to Hodgkin's disease or tuberculosis. The whole body should be searched for evidence of malignant disease elsewhere. The sputum should be examined repeatedly for tubercle bacilli and for cellular elements, and a radiographic examination made of the chest. Localised pulmonary collapse thus demonstrated may be a very early indication. By the stereoscopic method excellent evidence of pulmonary neoplasms is often obtainable. Lipiodol injection and radiographic examination or tomography may demonstrate the obstruction of a bronchus by the growth which often presents a tapering or "rat tail" appearance. Bronchoscopy is essential in the diagnosis of bronchial carcinoma. Temporary artificial pneumothorax may be helpful in diagnosis, particularly in differentiating simple tumours in the periphery of the lung, growths in the mediastinum and in the chest-wall.

The Pancoast tumour may give rise to special difficulty. It has to be differentiated from syringomyelia, cervical rib, apical pulmonary tuberculosis and secondary sarcoma.

**Course.**—This is progressive, the patient gradually losing strength and dying from cachexia or some intercurrent affection.

**Prognosis.**—Apart from those cases in which early recognition may in suitable conditions render lobectomy or pneumonectomy, with removal of the growth, possible, this is hopeless, death occurring in a few weeks, or being delayed for 2 or 3 years. The possibility of a successful pneumonectomy is more favourable with differentiated than with undifferentiated types of growth. In the latter the growth tends to be more infiltrating and the glands are more likely to be involved.

**Treatment.**—Benign tumours are often capable of complete removal with gratifying success.

In malignant growths lobectomy or dissection pneumonectomy with complete removal of the growth is only practicable for cases recognised early in which there are no secondary deposits.

Radiotherapy may be useful by diminishing local pressure and relieving symptoms, but cure by this method is rare.

Useless cough should be checked by sedative lozenges or a linctus. Dyspnoea due to pleural effusion may be relieved by tapping with or without air replacement; but the fluid often reaccumulates rapidly. Pain should be relieved by analgesic drugs, and in the later stages those containing opium or its alkaloids may be required.

## TROPICAL DISEASES OF THE LUNG

**Paragonimiasis or Distomatosis.**—Paragonimiasis is a disease contracted in parts of Korea, Japan, Formosa or China by bathing in, or drinking, infected water, or eating raw crabs or crayfish. The symptoms of cough, hæmoptysis and pleurisy are caused by the invasion of the lung by flukes.

**Pulmonary Schistosomiasis.**—This disease is found in North and South Africa and particularly in Egypt. It also occurs in South America and the West Indies. It is caused by the invasion of the lung by the ova of *S. hematobium* or *S. mansoni*. The ova form "tubercles" and there is an obliterating endarteritis of the arterioles.

These eventually cause pulmonary hypertension, angiomas and pulmonary artery dilatation.

**Pulmonary Amœbiasis.**—Invasion of the lung by *Entamoeba histolytica* is usually by direct spread from a hepatic abscess although primary amœbic abscesses, presumably embolic, have been described. Invasion is usually accompanied by effusion or empyema. The sputum coughed up from the abscess is described as being like anchovy paste and this is an apt description, although similar sputum sometimes occurs in pulmonary abscess not of amœbic origin.

Amœbiasis is a disease of world-wide distribution. It is not strictly a tropical disease but it only assumes serious proportions where sanitation is defective or human excrement is used in agriculture.

Emetine is usually effective in this condition combined with penicillin or other antibiotics.

## CYSTIC DISEASE OF THE LUNG

**Ætiology.**—Cysts may be congenital or acquired.

(i) **Congenital cysts** are lined with respiratory epithelium and have a wall in which elements of the bronchial wall are present. They do not always possess any obvious connection with a patent bronchus and are often associated with congenital abnormalities of the heart or skeleton or with cystic disease in other organs. The following varieties are described: (a) The solitary cyst. This may occasionally be inflated to balloon-like size and be mistaken for a pneumothorax. (b) Multiple cysts giving rise to either a soap bubble or honeycomb appearance of a lobe or lobes. The cysts usually contain air but may contain clear mucinous fluid or they may become full of pus if they are secondarily infected.

(ii) **Acquired Cystic Disease.**—Some doubt has been expressed as to whether cystic bronchiectasis is an acquired condition or represents infection of a congenital cystic condition of the lung. It is, however, probable that cystic bronchiectasis is the result of bronchiectasis acquired in early life. Cystic bronchiectasis has a characteristic multilocular radiological appearance usually in a lower lobe. Operative removal is advisable to prevent complications, although this type of bronchiectasis often has a relatively benign course. In staphylococcal pneumonia, thin-walled abscesses or cysts often appear and usually disappear by reabsorption. Occasionally the cysts remain and may give rise to no symptoms, although they are sometimes associated with bronchiectasis. They are probably caused by local alveolar distension due to the check-valve action of a partly occluded bronchus. The "ring" shadows of tuberculosis are of a similar nature, and cysts and cavities similar in character occasionally occur in asthmatics.

**Symptoms.**—These vary with the variety of cyst present. The large balloon cyst, met with in infants or young children, may result in severe respiratory and cardiac distress. In such cases there is cyanosis, dyspnoea and displacement of the trachea, mediastinum and heart to the opposite side of the chest. The percussion note over the cyst is hyper-resonant and the breath-sounds are absent. Solitary cysts often give rise to no symptoms and are only discovered on routine radiographic examination. When infected the clinical features may resemble those of lung abscess or bronchiectasis. With multiple medium-sized or small cysts no symptoms usually appear until infection occurs, though hæmoptysis may occur early. When infected, toxic symptoms develop, such as loss of weight, irregular fever, cough and expectoration which is sometimes offensive. Clubbing of the fingers may then soon be noted. On examination scattered areas of slight dullness, and weak air entry with a few persistent râles may be detected.

**Course, Complications and Sequelæ.**—The onset of complications usually

leads to the development of symptoms which call for investigation. Thus spontaneous pneumothorax may result from rupture of a cyst. In other cases suppuration occurs in the cyst with the formation of lung abscess, bronchiectasis or empyema. Cerebral abscess may be a late sequel.

**Diagnosis.**—This is suggested by radiography and by lipiodol examinations and possibly tomography. If the space in the cyst is free from fluid the radiographic appearances must be differentiated from those of pneumothorax, an emphysematous bulla, a thin-walled tuberculous cavity or, in some cases, a diaphragmatic hernia. If the cyst contains fluid, further investigations are required to exclude the presence of such conditions as lung abscess, encysted pleural effusion or empyema, hydatid cyst, dermoid cyst or a blood cyst. A definite diagnosis can sometimes only be made after operation by microscopical examination of a portion of the cyst.

**Prognosis.**—This varies with the type of cyst present, the development of complications, and the treatment adopted. In many cases the prognosis is good, apart from rupture or infection. In the large balloon cyst there is risk of sudden death during an attack of distension.

**Treatment.**—The large balloon cysts which are causing respiratory and cardiac embarrassment call for immediate treatment by the insertion of a needle. Subsequently the only hope of recovery lies in pneumonectomy.

When the cysts are infected, treatment by postural drainage should first be adopted. Failure usually follows attempts at surgical drainage or collapse operations. If the cysts are unilateral and infected, the only hope of cure lies in radical removal of the portion of lung involved, either by segmental resection, lobectomy or pneumonectomy; and so in bilateral cases it necessarily follows that no radical cure is possible.

## SARCOIDOSIS OF THE LUNG

Sarcoidosis is really a generalised disease, but it occurs often enough in the lungs to merit a separate description.

There are two main pulmonary forms. One in which the glands are predominantly involved and one in which there is generalised pulmonary infiltration. There is, however, no hard-and-fast division between the two conditions. The enlarged hilar glands are the commonest form and have been found to be common as a result of mass radiography. They usually cause no symptoms at all but they may be associated with other lesions in the bones, the eyes or the skin. Sometimes the discovery is made as the result of a chest radiograph suggested by the appearance of erythema nodosum. The differential diagnosis is from the adenitis of primary tuberculosis, lymphosarcoma and Hodgkin's disease, and other conditions causing mediastinal enlargement.

The glands of sarcoidosis are usually discrete from each other, well demarcated and bilateral. They may persist for months but their disappearance can often be measured in weeks. The Mantoux test is usually negative. The generalised pulmonary form sometimes follows the glandular form but if it always does, the glandular enlargement stage is often missed. The infiltration has the radiological appearance of miliary tuberculosis, pneumoconiosis or carcinomatosis. The nodules may be as small as the nodules of miliary tuberculosis but are sometimes larger and coarser. The hilar glands are often enlarged but not necessarily so. The commonest physical signs are similar to those of miliary tuberculosis, namely, generalised crepitations or fine râles.

**Symptoms.**—There are often no symptoms at all in either form, and the absence of symptoms is often strikingly at variance with the extensive radiological findings. Shortness of breath and slight cough are sometimes complained of.

**Course.**—The enlarged hilar glands often disappear in a few weeks or months. Sometimes the glands remain visibly enlarged after the main enlargement has disappeared. The miliary type of lesion may disappear completely with the passage of months but more frequently some striated opacity suggestive of fibrosis remains in some areas. Occasionally diffuse generalised fibrosis leading to cor pulmonale is described as a late result of miliary sarcoidosis. While cases of diffuse pulmonary fibrosis have been described as cases of sarcoidosis there is often no pathological evidence at post mortem of any sarcoïd changes.

Cavitation has occasionally been observed in cases diagnosed as sarcoidosis. Naturally such an event suggests a diagnosis of tuberculosis but cavitation probably occurs occasionally without tuberculous involvement. Some cases of sarcoidosis eventually develop pulmonary tuberculosis, but this is not evidence that sarcoidosis is a form of tuberculosis any more than is, for example, pneumoconiosis which is often complicated by tuberculosis. The course of sarcoidosis is usually benign.

**Diagnosis.**—This is almost entirely radiological and therefore open to errors of interpretation. Occasionally the presence of enlarged groups of glands or the co-existence of other sarcoïd lesion confirms the prescriptive diagnosis. In the majority of cases the Mantoux test is negative.

**Treatment.**—Most cases recover during or in spite of treatment. Streptomycin may be worth trying. Calciferol in large doses is sometimes given and cases have recovered during either of these treatments. Corticotrophin and cortisone are reported to produce symptomatic relief with or without streptomycin but are not usually necessary.

## HYDATID DISEASE OF THE LUNG

Hydatid cysts may develop in the lung in patients infected by the ova of the *Tænia echinococcus*.

**Ætiology.**—Man is the intermediate host of this parasite, and becomes infected directly or indirectly from the dog. The modes of infection and the life-history of the parasite are elsewhere considered (p. 324). Males are more often affected and the condition is commoner amongst agricultural labourers, especially amongst shepherds and dog handlers. In Great Britain it is occasionally found in Wales. It is common in the more primitive rural districts of the continent and especially in Argentina, Australia, New Zealand and the Middle East.

**Pathology.**—Hydatid cysts have been described in the lungs in from 5.6 to 16.8 per cent. of cases of hydatid disease in different parts of the world. The right lung is more often the site of the disease than the left, and the cyst is usually basic, though it may occur in the upper parts of the lung. It is generally supposed that infection of the lung is usually secondary to the liver, the ova reaching the lung through the diaphragm; but the occurrence of primary lung hydatid suggests the possibility of the embryo gaining access to the general blood-stream, and thus reaching the lung by the pulmonary artery. There is, as a rule, a single cyst in the lung, but multiple or multilocular cysts are occasionally observed. The cyst may become as large as a cricket ball, but usually ruptures before it reaches this size. It has the same structure as hydatid cysts of other organs, with ectocyst and endocyst. It may develop brood capsules and daughter cysts, but is often sterile in this situation.

The reactive changes in the lungs are at first irritative and congestive, but eventually some fibroid changes occur, producing a more or less definite fibroid capsule around the ectocyst. The overlying pleura may become inflamed, thickened and adherent when the cyst grows near the surface. Rupture may occur into a bronchus, into the pleura, pericardium or peritoneum, or occasionally into the aorta or pulmonary vein. Rarely the contents of a small cyst may become inspissated, thus producing spontaneous cure.

**Symptoms.**—Until the cyst becomes large enough to cause irritation, there may be no symptoms, but sooner or later cough and expectoration develop. The latter is generally mucoid, and frequently bloodstained. Dyspnoea becomes apparent and pain results if the pleura is involved. The signs may be: diminished vocal fremitus, localised dullness and weak or absent breath-sounds and voice-sounds over a limited area, generally in the lower lobe. A few râles may be audible round the dull area. Occasionally with a large cyst there may be some bulging on the affected side, and "hydatid fremitus" has been described. The heart may be displaced in rare cases. Radiographic examination generally shows a suggestive rounded shadow with very little change in the surrounding lung, except in chronic cases where some fibrosis may be observed.

Some degree of eosinophilia is common but not invariable. When rupture into a bronchus occurs, there is usually sudden copious expectoration of watery fluid containing hooklets. Daughter cysts and parts of the ectocyst may be coughed up and lead to dyspnoea and even suffocation from laryngeal obstruction.

After rupture, spontaneous cure may result if the ectocyst is expectorated. More commonly the cavity becomes infected, and the symptoms and signs become those of chronic abscess (see pp. 324, 1002). Rupture into the pleural cavity produces great pain, dyspnoea, cyanosis and shock, similar to the condition induced by pneumothorax. Rupture into the pericardium or into a vein is usually quickly fatal. When rupture occurs into a serous cavity, urticaria and severe toxic symptoms sometimes develop.

**Diagnosis.**—The clinical features of pulmonary hydatid may be suggestive of pulmonary tuberculosis, pleural effusion or new-growth. Diagnosis may be difficult before rupture occurs; after this the discovery of hydatid hooklets or pieces of cyst-wall may establish the diagnosis. In suspicious cases the radiographic findings may be of great assistance, and confirmatory evidence may be obtained from cytological and serological examination. The former frequently shows eosinophilia, and the latter gives complement deviation when a suitable antigen, such as extract of hydatid cyst-wall, is used. A precipitin reaction may also be obtained with the fluid from another cyst. The Casoni intradermal test with the appropriate antigen has established itself as having special diagnostic value.

**Course.**—This is generally progressive, though occasionally spontaneous cure occurs either before or after rupture. More commonly the cyst causes increasing pressure or irritative symptoms, and eventually rupture or suppuration produces acute manifestations.

**Prognosis.**—The prognosis is serious owing to the risks of rupture and suppuration. Spontaneous cure is rare, but can occur. After rupture into a bronchus, recovery may ensue, but more commonly abscess formation results. Rupture into a serous cavity is frequently fatal. Early surgical treatment either before or after rupture improves the outlook.

**Treatment.**—Aspiration of the cyst, either exploratory or therapeutic, is to be avoided. If the cyst can be diagnosed or localised before rupture, the lung should be exposed by thoracotomy, the pleura stitched together and the cyst incised, the endocyst removed and the cavity drained. Suppuration of a pulmonary hydatid must be treated as a pulmonary abscess. Removal of a lobe containing a single cyst may be the operation of choice.

## THE PNEUMONIAS

The ideal classification of the pneumonias would be an ætiological one and the old morbid anatomical distinction between lobar pneumonia, on the one hand, and lobular or broncho-pneumonia, on the other, would be even less important than it

has already been made by modern therapy. Scadding has devised a classification which ignores rigid morbid anatomical divisions and divides pneumonias into two main groups :

- (1) The acute specific pneumonias whose ætiology is more or less known, and
- (2) The aspiration pneumonias which include most of what used to be called broncho-pneumonias.

By using the term "aspiration pneumonia" he wished to indicate that the inflammatory changes were due to the aspiration of infected secretion, where there has been a breakdown in normal defensive mechanisms. Most of the broncho-pneumonias follow atelectasis produced by aspiration and the term aspiration, therefore, has ætiological significance. It is unlikely, however, to replace the well-established term broncho-pneumonia, which suggests very well pneumonia following bronchial infection. No exact classification can be made without certainty about ætiology, and the distinction between various anatomical types is often impossible and unnecessary, as they merge into each other. In the descriptions which follow, no hard-and-fast classification has been attempted, but the anatomical division into lobar pneumonias and broncho-pneumonias will be referred to since it has sometimes diagnostic significance.

### LOBAR PNEUMONIA

This term has become almost synonymous with pneumococcal pneumonia and this condition will be described first, although, as will appear, other pneumonias assume approximately lobar form.

### PNEUMOCOCCAL PNEUMONIA

*Ætiology.—Predisposing causes.*—Pneumonia may occur at any age. It is common in children up to the sixth year, the incidence being about equal in the two sexes. It is commonest between the ages of 15 and 40, when there is a preponderance in the male sex of 2 or 3 to 1. It is also a frequent terminal malady in the aged of both sexes. It may be doubted whether race has much influence, although in America and in the Rand mines and throughout Africa the incidence and mortality among the black races are both high. Pneumonia is met with all over the world. In this country its seasonal incidence is well marked; it is uncommon in the summer and autumn, and is most prevalent from November to March. Although pneumonia is, as a rule, endemic and sporadic in its incidence, it is generally admitted that localised epidemics occur. Urban conditions, defective sanitation, overcrowding and insufficient ventilation all conduce to the incidence of pneumonia. It is not uncommon to obtain a history of several previous attacks. Although the disease often attacks those in normal robust health, there can be no doubt that debilitating conditions and diseases predispose to it, among them being chronic nephritis, diabetes, over-fatigue, exposure and alcoholic excess.

*Exciting causes.*—The exciting cause in most cases is the presence of the pneumococcus (*Str. pneumoniae*). It may be the only pathogenic organism found in the lung lesions and in the sputum, but not infrequently others, such as streptococci, staphylococci or *H. influenzae* are also present.

*The pneumococcus.*—The pathogenicity of the pneumococcus has been the subject of an interesting study by Cole, Dochez, Avery and Gillespie and more recently by Georgina Cooper and her co-workers. Originally three types were described: Types I, II, III, which together account for more than 50 per cent. of all cases. The remainder were included in a group referred to as Group IV. This has now been separated into 29 other types, making 32 in all, by means of serological reactions.

The American observers have shown that 40 per cent. of contacts with cases of pneumonia due to types I and II may harbour the corresponding organism for an average of 23 days, and that they may develop pneumonia from it. They have further demonstrated that a convalescent patient may carry pathogenic pneumococci in his mouth for as long as 90 days from the onset of the disease. They have also found pathogenic pneumococci in the dust of rooms in which patients suffering from pneumonia have been nursed. The significance of this work is obvious. It confirms the view that pneumonia is an infectious disease, capable of being spread by carriers, by the convalescent patient, and by the dust of rooms.

Although the pneumococcus is the specific exciting cause, its activities are often determined by some other factor, such as chill, exposure, over-exertion or injury. The presumption is that these conditions lower the general resistance of the individual, and thus impair the defensive mechanisms. Post-operative pneumonia may be a further instance of this, but doubtless some supposed cases are in reality due to lobar collapse.

**Pathology.**—The pneumococcus is found in the pulmonary lesions and elsewhere when complications occur. In some patients it is found in the blood. These are referred to as bacteræmic cases and are usually more severe and often associated with complications. Experimental investigations on animals indicate that the avenue of infection to the lungs is by way of the trachea and bronchi, the blood infection being secondary to the pulmonary lesion. Four stages are commonly described in the process by which the lung becomes consolidated and returns to normal, namely, engorgement, red hepatisation, grey hepatisation and resolution.

In the stage of engorgement the affected part of the lung is slightly enlarged, deep red in colour and heavier than normal, although it still crepitates and floats in water. The pleura over it may be injected and lustreless and may even show early fibrinous exudate. On section, the hyperæmia is obvious and there may be some œdema. On squeezing, frothy, bloodstained fluid exudes. Microscopically, the engorgement of the capillaries, and the swelling and partial desquamation of the alveolar epithelium are the chief changes to be noted. In the stage of red hepatisation the affected area becomes completely consolidated, the general aspect on section being remotely similar to liver, hence the name hepatisation. The pleura is now notably inflamed and may be obscured by yellow fibrinous exudate. The hepatised area of lung is larger and much heavier than normal and bears the impress of the ribs upon it. On section, it is seen to be red in colour, solid and completely airless. It does not crepitate and it sinks in water. The lung tissue is found to be more friable than normal. On scraping the cut surface, which has a granular appearance, a reddish fluid is collected, containing small fibrinous plugs, which are practically alveolar casts. Microscopically, the alveoli are occupied by a coagulated exudate rich in fibrin and red blood corpuscles, with scanty leucocytes and a few larger cells derived from the alveolar epithelium. In the stage of grey hepatisation the lung tissue, although still solid, airless and non-crepitant, is greyish in colour, softer in consistence and still more friable. The surface of the section is less granular, and on scraping, a pale-yellowish, almost purulent fluid is obtained. Microscopically, the blood vessels are found to be relatively empty, the alveoli are now incompletely filled, the fibrin and red corpuscles have largely disappeared, and the alveoli are occupied by leucocytes and desquamated alveolar cells. In the stage of resolution, the exudate becomes more liquid and its cellular constituents undergo fatty degeneration. The liquefied exudate is largely absorbed, although expectoration may possibly assist in its removal. The lung returns to its normal spongy state and the alveolar epithelium is replaced. Some pleural thickening or adhesion may, however, result. In very severe and fatal cases, the stage of resolution may be replaced by one of purulent infiltration, in which the lung becomes paler, softer and in places almost diffuent. The scrapings are practically purulent.

Although these four stages are described, it should be remembered that they are



not sharply defined from one another, and that they only represent special appearances in a continuous process. Consequently, although the major part of the affected area of lung may be characteristic of any one of them, all four stages may be recognisable, especially in cases of a spreading type. The base is more often affected than other parts, and the right side more than the left, in the ratio of 3 to 2. The unaffected parts of the lung may show some catarrhal bronchitis, or some degree of collateral hyperæmia or œdema. Pleurisy is an integral part of the affection, but it may proceed to serous or purulent effusion. Pericarditis and less frequently acute endocarditis may be found in fatal cases. Pneumococcal meningitis, arthritis and otitis are very occasionally observed. The liver and kidneys may show cloudy swelling, and the spleen is often slightly enlarged and soft. Jaundice may be observed, especially in right-sided cases. The right side of the heart may be engorged and dilated.

**Symptoms.**—The following description is based on the symptomatology and progress of a patient untreated with antibiotic therapy. There was great variation in both even before antibiotic therapy, but this has very much curtailed and altered the course of the disease. The exact incubation period is not yet established, but it is short, being probably from 1 or 2 days up to a week. The onset is sudden and acute, with chill, shivering or rigor in the majority of cases. In children convulsions take the place of rigors. Vomiting at the onset is not infrequent, occurring in about one-third of the cases. Less commonly the onset is insidious, or is preceded by malaise and catarrhal symptoms. The temperature rises with the rigor, and, as a rule, a short, dry, irritating cough develops quickly, accompanied by a severe cutting pain on the affected side. The pain often becomes intense, and coughing may cause the patient great distress. The cough is frequently restrained as much as possible, and the breathing is rapid and shallow. By the second or third day the pain becomes less and the cough easier and more effective. Sputum, which at first is scanty, extremely viscid, tenacious and difficult to expectorate, now becomes more abundant, although remaining viscid. In typical cases it is characteristically rusty at this stage, containing mucus, altered red blood corpuscles, alveolar epithelium and large numbers of pneumococci. In a few instances a small but definite hæmoptysis occurs. Occasionally the sputum is thinner and of "prune juice" type.

Sleeplessness is often a distressing symptom, especially in the early and late stages. In some cases there are marked cerebral symptoms. Headache at the onset is common. Delirium is frequent, particularly in the asthenic type, in apical cases, and in alcoholics. In the latter it may be violent and is often like delirium tremens. The temperature is usually of high continuous type throughout, reaching 103°, 104° and even 105° F. or more on occasions. Defervescence is by crisis in about 60 per cent. of the cases. The most common day for the crisis is the seventh. It is rare before the third or after the ninth day. At the crisis the temperature falls to normal or subnormal in about 12 hours. The patient often sleeps soundly at this time and may sweat profusely; respiration is slower and easier and the pulse-rate falls. On waking, a dramatic change in the condition is usually noticeable. Pain and distress are ameliorated, cough is loose and easy, and the patient feels better, although weak. Looseness of the bowels and free diuresis are not infrequent, constituting the "critical evacuations". The crisis is sometimes preceded by a pseudo-crisis, in which a considerable fall of temperature occurs, with little or no improvement in the general condition. A slight post-critical rise of temperature of 1° or 2° F. is sometimes seen, but, as a rule, the temperature remains subnormal for a few days and slowly returns to normal. The pulse-rate may be slow for a time. Convalescence is generally rapid, although in cases which have had marked delirium, some mental confusion may be present for a day or two. Defervescence by lysis is more common in asthenic patients. The temperature remits and may take from 2 to 4 days to reach normal or subnormal levels.

The physical signs vary with the stage of the disease. At first there is some

restlessness, but soon the patient assumes a dorsal decubitus, or lies more on the affected side. The cheeks are flushed, often markedly so on the side of the lesion. The eyes are bright, but the expression is one of pain or anxiety. A crop of herpes on the lips is very common. The tongue is thickly coated and white, becoming dry and cracked in bad cases at a later stage. The skin feels dry and pungently hot. The *alæ nasi* are in action, and in children a puff or grunt accompanies each expiration, while the pause follows inspiration, instead of expiration. The respiration and pulse-rate are increased, the former disproportionately, so that the pulse respiration ratio becomes 3 or even 2 to 1, instead of the normal 4 or 5 to 1.

In the early stage the pulmonary signs are slight. At the most there is lessened movement and diminished vocal fremitus over the affected area, with dubious impairment of note, weak air entry and possibly a few crepitations (indux) or pleural friction sounds, vocal resonance being unaltered. Of these, lessened air entry is probably the most common. Slight hyper-resonance of the opposite lung, with harsh breathing, may lead to error in diagnosis as to the side affected.

The signs of consolidation (hepatisation) are generally apparent on the second or third day, except in cases where the disease starts deeply (central pneumonia). There is definite limitation of movement on the affected side, which is, however, slightly increased in size, as can be demonstrated by mensuration. Vocal fremitus is markedly accentuated over the affected area, except in massive pneumonia, and friction fremitus may be palpable. The note on percussion is dull, but has not the resistant stony character of that over an effusion. The note above or below the consolidated area is sometimes skodaic. The breath-sounds are tubular, and a few crepitations may be heard, but frequently adventitious sounds are absent. In some cases a friction rub is audible. Bronchophony and pectoriloquy are usually very marked over the consolidated area. Whispering pectoriloquy usually corresponds exactly to the area of bronchial breathing and often draws attention to it. The breath-sounds in other parts may be vesicular or harsh, and a few rhonchi may be present. The heart is usually in its normal situation, but is sometimes slightly displaced away from the affected side. In later stages the signs of dilatation of the right heart may become apparent.

During resolution, which begins after the crisis or during lysis, the tubular character of the breath-sounds disappears. Coarse moist sounds, known as *redux* crepitations, are heard both with inspiration and with expiration. The dullness gradually diminishes, and the voice-sounds return to normal.

In basal cases, in which the diaphragmatic pleura is involved early, there may be pain, tenderness and abdominal rigidity simulating peritonitis, perforation or appendicitis. It is rare for the spleen to be sufficiently enlarged to be palpable. The blood shows a leucocytosis up to 20,000, occasionally up to 50,000 in young patients. A low white count in a very ill patient is an ominous sign. Blood culture may yield *pneumococci*, although this was successful in only 30 per cent. of cases at the Rockefeller Institute. The urine is diminished in quantity, and there is a great reduction in the sodium chloride excretion until the crisis. Albumin and albumose are frequently found in small quantities in the urine during the febrile stage, and a few granular casts may be present. The uric acid excretion is increased to two or three times the normal, commencing the day before the crisis and generally falling to normal during the ensuing week. This is probably due to disintegration of the exudate in the alveoli, and so forms a measure of resolution, although some authorities maintain that it runs parallel with leucocytosis and not with cell destruction. *Pneumococci* can sometimes be obtained from the urine at the height of the disease.

The stages of the disease are very considerably modified by the early administration of penicillin, and to a less extent by the use of sulphonamides. Thus, if the penicillin injections are begun on the first day of the disease, when the physical signs are slight, the temperature will often fall to normal within 24 to 48 hours, with a

corresponding reduction in the pulse and respiration rates. The general condition of the patient also rapidly improves, pain disappears and toxic symptoms are abolished. On the second or third day, however, the physical signs of consolidation may be well marked, despite the absence of all signs of toxicity.

The disease does not always follow the typical clinical course, and certain varieties are described :

*Apical pneumonia.*—The consolidation may be limited to the apex or upper lobe of one lung. This is more common in children, the aged and alcoholics, and is often associated with marked cerebral symptoms.

*Creeping pneumonia (Migratory or wandering pneumonia).*—The consolidation spreads irregularly in one or both lungs. Partial resolution occurs, but there is no true crisis, and as successive portions of the lungs become involved the temperature exacerbates, eventually falling by lysis in cases that recover.

*Central pneumonia.*—The symptoms and appearance of the patient may suggest lobar pneumonia, and yet no abnormal signs can be detected in the lungs. In some of these cases there may be a deep-seated consolidation, which can usually be revealed by radiography. A typical crisis may occur.

*Massive pneumonia.*—The bronchi, as well as the alveoli, may be filled with a fibrinous exudate. It is a rare condition and leads to difficulty in diagnosis, as the physical signs resemble those of pleurisy with effusion, vocal fremitus being diminished and breath-sounds weak or absent. The heart, however, is not displaced, or only slightly so.

*Post-operative pneumonia.*—It is probable that some cases that were formerly described as post-operative pneumonia were in reality instances of massive lobar collapse (see p. 992). At times a pneumococcal pneumonia follows the administration of a general anæsthetic, but it does not present any peculiar features.

*Traumatic pneumonia.*—The fact that an injury to the chest may be followed after a short interval by a pneumonic process in the lungs has long been recognised. The condition was called "contusional pneumonia" by Litten in 1881. Külsb showed later that the changes in the lungs in dogs following local trauma were mainly hæmorrhagic, and that the lung opposite to the side injured may be affected by "contre-coup". In the recorded cases of traumatic pneumonia two types can be differentiated—(1) those with hæmorrhagic lesions only, and (2) those showing hæmorrhagic foci with a superimposed bacterial infection. The former recover rapidly, the latter often lead to a fatal issue. Both these types are found in blast injury to the lung produced by close proximity to explosions in air or in water.

*Pneumonia in children.*—This often presents certain characteristic features. There is rarely any sputum, the expectoration being swallowed. Convulsions at the onset are common. The lesion is often at the apex of the lung. Cerebral symptoms are frequent, and empyema or otitis media often occurs as a complication.

*Pneumonia in the aged.*—This occurs frequently as a terminal infection, often leading to a rapid and comparatively painless death. The onset may be insidious and the physical signs slight.

In *pneumonia in the insane*, lobar consolidation is often observed, without marked constitutional disturbance other than fever.

*Secondary pneumonia.*—Lobar pneumonia may develop during the course of certain acute specific fevers, notably enteric, typhus and plague. It is doubtful whether a true lobar pneumonia occurs in influenza, the condition to which the name influenzal pneumonia is applied being due to coalescing lobar pneumonia with hæmorrhagic extravasations.

*Complications.*—Delayed resolution not infrequently occurs, the signs of consolidation persisting for weeks instead of days. Frequent careful examinations should be made and possible errors in diagnosis considered, such as the presence of tuberculosis or empyema. Gangrene and abscess are rare but recognised complications.

Dry pleurisy is an invariable accompaniment when the consolidation reaches the surface, and in a considerable proportion of cases slight serous effusion occurs. This occasionally becomes frankly purulent and an empyema results. Bronchitis is common and may be due to a complicating secondary infection. Cardiac failure is a grave occurrence and can be recognised by increasing cyanosis, lividity and dyspnoea, with signs of enlargement of the right heart and with enfeeblement of the heart-sounds. Pericarditis is not very uncommon and is a serious complication. It may be dry or proceed to serous or purulent effusion. Acute endocarditis, sometimes of infective type, occurs. Abdominal complications are comparatively rare. They include pneumococcal peritonitis, colitis and nephritis. Acute dilatation of the stomach occurs in rare cases, and is usually rapidly fatal. Meteorism is more common and, although serious, is more amenable to treatment. Jaundice, due to hepatitis, or to hæmolytic, is sometimes present.

Pneumococcal meningitis supervenes in rare cases, and was invariably fatal before the use of sulphonamides and penicillin. Delirium has already been referred to, and is especially serious when occurring in alcoholics. Peripheral neuritis has been described, but is very uncommon. Otitis media and arthritis, proceeding sometimes to suppuration, occur as complications, both being commoner in children. A parotitis, sometimes going on to suppuration, is an occasional and serious complication, especially in old people. During convalescence, thrombosis of the veins of the legs may occur in rare instances.

Sequelæ of lobar pneumonia are uncommon. Perhaps the most remarkable is the liability to subsequent attacks, although a history of repeated attacks of "pneumonia" often suggests a diagnosis of bronchiectasis with recurrent pneumonitis. Some permanent pleural thickening or adhesion may occur, and after an empyema the usual sequelæ may result. Pulmonary fibrosis (chronic interstitial pneumonia) is rare, especially in comparison with its frequency after broncho-pneumonia; this may lead to bronchiectasis.

**Diagnosis.**—When the disease is well established and the history is available, diagnosis is, as a rule, easy. To prove the pneumococcal origin, sputum examination, lung puncture or blood culture is necessary.

At the onset, especially before the signs of consolidation develop, difficulties in diagnosis often occur. The initial rigor or convulsion with vomiting may suggest scarlet fever. In children, especially those with early apical pneumonia, headache, vomiting, convulsions, head retraction, squint and even slight Kernig's sign may lead to an erroneous diagnosis of meningitis. Pain in the side and cough, the altered pulse respiration ratio and the presence even of slight abnormal physical signs in the chest, usually suffice in both instances to suggest the correct explanation.

Occasionally the onset of pneumonia may simulate an acute abdominal condition, such as appendicitis or perforation of a gastric ulcer, owing to referred abdominal pain, sometimes with rigidity. The diagnosis may be very difficult, and laparotomy has not infrequently been carried out in error. The history, the pulse respiration ratio, the absence of tenderness on rectal examination and the presence of pulmonary signs usually enable a correct decision to be made.

Influenza may start acutely and simulate pneumonia, but the distribution of the signs and the examination of the sputum generally serve to distinguish between them. Typhoid fever less often gives rise to difficulty, but some cases of pneumonia pass quickly into a typhoid state, while some cases of typhoid fever develop consolidation in the first week.

When consolidation is well established, the chief conditions to be differentiated are—(1) Broncho-pneumonia. The slower onset, the more prolonged course, the bilateral patchy physical signs, and the marked predominance of the bronchitic manifestations usually suffice to differentiate this group of conditions. (2) Secondary pneumonias, such as those in plague, typhoid fever, and influenza, can be diagnosed

only from the history, the associated symptoms and signs, and from the bacteriological examinations. (3) Friedländer's pneumonia is rare. Its course is short, its prognosis grave, and it can only be recognised by bacteriological investigation. (4) Massive collapse. The diagnosis of this condition and its differentiation from pneumonia are discussed on p. 993. (5) Acute pneumonic tuberculosis. The onset and early signs may be identical with those of pneumonia. The persistence of the fever, its tendency to become remittent or intermittent and the occurrence of night sweats should suggest looking for tubercle bacilli in the sputum. (6) Pleural effusion and empyema. Differentiation is generally easy, except in cases of massive pneumonia. Investigation of the position of the cardiac impulse, and of vocal fremitus and resonance, affords the most valuable aid. Grocco's triangle may also assist. In some cases the diagnosis can only be established by the exploring needle. (7) Infarction of the lung in cardiac disease, causing pain, cough, bloodstained expectoration and dyspnoea, may simulate pneumonia. The absence of fever, the presence of the cardiac condition and the localised physical signs are generally characteristic. (8) Acute oedema of the lung, especially in mitral stenosis, may suggest pneumonia. Fever is generally absent, the sputum is typical, and the primary cause may be apparent. An attack of paroxysmal tachycardia may give rise to difficulty, when it leads to dullness and crepitations at the bases, but careful examination should establish the very rapid action of the heart and the evidence of venous engorgement in other parts.

**Course.**—The course depends on the type and virulence of the infection, on the resistance of the patient and the method of treatment employed. Since the use of sulphonamides and penicillin in treatment, the course is much more favourable and the temperature usually falls to normal or subnormal in 2 or 3 days. In fatal cases, death commonly occurs between the fourth and tenth days, although severe cases may prove fatal as early as the first or second day. After the tenth day a fatal result is generally due to complications.

**Prognosis.**—Lobar pneumonia is a serious disease. The prognosis is profoundly influenced by age and by recent methods of treatment. It is infrequently fatal in childhood, except in the first years of life. After the age of 60, the mortality, until the new chemo-therapeutic measures were employed, was from 60 to 80 per cent. The New York investigations at the Rockefeller Institute demonstrated the importance of the type of pneumococcus in prognosis; thus, it was found that the mortality of cases with types I and II was about 25 to 30 per cent., of those with type III 50 per cent., and of other types collectively only 12 per cent. The mortality in Great Britain before the use of sulphapyridine about the year 1938 was never as high as in the U.S.A., being at the outside about 16 to 20 per cent. in groups of all ages. With the sulphonamides and penicillin the average mortality of all types has been reduced to about 8 per cent.

The previous habits and history of the patient influence prognosis considerably; chronic alcoholism doubles the risk of a fatal issue, and the outlook is grave in patients who are the subjects of diabetes, chronic cardio-vascular disease, nephritis, marked debility or obesity. Unfavourable indications during the course of the disease are profound toxæmia, a pulse-rate persistently 130 or more, a blood pressure in millimetres of mercury lower than the pulse-rate, and a temperature remaining at 105° F. or over for several days. Absence of the usual leucocytosis is generally of sinister import. Dilatation of the right heart, with cyanosis progressing to lividity, is most grave.

Of complications, meningitis is serious, unless it responds to treatment by sulphonamides or penicillin, while septic endocarditis is extremely grave. Cases with abscess or gangrene, although serious, sometimes recover, especially if operative treatment is practicable. The prognosis of those with pericarditis is serious, but not uniformly unfavourable. Cases with bilateral empyemata show a high mortality. Late delirium is a very serious indication.

**Treatment.**—The patient should lie in a narrow bed away from a wall to facilitate

nursing. The room should be well ventilated, and the temperature maintained at 60° to 65° F. Treatment in the open air is not advisable except in very mild weather. Two important factors are rest and sleep. The patient should, therefore, be disturbed as little as possible by the examination of the physician and by the attentions of the nurse. His position in bed should be dictated by his own preference but most patients prefer to be propped up on two pillows. In severe cases where the patient tends to be immobile on his back, he must be turned to either side to prevent postural collapse. The patient usually has no appetite during the acute stage. He should, however, be encouraged to drink 3 or 4 pints daily of sweetened fluid flavoured with fruit juice. Sweetened milk suitably flavoured should be given if liked, but too much milk is not well tolerated. Soups with a little extra salt help to prevent salt depletion. As the temperature falls and appetite returns a digestible but high calorie diet should be encouraged.

The irritating cough which is so painful at the outset should be checked by a sedative linctus, but it may be necessary to inject gr.  $\frac{1}{2}$  diamorphine hydrochloride or gr.  $\frac{1}{4}$  morphine to reduce the pain and induce sleep in the early stage. The application of a kaolin poultice or Antiphlogistine is traditional and may afford some relief. Severe pain can be controlled by properly applied strapping. This has the theoretical disadvantage of diminishing movement and thus encouraging collapse, but nothing is more likely to prevent coughing up of sputum from the affected lung than severe pain. If strapping is applied it should be removed as soon as possible.

The sulphonamide group of drugs is very effective. Sulphadimidine is probably the best for an adult and the treatment should be started with an initial dose of 3 g. followed by 1 g. 4-hourly until the temperature has been normal for 36 hours and then progressively diminished until the treatment stops about 5 days after the fall of the temperature. The sputum should be taken for cultivation before treatment starts so that if there is no response to treatment the results of sensitivity will be available to guide any change in therapy.

The dosage in children depends on the body-weight, but as a rough guide an initial dose of 0.5 g. should be given to a child from 0 to 1 year with a maintenance dose of 1.0 to 1.5 g. in the 24 hours, and from age 1 to 3, 1.0 and 2.0 g. to 3.0 g. as maintenance and so up in proportion.

If there is any doubt about the response, or the patient is sensitive to sulphonamides or is very ill, it is wise to give penicillin instead of, or as well as, the sulphonamides. Particular care must be taken to see that these dehydrated patients have an adequate fluid intake and output during sulphonamide therapy.

If there is any cyanosis the patient should be given oxygen preferably in an oxygen tent. The B.L.B. mask, unless carefully supervised, is often ineffective, and in any case the cough and sputum complicate the use of a mask. If a tent is not available the nasal catheter in the naso-pharynx is better than the mask in most cases.

Digitalis is often given in small doses but is probably of no value. Injections of nikethamide (Coramine) are not of proved value but they are sometimes comforting to the patient and the doctor. Sleeplessness is a frequent and distressing symptom. In the early stages gr. 10 of Dover's powder or an injection of gr.  $\frac{1}{4}$  or  $\frac{1}{2}$  morphine are usually effective. It is best to avoid morphine if the patient is cyanosed. Chloral hydrate gr. 20 and potassium bromide gr. 20 can be tried, or amylobarbitone (Sodium Amytal) gr. 3 to 6. Paraldehyde min. 120, with syrup of orange in 2 oz. of water, is safe, or it can be given rectally in doses of 4 to 6 drams in 6 oz. of water.

If there is any tendency to delirium, the patient should have tepid sponging and be given any of the sedatives mentioned previously. They should not be left unattended as they are liable to get out of bed and fall down stairs or out of windows. Tympanites, when present, is distressing and exhausting and should be treated by the passing of a rectal tube or by giving an enema. Pituitary extract (0.5 ml.) or neostigmine (1 mg.) may be tried.

*Streptococcal pneumonia.*—This is often lobular but may be confluent so as to appear lobar. It usually follows streptococcal infection in other parts of the body, especially the throat or the skin. It is sometimes found as a secondary invader in nasal infections of the respiratory tract such as influenza or measles, but it occurs as a primary infection of the lung. The symptoms are often severe and the patient may appear more ill than in pneumococcal pneumonia. Thin purulent effusions (sometimes bilateral) occur at an early stage and require aspiration.

General treatment is as for pneumococcal pneumonias. Most streptococci respond readily to sulphonamide drugs or penicillin.

*Staphylococcal pneumonia.*—Staphylococci are found as secondary invaders in viral pneumonias but they also cause a particular type of pneumonia. The infection is usually blood-borne but may be bronchogenic. It may occur as a complication of a septicæmia or a pyæmia arising from a carbuncle, perinephric abscess, mastoiditis or some other focal lesion, but sometimes the source is not obvious. There is consolidation of varying degree not often conforming to any exact lobar pattern, with a tendency to necrose and form thin-walled distension cavities. Several areas of the lungs may be successively involved. Spontaneous pneumothorax may occur through rupture of the thin-walled cavities but it is not always followed by empyema as might be expected, and the cavities often disappear spontaneously. After recovery the cavities sometimes remain as thin-walled cysts. Bronchiectasis may be a complication.

General treatment is the same as described above, but large doses of penicillin and sulphonamides should be given. Many cases are resistant to penicillin but respond to the tetracyclines or erythromycin.

*Friedländer bacillus pneumonia.*—This organism causes pneumonia with a high mortality, especially in older patients. Prostration and cyanosis are often striking and the most seriously ill patients have little pyrexia and often a leucopenia. Death often occurs within 48 hours of onset. The organisms are not sensitive to penicillin or the sulphonamides but may be to streptomycin, chloramphenicol or chlortetracycline.

There is a chronic form of lung infection due to this organism which sometimes follows the acute infection but may also occur insidiously. The cases are often mistaken for fibrocascous tuberculosis which they resemble.

*P. pestis pneumonia.* This infection sometimes assumes a pneumonic form which is particularly lethal and infectious. It has been described in epidemics in Manchuria and West Africa.

*Myc. tuberculosis.*—Pneumonia due to this organism is described elsewhere, but although it is now rare in Great Britain it is occasionally mistaken at the outset for pneumococcal pneumonia and it must be remembered as a possibility when a lobar pneumonia does not quickly yield to treatment.

## PNEUMONIAS OF VIRAL ORIGIN

*Influenzal pneumonia.*—In 1933 Smith Andrews and Laidlaw showed that influenza was due to a filtrable virus of which two main strains labelled A and B respectively have been isolated. Influenza, a highly contagious disease, usually presents with fever, marked prostration, general aches, and inflammatory changes in the respiratory tract. Although it is often followed by marked depression, it is rarely fatal in otherwise healthy adults but occasionally pandemics occur in which pneumonia occurs and the disease is rapidly and frequently fatal. The pneumonia in these cases has been ascribed to secondary invaders amongst them *Hæmophilus influenzae*, streptococci, staphylococci, etc.

*Primary atypical pneumonia.*—Synonym, Virus Pneumonia.—This diagnosis probably includes a varied group of diseases. It was recognised before the war of 1914–1918, but came into prominence during the recent war as a result of the large epidemics which occurred amongst soldiers especially in the Mediterranean theatre.

**Pathology.**—Little is known of the post-mortem findings, as the mortality rate is low, about 0·2 per cent. Observations which have been made indicate that there is an interstitial broncho-pneumonia, with associated bronchitis, and areas of collapse and emphysema. The associated bronchi are filled with muco-pus. The inter-alveolar septa are infiltrated with monocytes.

**Symptoms.**—The incubation period varies from 2 to 21 days, or longer. The onset is often insidious with cough, malaise and muscular pains. Coryza may be marked at the onset, or there may be pain in the chest with dyspnoea. Some cases have been detected by routine radiographic examination of the lungs. Generally the temperature rises to 100° to 103° F. for about a week, but some cases are apyrexial. Cough may be very distressing, occurring in paroxysms and with severe headache. There is usually some mucoid sputum, at times blood-streaked, but never rusty. The sputum contains no predominating organisms, but mononuclear cells are often present. The physical signs in the lungs are rather indefinite. One or more areas of slight dullness may be detected, frequently at the bases, with weak air entry, and showers of medium râles heard after cough at the end of inspiration. The pulse-rate is often lower than would be expected from the pyrexia. The white cell count is usually normal or there may be slight leucopenia, and the sedimentation rate of the red cells is increased and may remain raised for some weeks or months. The Wassermann reaction may be positive for a short time. Cold agglutinins (auto-haemagglutinins) have been found in the blood from the second to the fourth weeks of the illness. Severe cases are also described with high irregular fever, prostration, a racking cough, cyanosis and dyspnoea. The temperature may remain raised for 2 to 3 weeks. There are no typical radiological findings. Woolly areas of consolidation of varying size may be seen, often at the bases, resembling those seen in chronic disseminated or local pneumonia. The hilar shadows are usually enlarged, more so than they are in early tuberculous lesions, and this may be of diagnostic importance.

**Complications and Sequelae.**—The majority of cases are uncomplicated but a pleural effusion may be expected in about 9 per cent. of cases, and this may be purulent. Rarely there are symptoms of encephalitis or meningism, venous thrombosis in the legs and polyarthritis.

**Diagnosis.**—Some cases have been diagnosed as tuberculosis, especially when the soft shadows are seen in the upper lobe. The prolonged febrile type with relative low pulse-rate and absence of leucocytosis may suggest typhoid fever. The presence of eosinophils in the sputum or the blood will help to differentiate Loeffler's syndrome, which sometimes resembles atypical pneumonia.

**Course.**—Febrile recurrences are not uncommon if the patient is allowed up too soon. Usually the patient is able to leave hospital in about a month from the onset. In some cases the radiographic shadows take 2 months or longer before they disappear.

**Prognosis.**—This is usually very good, although recovery may occasionally be slow.

**Treatment.**—The patient should be kept in bed for a few days after the temperature has returned to normal. He should not resume work until the sedimentation rate is normal and the radiographic findings are clear. Penicillin and the sulphonamides are useless and the sulphonamides may be harmful. Some cases respond well to chlortetracycline or chloramphenicol. Steam inhalations usually relieve the cough. Severe cyanosis or dyspnoea may be treated by oxygen inhalations.

**Psittacosis.**—This disease is transmitted by birds of the parrot family as its name implies, but it may be transmitted by other birds such as pigeons or canaries. The disease is similar to atypical pneumonia but is more severe and carries a mortality of up to 40 per cent. The diagnosis should be remembered where pneumonic symptoms are found in someone who is in close contact with birds kept as pets or professionally.



Chloramphenicol and chlortetracycline are often effective.

*Q fever*.—This is a rickettsial disease which resembles primary atypical pneumonia from which it can only be distinguished by agglutination reactions. Some of the epidemics of atypical pneumonia described in the Mediterranean theatre were of this character.

### PNEUMOCOCCAL LOBULAR PNEUMONIA

**Synonym.**—Primary Broncho-pneumonia.

**Ætiology.**—Pneumococcal infection in infants usually has a lobular form instead of a lobar one as in older children or adults. Lobular pneumonia is really a more correct name than broncho-pneumonia in this case, since there is no antecedent bronchial inflammation before the lobular pneumonia. It occurs equally in the two sexes and is commoner in the winter and the spring. Rickets, malnutrition and debility are predisposing conditions.

**Pathology.**—Widely scattered patches of consolidation are found in one or both lungs. These may be small and separated by areas of collapse or emphysema. Occasionally they are almost confluent and at first sight appear like lobar pneumonia, constituting the pseudo-lobar form; but careful observation shows that the distribution is lobular and that zones of incomplete consolidation or of normal lung tissue separate the solid areas. If the process reaches the surface some degree of pleurisy is present, although this is less than in lobar pneumonia.

Microscopically, the appearances approximate to those of the lobar form; the alveoli are found to be filled with exudate, in which leucocytes and desquamated epithelial cells are present, together with some fibrin and red blood corpuscles. Catarrhal changes are also present in the bronchi.

**Symptoms.**—The onset is acute, with vomiting and chill or convulsion, as in lobar pneumonia, but may be more gradual. Cough, cyanosis and dyspnoea develop rapidly. There is no expectoration, since infants and young children swallow the sputum. Cerebral symptoms simulating meningitis are common. The temperature rises quickly to 103°, 104° F. or higher, and the range is of the same character as in lobar pneumonia. Defervescence by lysis is the rule.

The physical signs are variable. In cases with widespread consolidation they are very similar to those of lobar pneumonia, with dullness, tubular breathing, increased voice-sounds and crepitations. In other cases, although the aspect of the infant appears characteristic of pneumonia, with rapid breathing, cyanosis, reversed rhythm of inspiration and expiration, sucking in of the lower ribs and dilation of the *alæ nasi*, the signs are more scattered. Tubular breathing and increased voice-sounds may only be heard in localised patches, especially in the lower lobes. Crepitations are commonly present, and rhonchi may be audible over both lungs.

**Complications and Sequelæ.**—These are similar to those of lobar pneumonia.

**Diagnosis.**—Pneumococcal lobular pneumonia has to be distinguished from the lobar form to which ætiologically and pathologically it is so closely related. The acute onset without previous respiratory symptoms will suggest its primary character, while the patchy distribution of the signs generally suffices to establish its lobular distribution. The cerebral symptoms at the onset, and the early absence of pulmonary signs may give rise to difficulty, as in the first stage of lobar pneumonia.

**Course.**—This is usually short, the temperature falling in from 3 to 7 days, but it may be more prolonged and be suggestive of tuberculosis, or some other form of secondary bronchitis.

**Prognosis.**—The prognosis is generally unfavourable, especially in very young or debilitated infants, but has been improved by the use of sulphonamides or penicillin.

**Treatment.**—This is practically identical with that of broncho-pneumonia in children.

## BRONCHO-PNEUMONIA

**Synonyms.**—Lobular Pneumonia, Aspiration Pneumonia, Secondary Broncho-pneumonia.

In this condition there is inflammation of the bronchi, spreading down to and involving the alveoli. It is generally a catarrhal process, but may go on to septic or suppurative manifestations.

**Ætiology.**—A secondary broncho-pneumonia may occur at any age, but is much more common in early and advanced life. It is equal in its incidence in the two sexes. It frequently occurs as a complication of measles, whooping-cough and influenza, less commonly in cases of diphtheria, scarlet fever and the enteric group. A bronchitis starting in the larger tubes may spread downwards to the alveoli. Broncho-pneumonia may develop during the course of acute gastro-enteritis. A secondary broncho-pneumonia occurs as a terminal infection in many old and debilitated persons and in those with chronic wasting or cachectic diseases, and also in chronic cardio-vascular conditions, chronic renal disease and in many progressive nerve degenerations.

**Bacteriology.**—This is, as might be expected, very varied. Streptococci are frequently present, especially the hæmolytic variety, generally associated with other organisms, such as the pneumococcus, *H. influenza*, staphylococci and those found in catarrhal conditions of the upper air-passages. *H. pertussis* may be found in cases associated with whooping-cough and occasionally *C. diphtheriæ* in diphtheritic broncho-pneumonia. The importance of Friedländer's bacillus was formerly overestimated in this connection.

**Pathology.**—When, from any of the above-mentioned causes, an inflammatory process reaches the finer bronchi, the alveoli become affected in three different ways. Owing to the blocking of the bronchi by secretion or exudate, small areas of collapse of lobular distribution are produced. The inflammatory process extends into some or all of these, and areas of lobular consolidation result. Not infrequently the adjacent groups of alveoli become distended and are thus in a condition of acute emphysema. The lungs are normal in size or slightly enlarged. The surface presents a somewhat uneven, mottled appearance. There are small projecting patches of firmer consistence and reddish-grey colour, due to the consolidated lobules. Adjacent areas may be depressed and slaty blue, from lobular collapse, while the intervening lung tissue is normal or pinkish and emphysematous. There may be dimness or slight roughening of the pleura where the consolidated areas reach the surface, but serous or purulent effusion is uncommon. On section, the lung is found to be congested and sometimes œdematous, especially at the bases, while the bronchi exude pus or muco-pus from their cut ends. The reddish-grey areas of consolidation are found to vary in size from a pin's head to a hazelnut. They are generally more abundant in the lower lobes, especially posteriorly. The consolidated and collapsed areas both sink in water, and do not crepitate. There is often some peri-bronchitis, and the bronchial glands are usually enlarged. Microscopically, the finer bronchi and the consolidated alveoli are found to be filled with an exudate containing large numbers of leucocytes and desquamated, proliferating epithelial cells, but in which few red blood corpuscles and little or no fibrin are found.

In the very acute condition to which the name capillary bronchitis was formerly applied, consolidation may not be apparent, but microscopical examination invariably demonstrates the involvement of the alveoli. In influenzal broncho-pneumonia the pathological changes probably commence as an exudative bronchiolitis, associated with capillary hæmorrhages. Secondary infections are probably responsible for the consecutive broncho-pneumonic process, which results in flooding of the alveoli with an exudate containing red cells, but little or no fibrin.

**Symptoms.**—In the cases ensuing on bronchitis in infants or old people (formerly

called capillary bronchitis), initial symptoms may be slight, and simply those of ordinary bronchitis, namely, malaise, slight fever and cough, with or without expectoration. The implication of the finer tubes and alveoli is usually marked by a rapid rise of temperature, great prostration, quick breathing and an irritating, persistent and often ineffective cough. In children, the *alæ nasi* work, the lower ribs are sucked in and the pneumonic type of breathing develops. The patient becomes cyanosed, the pulse is rapid, 120 or more, and the respirations 50 or 60 per minute. In old people, cyanosis, restlessness and delirium may occur, and later the cough becomes less frequent, the patient being drowsy and tending to sink down in the bed, whereas previously there was orthopnoea. These symptoms are ominous and indicate failure of the respiratory centre.

The physical signs are often those of bronchitis, harsh or weak inspiration and prolonged expiration, sibilant and sonorous rhonchi and crepitations or crepitant râles, especially at the bases. Patches of tubular breathing with increased voice sounds may develop, but are not always present.

In other forms of secondary broncho-pneumonia similar symptoms and signs develop more insidiously in the course of the primary disease. Broncho-pneumonia should be suspected when cough, expectoration and dyspnoea, together with a remittent type of temperature, develop in the course of an acute specific fever or other severe illness. In all forms, anorexia is common, the mouth and tongue become dry, and thirst is complained of. The urine presents the usual high-coloured, concentrated character of febrile conditions. It is often diminished in quantity, may contain a small quantity of albumin and not infrequently deposits urates.

**Complications and Sequelæ.**—These are relatively infrequent. Pleurisy may proceed to effusion, and when this occurs it is often purulent. Abscess and gangrene are rare, but develop rather more frequently than after lobar pneumonia. Other complications, such as pericarditis, endocarditis, meningitis and nephritis, are probably due to blood-borne metastasis.

The most important sequel is bronchiectasis which sometimes follows this condition, although it may not give symptoms for a long time afterwards. Pulmonary tuberculosis is frequently described as a sequel, especially after measles, and may be due to inflammatory changes in the bronchial glands activating a quiescent tuberculous deposit there. In many cases of tuberculosis described as following on broncho-pneumonia, it is more probable that the original lung affection was tuberculous.

**Diagnosis.**—The development of pulmonary symptoms, and of more or less characteristic physical signs in the course of measles, whooping-cough or one of the other diseases mentioned above, usually renders the diagnosis easy. Difficulty may arise in regard to tuberculosis, which in one form produces lobular pneumonic lesions with symptoms and signs indistinguishable from other varieties of secondary broncho-pneumonia. In any case where the fever lasts more than 3 weeks, or where the signs show no tendency to resolve or are chiefly apical, tuberculosis should be suspected. Unfortunately in children sputum is rarely available. An attempt is sometimes made to obtain it on gauze held in forceps, after exciting cough by touching the fauces. The mucus in the fauces may also be examined for tubercle bacilli. The diagnosis may, however, remain doubtful, until signs of softening become established.

Bronchitis rarely gives rise to difficulty. The fever is usually less high, and of shorter duration, while the physical signs are different, signs of consolidation being entirely absent. Hypostatic pneumonia may have to be considered. There is usually some obvious cause for this, such as cardiac disease and failure, or prolonged confinement to bed. The temperature is generally lower and the distribution is lobar.

Pleural effusion and empyema can generally be differentiated by the alteration of vocal fremitus and the displacement of the cardiac impulse. In case of difficulty the exploring syringe enables a distinction to be made.

**Course.**—Secondary broncho-pneumonia generally has a longer course than either

the primary form or the lobar variety of pneumonia. The fever often persists in remittent type for 2 or 3 weeks, and sometimes even for 2 or 3 months, although in this case tuberculosis should be suspected. The decline is almost always by lysis. Convalescence is often slow, the patient being left thin, weak, anæmic and debilitated.

**Prognosis.**—The prognosis in secondary pneumonia is serious. Many deaths occur from this complication in the acute specific fevers, particularly with measles and influenza. Even the form following on severe bronchitis is frequently fatal, especially in old people and in wrongly fed or debilitated infants. The development of delirium, of a pulse-rate over 150, of marked cyanosis and dyspnoea is unfavourable. In old people, drowsiness, sinking down in the bed and cessation of cough are very grave indications.

**Treatment.**—The treatment is very similar to that of lobar pneumonia, except that stimulant and expectorant drugs may be necessary from the first. In cases due to pneumococcal infection sulphadiazine or one of the other sulphonamides should be employed (see p. 22). If streptococci are established as the infecting agent, one of the sulphonamide preparations should be given at once. Penicillin may be given alone or with the sulphonamide preparation, but antibiotic preparations are much less effective than in pneumococcal pneumonias. The sputum should be tested as soon as possible in order to determine the sensitivity of the predominant organisms.

The patient must be in bed, and the position should often be changed so as to prevent hypostatic congestion. The room should be well ventilated, but without draughts, and the temperature kept at 65° F. both night and day. Oxygen should be given if there is any cyanosis, however slight. The most effective method of giving it is by oxygen tent. The next most effective is by post-nasal catheter. The B.L.B. mask is rarely used effectively. The diet should be restricted to fluids and semi-solids, as in pneumonia. The dry, distressing cough at the onset may be loosened by giving a simple alkaline febrifuge mixture, such as liq. ammon. acetat. min. 120, pot. citrat. gr. 10, sod. bicarb. gr. 10, with flavouring agents, such as syrup of tolu and chloroform water. Later, ammon. carb. and tinct. ipecac. may be given, but large doses of expectorants are to be avoided because of their irritant effect on the stomach. Opiates should not be administered except as tinct. opii camphorata or possibly Dover's powder in the early stages. In infants they should not be given at all.

When in infants or children the bronchi are becoming blocked by the secretion within them, as evidenced by increasing dyspnoea, an emetic should be given. For this purpose tinct. ipecac. or ammon. carb. in emetic doses is the most effective. In old people, ammon. carb. may be given in milk in doses of gr. 10 two or three times a day. Deep breathing at regular intervals should be encouraged.

Nikethamide (Coramine) or camphor injections and cardiac tonics are of limited value but sometimes give comfort.

#### INHALATION AND DEGLUTITION BRONCHO-PNEUMONIA

Acute broncho-pneumonic processes may be caused by the inhalation or aspiration of fluid or solid particles, derived from the upper air-passages or from other parts of the lung. To this form the name of aspiration, or inhalation pneumonia is applied. When from any cause food particles are drawn into the bronchi and broncho-pneumonia results, the condition is referred to as deglutition pneumonia. The resultant processes are similar, and are in effect analogous, to those caused by other septic or infected foreign bodies inhaled into the bronchi.

**Ætiology.**—These conditions may occur at any age, but are more common in adult life. They result from septic processes in the mouth, naso-pharynx, larynx or

trachea, and from any morbid state leading to anæsthesia of the pharynx, or to difficulty in deglutition. They occur in association with ulcerating growths of the mouth, tongue, tonsil, pharynx or larynx, and after operations for these conditions or upon the nose and throat, including tracheotomy. They occur as a complication of achasia or œsophageal pouches. Aspiration broncho-pneumonia may also result from vomiting during or after the administration of an anæsthetic. Carcinoma of the œsophagus eroding the trachea may be a cause. Diphtheritic or other forms of paralysis, coma from any cause, especially cerebral vascular lesions and uræmia, may lead to the passage of food particles into the air-passages. Recent work with opaque substances has shown that aspiration of foreign particles occurs more frequently after dental extractions and other surgical operations than is usually realised. Other cerebral lesions, such as abscess or tumour and bulbar paralysis, can also produce the same condition. Infected material may be aspirated from diseased to healthy parts of the lung, as in hæmoptysis, abscess, gangrene and bronchiectasis, or after rupture of an empyema into a bronchus.

**Pathology.**—Any material reaching the air-passages in this manner is certain to be laden with infective micro-organisms, which may induce bronchitis and broncho-pneumonia. Since pyogenic organisms are often present, suppuration is frequent and single or multiple abscesses result, or even gangrene. If the pleura becomes involved, empyema may develop.

**Symptoms.**—These are in general similar to those of secondary broncho-pneumonia and are superadded to those of the primary condition. There is generally high temperature, sometimes with rigors, cough and expectoration which is occasionally offensive. It may be mixed with food material and with blood. The physical signs are those of bronchitis and widespread broncho-pneumonia.

**Complications and Sequelæ.**—These are somewhat similar to those of other inhaled foreign bodies, and comprise abscess, gangrene and empyema.

**Course.**—The course is often short, owing to the severity of the process and the gravity of the primary cause. In the comparatively rare cases that recover, the course may be severe and protracted.

**Prognosis.**—From the nature of the primary condition and the intensity of the resulting broncho-pneumonia, this is usually grave.

**Treatment.**—**Prophylactic.**—The utmost care should be paid to the toilet of the mouth and pharynx in disease of, or operations upon, these parts. In paralysed or unconscious patients it may be necessary to resort to nasal feeding. In hæmoptysis or bronchiectasis the patient should lie rather on the affected side.

In most instances the general treatment is similar to that of broncho-pneumonia. Postural drainage should be given.

## TUBERCULOUS BRONCHO-PNEUMONIA

This constitutes one form of pulmonary tuberculosis (see Acute Caseous Tuberculosis, p. 1019).

## PNEUMONITIS

Pneumonitis is a term sometimes used as a general term for inflammatory conditions of the lung. It has some convenience in describing the inflammatory changes which are found in direct spread from a suppurative bronchiectasis, or in association with a neoplasm of the lung, which are neither broncho-pneumonia nor lobar.

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## DISEASES OF THE PLEURA

## PLEURISY

Pleurisy or pleuritis is an inflammation of the pleural membrane covering the lung, or of its parietal reflexions.

An ætiological classification, based on the bacteriological findings, would be the most satisfactory one, but is at present impracticable, chiefly owing to the difficulty of establishing the bacteria concerned in many cases. The classification usually adopted depends upon the effects produced. If the process leads only to fibrinous deposit it is described as *dry pleurisy*. If, in addition, much serous fluid is poured out, the condition of *pleurisy with effusion* results, while if pus is formed, the affection is described as *purulent pleurisy* or *empyema*.

It is, however, important to recognise that, although such a classification is convenient from a clinical standpoint, the three conditions are in reality only stages or degrees in the pleural response to irritative or noxious agents. The form occurring in any given case depends upon the nature of the cause, the extent of the infection and the degree of resistance possessed by the individual affected. Further, pleural inflammations may be primary or secondary to local disease or to blood infection, and they may be acute or chronic in course.

## A. ACUTE DRY PLEURISY (ACUTE FIBRINOUS OR PLASTIC PLEURISY)

**Ætiology.**—This affection has been described as primary and secondary. It is doubtful if such a condition as primary pleurisy exists and it is wise to regard it as secondary to some pulmonary condition. At all events the alleged predisposing effects of exposure to cold and wet probably play no part, other than by reducing the general resistance and precipitating pulmonary disease.

**Dry pleurisy secondary to pulmonary disease.**—Dry pleurisy is a frequent complication or concomitant of many diseases of the lungs, notably of pulmonary tuberculosis in any form. It is almost invariably present in lobar pneumonia. It occurs in association with pulmonary collapse, interstitial pulmonary fibrosis, bronchiectasis, abscess, gangrene, infarcts and new-growths of the lung. Injuries of the chest-wall, disease of the ribs, chronic nephritis, septicæmia or pyæmia may all be complicated by acute dry pleurisy.

**Pathology.**—The inflamed area is often localised, but the process may be widespread or even involve the whole pleural surface. Either the visceral or parietal layer may be first affected, but, as a rule, both become involved. There is at first hyperæmia with exudation of serum into the subpleural connective tissue. The pleura then appears slightly dull or matt, instead of shiny. Further exudation leads to the deposit of fibrin on the roughened pleural surfaces in the form of a thin false membrane, which often presents a rough or even shaggy appearance. This membrane consists of fibrin entangling leucocytes, a few red blood corpuscles and desquamated endothelial cells.

During the process of resolution, localised adhesions commonly form, but this is not invariable, and a patch of thickening without adhesion may be the ultimate result.

**Symptoms.**—The onset is usually sudden, with acute pain in the side, often described by the patient as a "stitch". Occasionally a sense of malaise may precede the development of the pain by a few hours or even days, but this is not the rule. The pain is aggravated by deep inspiration, by coughing or even by movement. It is often very severe, sometimes agonising, and the increase of pain, which sometimes

comes as a result of an involuntary cough on deep inspiration, is often described as if a knife was being driven into the chest. It makes the patient catch his breath, or cry out, and he often claps his hand to his ribs in an involuntary effort to prevent the movement of his chest-wall. Cough is generally an early symptom, and it is characteristically short, dry, ineffective and distressing. The temperature is usually raised, but, as a rule, only to 100° or 101° F., and some cases are practically apyrexial.

The decubitus is variable. The patient may lie on the affected side, but in some cases this aggravates the pain, and it is more comfortable to lie on the back or slightly turned towards the sound side. There is diminished movement on the affected side, and breathing may be rapid, although not dyspnoeic. On palpation, vocal fremitus is unaffected, but local tenderness of the skin or muscles is sometimes found, and occasionally a friction fremitus may be found, although this is likely only in the stage of recovery when the pain has almost disappeared. The breath-sounds are generally unaltered, but they may be short or jerky in the neighbourhood of the lesion. The sign of dry pleurisy is the friction rub. The characteristics of these rubs depend on the stage of the inflammation and extent of the area involved. The most painful rubs are often nearly inaudible because the patient's respiration is inhibited at the time of contact. All that may be heard is a sound like a single localised râle, which can only be recognised by its tendency to remain in the same place and to coincide with the catch in the patient's breath as he feels the pain. At other times the rub sounds like a series of superficial dry crepitations. As the friction rub becomes less painful it becomes more like creaking or rubbing leather, or like the sound of a foot-step on crisp, crunchy snow. The louder the rub the less the pain as a rule. The friction sounds may be quite localised or very widespread and they may not be present with every respiration. In the acute stage it is inadvisable to ask the patient to take a deep breath or, worse still, to cough in order to produce the sound. The voice-sounds are not altered.

**Complications and Sequelæ.**—Dry pleurisy may proceed to effusion but in most cases results in the formation of pleural adhesions. The most common sequel is pulmonary tuberculosis, sometimes after an interval of years, the explanation being that the original pleurisy is frequently tuberculous. Aching pain in the side with some dyspnoea may be a temporary sequel of dry pleurisy.

**Diagnosis.**—The differentiation of dry pleurisy from the other causes of pain produced in, or referred to, the chest-wall is not always easy and requires careful observation of the case. The distinction is important, since an erroneous diagnosis of pleurisy may arouse a suspicion of tuberculosis in subsequent febrile diseases. The term *pleurodynia* has been used to include fibrositis of the intercostal muscles and membranes and intercostal neuralgia. The term should be avoided, since it has a sound full of pomp, signifying, most often, ignorance. The terms it comprises are themselves suspect for the same reason.

It is wise to treat any chest pain which has the characteristics of pleurisy as being pleurisy until it is proved otherwise. It is, however, quite true that inflammatory or traumatic changes in intercostal muscles may produce pain on respiration rather similar to the pain of pleurisy. Inflammation of the intercostal nerves does also occur, but pain and tenderness tends to follow the distribution of the intercostal nerve or its anterior or posterior branches, and sometimes when there is infection of the posterior ganglions it is followed by herpes zoster. Other conditions inducing pain referred to the chest-wall are tumours or aneurysm pressing on the intercostal nerves, malignant disease of the spinal cord or of its membranes, and caries of the vertebrae. Where the pain lasts more than a few days, and no friction is heard, these conditions should be borne in mind.

Bornholm disease is an epidemic disease which causes acute pain of a pleuritic nature. Usually the pain appears to be in the muscles of the chest-wall but in some

cases pleural rubs have been described. In the absence of an epidemic an isolated diagnosis of Bornholm disease should be made with reserve or it may become as unsatisfactory as the diagnosis of pleurodynia.

Occasionally, adventitious sounds of extra-pleural origin may give rise to some difficulty. Contraction of the muscles of the chest may cause a muscular "susurrus"; grating sounds may be produced in the shoulder-joint or in the fascial planes of the back muscles. The origin of these sounds can usually be determined by causing the patient to cease breathing while carrying out movements of the shoulder or back muscles. Occasionally true friction sounds may have a cardiac rhythm as well as a respiratory one, when the area of pleura involved is near the pericardium. It is then referred to as pleuro-pericardial friction.

Having established the evidence of dry pleurisy, a careful search should be made for the primary condition. Pulmonary tuberculosis, pneumonia, bronchiectasis and the other causes mentioned above should be considered and excluded.

**Course.**—The temperature and pain may subside in 2 or 3 days and convalescence may be rapid if effusion does not occur. Occasionally the pain persists off and on for a few weeks but these cases are usually tuberculous and terminate in effusion.

**Prognosis.**—Depends entirely on the primary condition of the lung or the disease of which it is a complication.

**Treatment.**—The patient should be kept in bed, no matter how mild the attack. The diet will depend on the general condition and appetite of the patient. The pain can often be relieved by strapping the affected side. Strips of adhesive plaster are moulded to the chest wall about 2 in. from the vertebræ on the sound side of the chest. The patient is asked to breathe out and while in this position the strapping (nicked to make it lie flat) is stretched round the affected side and moulded over the sternum on to the sound side again. The application should be from below upward and, properly applied, one or two strips will often be enough to relieve the pain. They should be removed as soon as possible to prevent irritation of the skin. If the strapping is ineffective and it is certain that it has been properly applied, it should be removed.

If the pain is intense, an injection of gr.  $\frac{1}{4}$  or  $\frac{1}{2}$  of morphine should be given and a small injection of morphine or heroin is often the best way to start any treatment, since the patient is often tired and terrified. Local applications to the chest such as capsicum ointment or capsicum tissue are of little value, but a large kaolin poultice if well made does often give some relief and many patients derive comfort from them.

Pain, however severe, can usually be controlled by sedatives and strapping, but an artificial pneumothorax has been induced in cases where these resources failed and the pain has been especially excruciating. Such occasions must be extremely rare, and the operation under such conditions might produce empyema. A linctus should be prescribed for the cough that often accompanies pleurisy, and a sedative given at night.

Convalescence is usually rapid, but the patient should not be allowed to resume work until fully restored to health, and if a tuberculous origin is suspected, prolonged treatment on sanatorium lines should be advised.

Certain localisations of dry pleurisy require separate notice. These are the *diaphragmatic and interlobar forms*.

#### DIAPHRAGMATIC ACUTE DRY PLEURISY

**Ætiology.**—This affection may occur under conditions similar to those causing dry pleurisy in other parts; not infrequently it is secondary to pathological changes in the abdomen. Thus hepatic cirrhosis, perihepatitis, perisplenitis, hepatic abscess, perinephric suppuration or peritonitis may lead to a spread of infection through the



diaphragm to the adjacent pleura. It may also occur as a localised variety of secondary dry pleurisy, when the primary lesion is situated near the base of the lungs.

*Symptoms.*—Pain is usually very severe and may be referred to the shoulder or to the abdomen. The former is caused by nociceptive impulses ascending the phrenic nerve to its origin in the third to the fifth cervical segments of the spinal cord, leading to pain and hyperæsthesia referred to the cutaneous area of distribution of the fourth cervical root, at the summit of the shoulder. The abdominal pain is in the epigastric and hypochondriac regions, and in addition there is a localised tender spot, known as the "bouton diaphragmatique" of Guéneau de Mussy. This is situated in the sub-costal plane, about 2 in. from the mid-line. The diaphragm is nearly motionless on the affected side, and there is often some rigidity of the corresponding upper abdominal muscles. Hiccough may be a noticeable and troublesome symptom. The diaphragm, being nearly fixed in the inspiratory position, may cause a slight downward displacement of the liver if the pleurisy is on the right side. A pleural friction rub is rarely heard, the only abnormal signs commonly present being diminution of air entry, and possibly slight dullness over the corresponding lower lobe of the lung.

*Diagnosis.*—This is often difficult, owing to the fact that the severity of the symptoms and their localisation frequently suggest the occurrence of some acute abdominal catastrophe, such as perforation of a hollow viscus. The abdomen should be most carefully examined in every case. The history, the collapsed state of the patient and the evidence of free gas in the peritoneal cavity in perforation may assist in distinguishing between these conditions. The symptoms, however, are not by any means always as severe as is suggested by the foregoing.

Often this form of pleurisy can only be differentiated from ordinary pleurisy by the fact that the pain is made especially severe by any involuntary movement affecting the diaphragm such as laughing, yawning, sneezing or coughing, when the pain is like a knife thrust in the upper abdomen.

*Treatment.*—This is similar to that of simple dry pleurisy elsewhere, save that morphine should be withheld until the diagnosis is conclusively established.

#### INTERLOBAR DRY PLEURISY

Just as inflammation may be limited to the diaphragmatic portion of the pleura, so the membrane in the cleft between two lobes of the lung may be alone affected. This does not give rise to definite symptoms and signs by which it can be diagnosed during life, though its effects are not infrequently seen in radiograph films. It is frequently discovered on necropsy, but is generally secondary to pulmonary tuberculosis or pneumonia, and there is usually evidence of pleurisy elsewhere. It only assumes clinical importance when followed by effusion, and this condition is considered later.

#### B. CHRONIC DRY PLEURISY

Under this heading a variety of conditions are included. Strictly, it should be restricted to those rare cases, probably usually tuberculous in origin, in which the signs of dry pleurisy persist for long periods, or recur at frequent intervals. In such cases coarse, dry friction may be heard over large areas of one lung, often with little or no accompanying pain.

Pleural adhesion and thickening are usually included in the group of chronic dry pleurisy. There may be no symptoms, or, at most, slight dyspnoea on exertion, with aching or pain on straining or on lifting weights. Signs suggesting adhesion are local flattening and limitation of movement of the chest-wall. Litten's sign is also absent or diminished when the adhesion is basic, that is, the shadow cast by the movement of the diaphragm, best seen in the region of the seventh and eighth ribs in the anterior and mid-axillary lines, is not present or is much restricted. The vocal

fremitus may be diminished and the percussion note impaired. The breath-sounds are often slightly weaker, and the voice-sounds may be diminished over the area where the thickening or adhesion exists.

Chronic diaphragmatic pleurisy or adhesion may give rise to a group of symptoms simulating chronic gastric ulcer. There is pain in the hypochondrium extending through to the back and aggravated by food. Radiographic examination may be of value in demonstrating limitation of movement of one cupola of the diaphragm, together with an angularity due to alteration of its normal contour. Investigation of the gastric functions may also prove of value in diagnosis.

The treatment of chronic dry pleurisy is mainly symptomatic.

### C. PLEURISY WITH EFFUSION

Many cases of pleurisy, possibly the majority, proceed to effusion. The effusion is usually serous in character, but may be hæmorrhagic. Inflammatory effusions must be distinguished from passive transudates, which will be considered separately under the heading of hydrothorax.

#### SERO-FIBRINOUS PLEURISY

**Ætiology.**—This is in the main identical with that of dry pleurisy, of which it is, in effect, a later stage. It has now been established that the majority of cases of sero-fibrinous pleurisy are due to the tubercle bacillus. The evidence on which this conclusion has been arrived at is—(1) the subsequent history of the cases shows that a considerable proportion develop active lung signs within 5 years; (2) the cytological and bacteriological examination of the exudate; (3) post-mortem examination of fatal cases; (4) the results of tuberculin reactions.

Other conditions which may give rise to serous effusions are lobar and lobular pneumonia, pulmonary infarcts and new-growth. It may also occur in the course of generalised infections such as the enteric group, acute rheumatism and septicæmia due to streptococci or staphylococci. In most of these conditions the exudate often becomes purulent. Inflammatory serous effusion may also occur as a complication of severe anæmias, leukæmia, chronic nephritis, injury to the chest-wall and inflammatory conditions below the diaphragm or in the pericardium. It is also a common feature of polyorrrhomeningitis.

**Pathology.**—The affection commences with dry pleurisy, spreading over the visceral and parietal pleura, the fibrinous exudate soon forming a thick, rough layer on the surface. Further exudation of fluid occurs and accumulates in the pleural cavity, the lung collapsing *pari passu* to accommodate it. Owing to the hilar attachment of the lung, it retracts upwards and inwards, allowing the fluid to accumulate at the bases and in the axillary region, where it reaches its highest level unless previously existing adhesions prevent it. The lung retracts in this way owing to its elasticity, until the pleural negative pressure is completely abolished. In like manner the mediastinal contents, including the heart, are displaced away from the affected side. If fluid continues to be effused after the lung has retracted to the full extent, and after the negative pressure has become abolished, a positive pressure is produced. The lung is now compressed, and the diaphragm with the liver and spleen are pushed down, while the mediastinal structures are now displaced further towards the sound side. In long-standing cases the lung may undergo the change known as *carnification*, as the result of the compression apneumotosis. The lung appears dark red or slaty grey in colour, is firm, airless and heavier than water. If old adhesions are present, the effused fluid may be loculated and the collapse of the lung may be only partial.

If there is much positive pressure, collateral hyperæmia of the sound lung may result and progress to œdema. The fluid in the pleural cavity is pale and clear; it

often coagulates after withdrawal. Its characters are further described on p. 1070. The quantity may amount to as much as 5 or 6 pints.

**Symptoms.**—The onset is usually similar to that of dry pleurisy, but the constitutional symptoms are often more marked. There may be an initial rigor, but, as a rule, pain and dry cough are the earliest symptoms. The fever is of moderate degree, although it may reach 103° F. or more. When effusion develops the pain is often relieved owing to the separation of the inflamed pleural surfaces. If a large quantity of fluid is poured out rapidly, distress of another kind becomes apparent, namely dyspnoea caused by the mechanical effects of the fluid, collapsing the lung and displacing the mediastinum. In more slowly developing effusions there may be little or no dyspnoea, except on exertion. Expectoration is not common, unless there is coexisting pulmonary disease, or unless œdema of the sound lung develops.

The patient often lies on the affected side or may be propped up in bed. Cyanosis is not a marked feature even in large effusions, unless there is collateral hyperæmia of the sound side. There is generally some prominence on the side of the effusion, but the intercostal spaces are rarely bulged. Movement is restricted or absent in the lower part of the chest on the affected side, although with a moderate effusion the apical region may still expand. The cardiac pulsations may be seen in an abnormal position, the impulse being displaced away from the side of the fluid. In left-sided effusions, the pulsation may be most marked in the fourth space on the right side as far out as the nipple line. On palpation, the position of the impulse should be verified, and then the amount of chest movement and the character of the vocal fremitus determined. The latter is diminished or completely absent over an effusion of moderate or large size, although it may be obtained over the area where the collapsed or relaxed lung is in contact with the chest-wall. The percussion note over the fluid is one of stony dullness, and the sense of resistance is greatly increased. The exact limits of this area of dullness should be determined with the patient sitting up and recumbent. With moderate effusions the upper border of the dull area follows a curved line with the convexity uppermost known as the S-shaped curve of Ellis or Damoiseau's line. This is lowest at the back near the spine and reaches its summit in the mid axilla; it then slopes downwards as it passes anteriorly towards the sternum. In large effusions, the dullness may extend up to the level of the clavicle and reach across the mid-line of the sternum; moreover, in left-sided effusions it blends with the cardiac dullness, and the area of gastric resonance, known as Traube's space, may be encroached on or obliterated. The relaxed lung above the effusion in front often yields a skodiac note, which becomes dull if the quantity of fluid increases. At the back there is a triangular area of impaired resonance or relative dullness above the stony dull area of fluid. This is known as Garland's triangle. It also corresponds with the relaxed or collapsed lung. If the patient is examined while sitting upright there is often found at the base, on the sound side opposite the effusion, a small area of dullness known as Grocco's triangle. The base of this triangle extends outwards from the vertebral column along the lower margin of the lung for one to three inches; the vertical side extends upwards at a right angle to the base, alongside the spinal column, to about the highest level of the effusion; the hypotenuse joins these two lines. This paravertebral dull area is caused by the bulge of the fluid forming the effusion. Elsewhere over the sound lung the note may be slightly hyper-resonant. The area of deep cardiac dullness should be carefully marked out. In left-sided effusions it is displaced to the right and extends beyond the sternum in the third and fourth spaces, even to the nipple or beyond it. In right-sided effusions, the displacement may be very obvious, the left margin of the dullness extending as far out as the left mid-axillary line. The auscultatory signs are very variable, and much less characteristic than those obtained by palpation and percussion. In some cases, the breath-sounds over the dull area are distant and weak or even absent, in others they are loud and bronchial or tubular. This inconstancy probably depends upon

the extent of pulmonary collapse and the degree of patency of the bronchi. With marked collapse and patent bronchi, bronchial breathing is heard; with partial collapse and obstructed bronchi, the breath-sounds are almost or quite abolished. As a rule, no adventitious sounds are heard, but râles may be audible in the lung above the effusion. Conduction of spoken voice is diminished or abolished, but towards the upper part of the effusion and just above it, the sound produced is heard distinctly and with a peculiar nasal or bleating twang, a condition known as *xëgophony*. The breath-sounds heard under the clavicle over the relaxed lung above the effusion are frequently harsh or puerile. In the contralateral lung the breath-sounds may be vesicular or exaggerated, and in cases of large effusions, where there is marked circulatory obstruction, there are frequently signs of congestion or *œdema* at the base. Similarly, pressure on the descending thoracic aorta may cause lowering of the blood pressure in the leg as compared with that in the arm (O. K. Williamson). There may be a *systolic murmur over the cardiac region* (*displacement murmur*). The abdomen should be examined to determine any downward displacement of the liver or spleen. The blood count in sero-fibrinous pleurisy rarely shows any leucocytosis, apart from complications.

**Complications and Sequelæ.**—Acute *œdema* with albuminous expectoration is rare, but is a dangerous condition unless treatment is prompt. Permanent collapse and carnification of the lung may remain after absorption in prolonged cases, and may progress to diffuse interstitial fibrosis. More commonly some degree of pleural thickening and adhesion persists and expansion of the lower lobe may never be completely restored. Sero-fibrinous effusion due to tuberculosis rarely becomes purulent, but this sequence is common in other forms. Tracking of the fluid externally through the chest-wall and rupture through the lung occur but rarely. An infrequent complication is hemiplegia, probably due to an embolus derived from a thrombus originating in a pulmonary vein. Miliary tuberculosis occasionally follows rapidly on an effusion; more commonly active tuberculosis of the lungs occurs after a lapse of some years.

**Diagnosis.**—The recognition of the presence of fluid in the pleural cavity is generally easy, but with small or localised effusions it may be difficult. The most valuable signs are the displacement of the heart, the absence of vocal fremitus and the stony, resistant dullness. The auscultatory signs are of less value, and may even be misleading. The chief conditions which may simulate effusion are fibroid lung with thickened pleura and bronchiectasis, pneumonia, particularly the massive form, malignant disease of the lung, pleura or mediastinum, massive collapse, a large pericardial effusion and an aneurysm pressing on one or other main bronchus. Sub-phrenic abscess may also give rise to difficulty (see *Empyema*). Fibroid disease can usually be recognised, since there is generally flattening and sinking-in of the affected side instead of bulging. The heart, if displaced, is drawn towards instead of away from the affected side, vocal fremitus is present although possibly diminished, and the dullness is rarely of the stony character obtained over fluid. The breath-sounds may be weak or bronchial, and if bronchiectasis is also present, the characteristically variable signs of that condition should be helpful in diagnosis. In massive pneumonia the differentiation may be difficult, since breath-sounds and voice-sounds are sometimes completely absent if the bronchi are also occluded, but the position of the cardiac impulse is generally of decisive importance. In malignant disease and aneurysm, careful observation should afford diagnostic indications, such as glandular enlargement or abnormal pulsation, and in both instances the radiograph may establish the diagnosis. Malignant disease of the pleura may first show itself as a pleural effusion; the tendency to recur after tapping, the presence of blood in the effusion, and the onset of emaciation may help to suggest the cause. In massive collapse there is, as a rule, but little difficulty, owing to the displacement of the cardiac impulse to the affected side. In pericardial effusion the shape of the cardiac dullness may be sugges-

tive, and the dislocation of the impulse may indicate the real condition; moreover, the dullness over the lung behind is rarely of extreme degree unless pleural effusion coexists. Radiographic examination is always desirable. The shadow of fluid is generally dense, but does not obscure the rib shadows completely. The upper level tends to be curved and shifts to some extent with the patient. It merges into the shadow of the collapsed lung above. The diaphragm is immobile on the affected side. A further aid to diagnosis consists in exploratory puncture, which has the advantage of establishing the nature of the fluid as well as its presence. The technique of puncture is similar to that of paracentesis described below save that a hypodermic syringe with a Record 1 or 2 needle is often quite sufficient for diagnostic purposes. Preliminary local anæsthesia by procaine (Novocain) or some similar preparation, should be employed in every case. The same syringe and needle used for anæsthesia may also be used for the diagnostic puncture. Serous pleural fluid of inflammatory origin varies in colour from pale greenish-yellow to brown. The specific gravity is usually 1.018 or over. Protein is present as serum albumin, serum globulin and fibrinogen, the total quantity being, as a rule, over 4 per cent. The fluid generally clots spontaneously after withdrawal. The cytology of the fluid is varied, showing lymphocytes, polymorphonuclear cells, erythrocytes and altered endothelial cells in varying proportions. A marked preponderance of lymphocytes is very suggestive of a tuberculous origin, while the presence of large numbers of polymorphonuclear cells is usually an indication of some other infection, generally by a pyogenic organism. In rare cases large numbers of eosinophils have been found. The origin of these cases of so-called "eosinophil pleurisy" is at present doubtful. Cultural examination of tuberculous fluid usually proves sterile unless Loewenstein's or Dubos' medium is used, but in fluid from other causes the infecting organism can often be grown. To establish the tuberculous nature of a pleural fluid, inoculation of 15 ml. of the fluid into a guinea-pig may be tried. The methods of differentiation of an inflammatory exudate from a passive transudate are given on p. 1076.

**Course.**—In effusions of moderate size the temperature usually subsides in from 7 to 10 days, and spontaneous absorption is complete in 2, 3 or 4 weeks. In large effusions reaching up to the second rib or higher, the course may be less favourable. The fever may persist even for weeks, and absorption of the fluid may be slow or wanting entirely. Aspiration may accelerate the resolution, and usually only one tapping is necessary, the fluid left behind being absorbed rapidly. In rare cases fluid reaccumulates quickly after repeated tappings, and a so-called inexhaustible effusion occurs. In some such patients fluid may remain in the pleura for the rest of life.

**Prognosis.**—The immediate prognosis is good, although with large effusions of 4 pints or more, sudden death sometimes occurs from acute œdema of the lungs, cardiac failure or embolism. The ultimate result depends on the cause. In non-tuberculous effusions, recovery may be complete, save for pleural adhesion, or they may progress to empyema. In tuberculous effusions arrest may remain complete, but, as already stated, a considerable proportion of the cases develop pulmonary disease after years.

on to the unaffected side. The skin should then be prepared as for an operation and the whole procedure should be carried out as a sterile operation. The skin and muscles should be well infiltrated down to the pleura with procaine 2 per cent., and the needle used for the anæsthetic should be pushed into the pleural space to make certain that anæsthesia is complete and to confirm the position of the fluid. A sharp needle or a small trocar and cannula should be pushed into the pleural space, just above a rib, in order to avoid the intercostal artery on the under-surface of the rib above. The site chosen depends on the position of the fluid, but the most convenient ones are the sixth space in the mid-axilla, the seventh space in the posterior axillary line or the eighth space just below the angle of the scapula. Aspiration should be stopped if cough occurs or the patient complains of any general malaise or discomfort. Aspiration is exhausting to the patient so should not be too prolonged. Removal of 1 to 2 pints is all that it is safe to remove at one aspiration and removal of more and too rapid removal of as much may produce œdema of the lung and albuminous expectoration by affecting the pulmonary circulation. Removal of only part of an effusion sometimes seems to accelerate the absorption of the whole probably by the chain effect of increasing mobility. One of the risks of paracentesis is said to be sudden death from pleural shock. Sudden death does very occasionally occur but is probably due to air embolism, a risk inseparable from the use of a hollow needle. Other risks are also due to faulty technique and comprise entrance of air into the pleural cavity from ill-fitting needles or wrong connections or from puncture of the lung.

The operator must always keep in mind the danger of infecting the pleural cavity through a failure in sterility.

Exploratory puncture is advisable to permit the examination of the fluid. Opinions differ somewhat as to the indications for paracentesis, which, however, is nowadays performed earlier and more frequently than was formerly the case. It is unnecessary in cases in which absorption of the fluid is apparent within 10 days. The following conditions may be considered to suggest its employment: (1) if the effusion is large and causing positive pressure, as shown by dullness up to the clavicle, marked dyspnoea, downward displacement of the liver or spleen and collateral hyperæmia of the sound lung; (2) if absorption is slow, the fluid remaining at the same level for a fortnight or more; (3) if acute œdema with albuminous expectoration occurs; (4) in cases of bilateral effusion with increasing dyspnoea, the side with the larger effusion may be aspirated; (5) if the effusion is accompanied by persisting high temperature and constitutional symptoms.

The old cliché that the pleural effusion is Nature's splint and other old saws have been responsible for a great deal of unnecessary permanent disability as a result of not aspirating large effusions. Generally speaking, large effusions should be aspirated early and the aspiration repeated if necessary. Often, however, the aspiration of a moderate amount of fluid facilitates the reabsorption of the rest through increasing the momentum of the pulmonary movements. There are, however, still many different opinions on the subject of whether or not to aspirate a tuberculous effusion. It has long been a common custom to leave the effusion unaspirated on the ground that it acts as a form of collapse therapy. There is no evidence that this is true and it is certain that this belief leads to unnecessary discomfort and avoidable disability. If collapse therapy is necessary in these cases, air replacement would be a more logical and effective remedy.

**General Management.**—Patients with large effusions should be nursed propped up on pillows; they should be discouraged from sudden lateral alteration in position as the sudden displacement of the mediastinum may cause distress and cardiac embarrassment. The patient should be told that he will be away from work for not less than 6 months. For about the first 3 months, he should be kept in bed, although if the fluid has reabsorbed and the temperature and the sedimentation rate have been normal for 3 weeks he may get up by degrees towards the end of the period. He

half of the cases. Occasionally the pus proves to be sterile on culture; such cases are generally the result of the tubercle bacillus, or of a pneumococcus which has died out. Other organisms less commonly found are staphylococci, *H. influenzae*, *Salm. typhi*, *Bact. coli* and Friedländer's bacillus. Streptothrix organisms are occasionally found (see Actinomycosis), also various saprophytes and anaerobic organisms, especially in fetid empyema.

**Pathology.**—The initial stages are similar to those of dry and sero-fibrinous pleurisy, but when the effusion occurs, it proves to be rich in leucocytes undergoing disintegration and to contain the infecting organism. It varies from a slightly turbid, semi-translucent fluid to typical thick, opaque, creamy pus. Its colour ranges from pale amber to green or greenish grey. It may be odourless or extremely offensive. In cases secondary to gangrene, it may be thin and horribly fetid, while in pneumococcal cases it may be curdy and of slightly sweetish odour. The pleura is covered with a more or less thick layer of sodden fibrinous exudate. In cases due to the pneumococcus this false membrane may be very thick. Adhesions form quickly, leading to encystment or loculation of the pus. Such adhesions also prevent the lung from expanding after evacuation of the pus, with the result that the lung becomes carnified and interstitial fibrosis results. There is usually some enlargement of the bronchial glands. In long-standing cases there may be lardaceous disease of the liver, spleen, kidneys and intestines.

**Symptoms.**—Since empyema usually develops in the course of, or as a sequel of, some other disease, its symptoms are often masked by those of the primary disease and may easily be overlooked. In primary cases due to the pneumococcus the onset may be like that of pneumonia; in the more common secondary cases a rise of temperature and increase of signs develop after the crisis. In general, it may be stated that the symptoms are similar to those of sero-fibrinous pleurisy, but more severe. There is more malaise, and the patient may appear profoundly ill, with rigors, sweats and dyspnoea. The temperature ranges higher, up to 103° F. or more, and may be of septic type with marked daily remissions, but some cases are almost, if not completely, apyrexial. The signs are usually exactly similar to those of sero-fibrinous effusion, but in some instances special features may be noticed. In neglected or prolonged cases, wasting, pallor and cachexia become marked. The intercostal spaces may be found to bulge, and œdema of the chest-wall is sometimes apparent. The pus may track through an intercostal space, generally the fifth near the nipple, producing a fluctuating swelling known as a pointing empyema or *empyema necessitatis*. This may infiltrate the skin and simulate a superficial abscess. The swelling so induced may pulsate, especially if it be on the left side—a condition known as pulsating empyema. Pulsation communicated to the chest-wall may also be observed in some large left-sided purulent effusions without local swelling. The displacement of the liver or spleen may be greater than with serous effusions, probably owing to the higher specific gravity of the pus, which is usually 1.030 or more, and to the associated inflammation of the diaphragm. In fetid empyema, the breath and sputum may be offensive, even before rupture into a bronchus occurs. Clubbing of the fingers and toes occurs in empyema of long standing, but may develop in a few weeks. Blood examination reveals a moderate leucocytosis in the majority of cases. Counts of 15,000 leucocytes per cubic millimetre are usual, and in some instances figures up to 100,000 per cubic millimetre are obtained.

**Complications and Sequelæ.**—In neglected or untreated empyema the pus may track and become discharged in various directions. The commonest is rupture through the visceral pleura into the lung and discharge through a bronchus. This may lead to sudden death from suffocation; on the other hand, in small empyemata spontaneous cure may follow this evacuation of the pus. In other instances pyopneumothorax results, and occasionally gangrene of the lung. A second method of discharge is through the chest-wall, as an *empyema necessitatis*. Perforation may

occur into the pericardium, or into the œsophagus with the formation of a pleuro-œsophageal fistula. The diaphragm may be perforated with the production of a subphrenic, lumbar or psoas abscess, while in other cases general peritonitis may ensue.

The pericardium or the mediastinum may become infected without perforation; similarly costal periostitis may be induced. After spontaneous or operative evacuation the cavity may fail to close and a chronic empyema or sinus result. This is generally due to the lung being permanently collapsed and adherent, and therefore failing to expand. It subsequently undergoes fibrosis with development of bronchiectasis. Sometimes the failure to close may be due to the nature of the infection, particularly when it is due to tuberculosis or actinomycosis. In other cases it may be due to a bronchial fistula, or to a foreign body in the pleura. Generalised infection is rare, but cerebral abscess, probably of embolic origin, is not very uncommon, especially in cases due to streptococci. Chronic pulmonary osteoarthropathy is an occasional complication, and lardaceous disease sometimes occurs in cases of long duration. Diphtheritic infection of the wound, with subsequent paralysis, has been recorded after operation, more especially in cases secondary to influenzal bronchopneumonia.

The sequelæ in untreated cases may be fistulæ, such as pleuro-bronchial, pleuro-œsophageal or external, and various deformities. The sequelæ after operation may be a small amount of pleural thickening, or if operation were delayed, and re-expansion incomplete, there is falling-in of the chest, with flattening, dropping of the shoulder and secondary scoliosis. In other cases, as mentioned above, a chronic sinus may result.

**Diagnosis.**—The diagnosis of empyema involves two distinct problems—one, the recognition of the presence of fluid in the pleura, which is considered under sero-fibrinous pleurisy; the other, the demonstration of its purulent character. In spite of the more severe symptoms, empyema is frequently overlooked even by physicians of experience. This is partly due to the fact that its development may be insidious, with signs increasing but little from day to day, and partly to its secondary character, its onset being obscured by the clinical features of the primary condition. It is wise, therefore, to suspect its existence in any case of obscure lung signs, especially those with dullness, cardiac displacement and fever, consequent on pneumonia of any variety.

There are a few special difficulties as compared with sero-fibrinous effusion which merit separate mention. The first of these is subphrenic abscess. This may lead to immobilisation of the diaphragm on one side, more commonly the right, and cause collapse of the lung and even pleural effusion. The difficulty is greater when the subphrenic abscess contains gas as well as pus. The history, the absence of displacement of the heart's impulse and radiography may all assist, but the differentiation is often extremely difficult.

*Empyema necessitatis* may simulate a tuberculous or other abscess about a rib, and empyema should always be suspected in any case of local fluctuant swelling about the chest-wall. Pulsating empyema requires to be distinguished from aortic aneurysm; the pulsation is less forcible and little, if at all, expansile in the former. The cardiac displacement, the radiograph and cautious exploratory puncture, enable the nature of the condition to be recognised.

In any case in which empyema is suspected three examinations may be undertaken—a blood count, radiographic investigation and exploratory puncture. A polymorphonuclear leucocytosis of 15,000 per cubic millimetre and over, a dense shadow in the radiograph obscuring the ribs, together with cardiac displacement may be very suggestive, while puncture may prove the presence of pus. Sometimes however, puncture may fail, although pus is present. This may be due to the pus being too thick to pass through the needle, to loculation of the pus or to wrong choice of the site for puncture. The latter explanation is usually the real one, since quite thick pus will often pass through quite a thin needle. In this case, if



the other signs indicate pus, repeated punctures with a larger needle under anæsthesia are called for, but it is well to be prepared to proceed to operation if pus is found.

**Course.**—Apart from spontaneous cure of small empyemata by inspissation of the pus, or discharge through a bronchus or through the chest-wall, death generally occurs in untreated cases within a month or two. As in sero-fibrinous pleurisy, sudden death may occur. Death may occur after operation, from exhaustion or from cerebral abscess.

**Prognosis.**—This depends upon the primary cause, the method of treatment adopted, and the duration of the effusion before the operation. The most favourable forms are those due to the pneumococcus, which are recognised and treated at an early stage. In neglected cases, with profound toxæmia, with gangrene of the lung or lardaceous disease, the outlook is extremely grave. Empyemata due to streptococcal infection are serious, unless recognised early; similarly with cases of fetid empyema due to anaerobic infections. Infected hæmothorax consequent on gunshot wounds of the chest is of grave prognosis. The outlook is serious in cases of bilateral empyema, but recovery may follow evacuation of the pus on the two sides.

**Treatment.**—The pus aspirated should be sent for cultivation and the organisms identified and examined for sensitivity to various antibiotics. In the meantime, as much of the pus as can be conveniently and comfortably removed should be aspirated, and in the absence of more definite information as to the susceptibility of the organisms up to 500,000 units of penicillin should be put into the pleural cavity at the end of aspiration. Cultivation of the organisms may show that other antibiotics would be more appropriate if there are to be subsequent aspirations.

Some cases of empyema may clear up with aspiration and antibiotics alone, but it is wise to assume that operation will probably be necessary when the empyema has become localised in the chest. Indications that suggest that operation might not be necessary would be that the fluid showed signs of disappearance, that the fluid had become sterile, and from being purulent and thick was becoming serous and thin, while the leucocytosis and temperature had subsided. Neglected or missed empyemata are rarely seen in Great Britain nowadays, but the desperately ill case with a large empyema is often best treated at first by the use of a trocar and cannula and the insertion of an intercostal catheter which is led off into a drainage bottle with a water seal. Controlled drainage of this sort is less exhausting to these patients than aspiration, and soon makes them fit for operation which would probably have been fatal beforehand.

Before the use of antibiotics, treatment consisted in the evacuation of the pus by operation as soon as the diagnosis was established in pneumococcal cases. In those of streptococcal origin, operation was not resorted to while the fluid was of thin sero-purulent character, but was postponed until it was definitely purulent. Premature operation in streptococcal cases has been shown by the American Empyema Commission to be a very dangerous procedure, since the fluid is not shut off by adhesions and operation may lead to open pneumothorax, with flapping mediastinum. At this stage, the condition is described as pyothorax. A preliminary aspiration is of advantage in large effusions, and may be repeated in streptococcal effusions until they are ready for operation. The operation consists in drainage by removal of a piece of rib subperiosteally and incision of the parietal pleura.

In cases of chronic empyema, or of sinus failing to close, the question of some plastic operation must be considered. Various forms of operation have been devised, involving removal of portions of many ribs, and the decortication operation of Fowler and Delorme. The general condition of the patient must be carefully considered before these operations are advised.

**SPECIAL VARIETIES OF EMPYEMA.**—Certain special localisations of purulent pleurisy require separate consideration, notably apical, interlobar and diaphragmatic empyemata.

**Apical empyema.**—This condition is usually secondary to apical pneumonia, less

commonly to pulmonary tuberculosis. It is one variety of encysted empyema, the pus being shut off from the rest of the pleural cavity by adhesions. The symptoms and signs are not characteristic, but may be suggestive. There is very marked dullness below the clavicle, not transgressing the middle line, with weak or absent breath-sounds, and possibly some indications of mediastinal displacement. Diagnosis can, as a rule, be established only by the radiograph and exploratory puncture, the latter being carried out in the second space near the mid-clavicular line. The treatment consists in drainage by incision as near the lower limit of the effusion as possible.

*Interlobar empyema.*—Pus collecting between two of the lobes may be difficult to differentiate from pulmonary abscess, gangrene and bronchiectasis. It is often not diagnosed until rupture into a bronchus draws attention to it. The signs are generally most marked in the axilla or near the angle of the scapula. They are often slight until rupture occurs, and even then there may be only a small area of dullness in the line of an interlobar fissure, with distant or weak bronchial breathing and a few râles. The pus expectorated may be fetid, and the patient's breath may be offensive a few days before rupture occurs. The condition simulates abscess of the lung and may be almost impossible to differentiate from that affection. Radiographic examination gives the greatest help in the diagnosis. Recent observations suggest that interlobar empyema is much less common than abscess. The treatment is identical with that for pulmonary abscess.

*Diaphragmatic empyema.*—The pus is usually encysted, and may be so deeply situated as to give but few signs. The initial symptoms are generally severe, being those of diaphragmatic pleurisy, but hiccough is often a troublesome feature. When pus forms there may be marked constitutional symptoms, and obscure signs may develop, such as dullness, at a point just above the base behind, with weak or distant bronchial breathing. With such a history and obscure basic signs, especially when they occur after an attack of pneumonia, the use of the radiograph and of the exploring needle should not be neglected. In cases not recognised and treated, rupture into a bronchus or through the diaphragm may occur. The treatment is similar to that for ordinary empyema.

## HYDROTHORAX (DROPSY OR HYDROPS OF THE PLEURA)

Hydrothorax is the name applied to a collection of clear fluid in the pleural cavity, the result of passive transudation from the capillaries.

*Ætiology.*—The commonest cause of hydrothorax is cardiac failure. It occurs in acute and chronic renal disease, under conditions similar to those leading to dropsy in these affections. It is sometimes found in severe anæmias, especially pernicious anæmia. Obstruction to the azygos veins may lead to transudation into one pleural cavity or into both. This obstruction may be induced by pressure from without by a mediastinal or pulmonary new-growth, or by internal causes such as thrombosis. An ovarian fibroma may be complicated by ascites and hydrothorax, a condition known as Meigs' syndrome.

*Pathology.*—The pathology of hydrothorax is that of dropsy elsewhere. It is produced by mechanical or chemical conditions affecting the blood flow through the capillaries, and it must be distinguished carefully from inflammatory effusion. There is a difference in the composition as well as in the origin of the two kinds of pleural fluid. The characters of inflammatory effusions have been described under pleurisy with effusion. The fluid in hydrothorax is pale yellow in colour, and the specific gravity is 1.015 to 1.010 or less. It is clear and does not clot after removal. There is little protein, often not more than 1 per cent., but transudates due to local obstruction may contain as much as 3 per cent. The cellular elements are scanty, although some endothelial cells may be present, often united together in plaques. The fluid may be definitely blood-stained, when it is described as hæmo-hydrothorax.

Hydrothorax is usually bilateral in cases due to cardiac or renal disease, but in the former there is often more fluid on the right side, or the fluid may be confined to that side. The explanation of this is somewhat obscure. It has been suggested that it is due to pressure or traction on the vena azygos major by the enlarged right heart, but according to Fetterolf and Landis, a more likely explanation is pressure of the distended right auricle upon the pulmonary veins. Fluid may also collect in greater quantity on the side upon which the patient lies most constantly. In cases with unilateral pleural adhesion, œdema of the lung may occur on that side, while hydrothorax occurs upon the other.

**Symptoms.**—The symptoms of hydrothorax are generally overshadowed by those of the condition causing it, but the occurrence of dyspnoea and cyanosis in any case of cardiac or renal disease should suggest careful examination of the bases of the lungs. In the absence of inflammatory complications the condition is afebrile. The signs are identical with those of sero-fibrinous pleurisy, save that no friction sounds are audible at any stage. It is, however, more difficult to assess the significance of displacement of the cardiac impulse, owing to the increased size of the heart in the cases of cardiac origin.

**Diagnosis.**—This depends upon the presence of signs of fluid in the pleura in association with cardiac or renal disease, with absence of fever, and also upon the characters of the fluid withdrawn by puncture or aspiration. Meigs' syndrome is liable to be mistaken for a malignant ovarian tumour.

**Treatment.**—Removal of the fluid may give great relief. It may be necessary to repeat the operation, since the fluid often reaccumulates. The treatment of the primary condition should also be carried out. Mercurial diuretics are sometimes effective and may be given where there is no evidence of renal disease.

## HÆMORRHAGIC PLEURAL EFFUSIONS

All fluids poured out into the pleura contain a certain number of red blood corpuscles. It is only when a number sufficient to give a definite red colour is present, that the fluid is regarded as hæmorrhagic.

For convenience of description three forms may be differentiated—(1) Hæmorrhagic pleurisy or hæmo-serothorax; (2) hæmo-hydrothorax and (3) hæmothorax.

### 1. HÆMORRHAGIC PLEURISY.

This is simply a pleurisy with effusion, in which the exudate is blood-stained.

**Ætiology.**—The usual causes are malignant disease of the lungs, pleura or mediastinum, and sometimes tuberculosis of the lung and pleura. Hæmorrhagic pleurisy may occur in association with hepatic cirrhosis, but in this case it is often the result of a terminal tuberculosis. It occurs less frequently in association with blood diseases, such as purpura, and with the malignant or hæmorrhagic varieties of acute infectious fevers such as scarlet fever and small-pox, and occasionally with lobar pneumonia. Sometimes in tapping a sero-fibrinous effusion for the second time, it is found that the fluid, which was originally clear, is now blood-stained. This is not necessarily an indication of increase in the severity of the process, but may be due to injury of a blood vessel at the first operation.

**Symptoms.**—The symptoms and signs are identical with those of serous effusion, and the hæmorrhagic character can only be recognised by withdrawal of the fluid. An interesting point is the frequency of excess of eosinophils in these effusions. Diagnosis and treatment are the same as for sero-fibrinous pleurisy.

### 2. HÆMO-HYDROTHORAX.

This condition has been referred to under hydrothorax. It consists simply in blood-staining of a passive transudate into the pleura.

### 3. HÆMOTHORAX.

Hæmorrhage into the pleural cavity is the result of injury or disease of the vessels of the lung, mediastinum or chest-wall.

**Ætiology.**—The chief causes are injury, such as penetrating chest wounds or fracture of the ribs, rupture of an aneurysm and erosion by new-growth. Experience of the traumatic group has been largely increased during the War of 1914–1918 and the War of 1939–1945. Hæmothorax was noted in about 70 per cent. of chest wounds. Occasionally it occurs after the spontaneous rupture of adhesions and it is a rare complication of artificial pneumothorax treatment and a less rare complication of adhesion section in pneumothorax treatment.

**Pathology.**—The effused blood generally comes from the lung vessels, less commonly from the intercostals. It is “whipped” by the movements of the heart and lungs, with the result that fibrin is deposited in layers upon the diaphragmatic pleura, and the parts of the visceral and parietal pleura in contact with the blood. The fluid remaining in the pleura or withdrawn by aspiration is largely defibrinated and therefore does not clot, unless a secondary pleurisy develops.

The lower lobe of the lung on the affected side becomes collapsed and eventually carnified, unless absorption occurs or unless the blood is aspirated. The upper lobe may show some compensatory emphysema, and adhesions may form in the pleura, separating it from the hæmothorax below. When secondary infections of the bronchi or lungs occur, such as bronchitis or broncho-pneumonia, the collapsed lower lobe is not affected.

**Symptoms.**—The symptoms of hæmorrhage into the pleura from medical causes, such as rupture of an aneurysm or erosion of a large vessel, are collapse and rapid death. When due to disease or injury of an intercostal vessel, they may be insidious and slowly ingravescent until dyspnoea, restlessness and the other indications of internal hæmorrhage develop. When due to injury, similar symptoms occur, but may be masked or overshadowed by the shock, hæmoptysis and cough, induced by the wound of the lung or chest-wall. The signs are those of pleural effusion, but in traumatic cases certain special features may be mentioned. There is a great tendency to retraction of the chest-wall on the affected side, and the cupola of the diaphragm on this side is displaced upwards. Irritation of the diaphragmatic pleura by the presence of blood may cause rigidity of the upper abdomen which sometimes gives rise to an erroneous diagnosis of intestinal perforation. Vocal fremitus is usually diminished or absent. Breath-sounds will usually be absent but bronchial breathing may be heard and in these cases the voice conduction is also increased.

**Complications and Sequelæ.**—The most serious complication is infection of the effusion. This is generally due to organisms introduced at the time of the wound, either by the missile or by portions of the clothing or skin carried in with it. Aerobic organisms, such as a streptococcus, or anaerobic ones, as the *Clostridium Welchii* or *Cl. sporogenes*, may be present. A hæmo-pneumothorax may develop, the gas entering the pleural cavity from the wound in the lung or through the chest-wall. Gas may also be formed by gas-producing infecting organisms in the effusion. Massive collapse may occur in the contralateral lung, or other complications may arise, such as bronchitis, broncho-pneumonia, lobar pneumonia or œdema of the lungs. If the effusion is small and not infected, there are usually no permanent after-effects. In severe cases sequelæ, similar to those of sero-fibrinous pleurisy and empyema, may result.

**Diagnosis.**—Hæmothorax should be suspected when basic dullness develops shortly after a gunshot wound of the chest. The mistake that is most likely to be made in such cases is to confuse hæmothorax with lobar pneumonia. The cardiac displacement and the diminution of vocal fremitus over the dull area are the most valuable diagnostic signs. An active lobar collapse is distinguished by the fact that

the heart is displaced towards the affected side. Radiography affords valuable confirmatory evidence in most cases. When air and blood are present, the upper border of the dark area in the radiograph has a sharply defined edge, while the pleural cavity above is very translucent. The use of the exploring syringe generally settles the diagnosis, except in certain cases in which, although a considerable quantity of blood may be present, none is removed by aspiration owing to the needle entering the clot.

**Course.**—This depends upon the cause and size of the hæmothorax, and upon the mode of treatment adopted. It is profoundly and gravely influenced by infection of the effused blood. A small sterile hæmothorax is generally absorbed spontaneously. Medium-sized and large effusions may not disappear unless aspirated. An infected hæmothorax will inevitably prove fatal, if untreated.

**Prognosis.**—In a sterile hæmothorax due to a chest wound the prognosis is good. If infection occurs, the prognosis depends upon the promptitude with which this condition is recognised and radically treated.

**Treatment.**—The blood in the pleural cavity and the fluid exuded from the pleura in response to the irritation of the blood form an ideal culture medium for infecting organisms. All hæmothoraces should therefore be aspirated at short intervals until the pleura remains dry. It is probable that the blood in the pleural space clots in most cases quite quickly; that it is then defibrinated by the whipping effect of the movement of the heart and lungs; then the fibrin sinks to the bottom of the pleural space on the diaphragm or is deposited on the pleura and pericardium. The defibrinated fluid can be aspirated and its presence causes dilution with serous fluid until eventually the fluid becomes clear and yellow as the percentage of blood falls. Incidentally the serous effusion contains fibrinogen so that the whole contents may clot again unless they are aspirated. Such a clot becomes organised and forms a thick fibrous lining on the visceral and parietal pleura which impedes re-expansion. In such cases thoracotomy to evacuate the clot and decorticate the pleura is necessary.

In view of the danger of infection it is wise to give penicillin or the sulphonamides from the start. If infection takes place, treatment is the same as that for empyema (*q.v.*).

Hæmothorax due to rupture of adhesions or to trauma may on occasion cause severe blood loss and thoracotomy accompanied by transfusion may be necessary in order to find the bleeding point and save life. Patients should be given adequate doses of iron, but it is often wise to start convalescence with a transfusion of blood.

## CHYLOUS AND OTHER MILKY EFFUSIONS

A milky fluid is occasionally obtained on exploratory puncture or aspiration of a pleural effusion. It is usual to classify such fluids into three groups—(1) Chylothorax; (2) chyloform fluid; (3) pseudo-chyloous fluid.

### 1. CHYLOTHORAX.

There is an effusion of pure chyle or of serous fluid mixed with chyle.

**Ætiology.**—Chylothorax is usually the result of injury to, or disease of, the thoracic duct. The traumatic form is, as a rule, secondary to crushing of the chest-wall with fracture of the ribs. In disease, the thoracic duct may be pressed on by a malignant growth or enlarged mediastinal glands, or the flow may be obstructed by thrombosis of the left subclavian vein. Invasion of the thoracic duct by *Filaria bancrofti* may also be a cause.

**Pathology.**—The fluid in true chylothorax is a milky emulsion which remains so on standing, although a cream-like layer may form at the top. With the microscope fat globules can be seen, which stain with the usual fat stains and can be dissolved by ether.

## 2. CHYLIFORM EFFUSION.

In this condition fat is present, but it is not derived from the thoracic duct.

**Ætiology.**—Chyliform effusions occur in association with tuberculosis and carcinoma of the pleura or lung.

**Pathology.**—The fluid is milky and contains fat in emulsion, although in smaller quantities than in true chylothorax. On microscopical examination large fat droplets are seen and numbers of cells, chiefly leucocytes, undergoing fatty degeneration. It is, no doubt, from this process that the fat is derived.

## 3. PSEUDO-CHYLOUS EFFUSION.

In this condition the milky appearance is not due to fat, but to other particles causing opalescence.

**Ætiology.**—Pseudo-chyloous fluid has been observed in chronic effusions due to heart disease, nephritis, tuberculosis and malignant disease.

**Pathology.**—The milky appearance is due in some cases to a lecithin globulin complex (Wallis and Scholberg). Other rare causes of milky, opalescent or turbid effusions are the presence of particles of calcium phosphate, cholesterol or filarial embryos. These fluids are distinguished from the above by showing a deposit on standing.

**Diagnosis.**—This can only be established by microscopical and chemical investigation of the fluid withdrawn.

**Prognosis.**—The prognosis in most cases of milky effusions is serious, owing to the gravity of the primary condition. Some traumatic cases of true chylothorax recover.

**Treatment.**—The treatment is for the most part symptomatic and dependent upon the primary condition. In true chylothorax, removal of the fluid is inadvisable, unless it is causing dyspnoea or other symptoms of pressure. The drain of fat caused by it is a serious loss, especially if the tapping has to be repeated frequently. In chyliform effusions there is a marked tendency to recur after removal of the fluid.

## PNEUMOTHORAX

In pneumothorax, gas, usually air, collects between the layers of the pleura, which now becomes a real, instead of a potential, space. When serous fluid is present as well as the gas it is called a hydro-pneumothorax, when pus forms the condition is described as pyo-pneumothorax, and when blood and gas collect the term hæmo-pneumothorax is applied.

**Ætiology.**—Pneumothorax is more common in men, and the maximum incidence is between the ages of 20 and 40 years, but it may occur at any age. The air may gain access to the pleural cavity in the following ways: (1) Through the visceral pleura from the air in the lungs and bronchi. This accounts for 95 per cent. or more of the cases. The commonest cause is probably the rupture of a subpleural emphysematous vesicle. Pulmonary tuberculosis is a much less common cause, although the ruptured vesicle may be in the scar of a healed lesion. Since emphysema is an almost invariable concomitant of asthma and the severe pneumoconioses, spontaneous pneumothorax is a not uncommon complication in these conditions, although the diagnosis is more often made by radiological examination than by any other way. Other pulmonary causes are rupture of an empyema into the lung, gangrene of the lung or pulmonary abscess rupturing into the pleural space. Accidental puncture of the lung during paracentesis is an extremely common event. A broken rib perforating the lung can also induce it. It may also occur as a complication of artificial

pneumothorax treatment, especially when this is bilateral. (2) Through the chest-wall, as a result of penetrating wounds, although pneumothorax is not a common result. An abscess in the chest-wall opening externally and through the pleura, or a discharging *empyema necessitatis*, may be a cause. (3) Through the mediastinum, by ulceration of an œsophageal growth, or of a diseased bronchial gland, into the pleura, or from accidental perforation of the œsophagus during the passage of an œsophageal bougie or œsophagoscope. (4) Through the diaphragm, from some hollow abdominal viscus, e.g. an ulcer of the stomach or duodenum may perforate, leading to the formation of a subphrenic abscess, which in turn may break through the diaphragm into the pleura, or through therapeutic pneumoperitoneum where there is a congenital pleuro-peritoneal sinus. (5) Gas may accumulate in the pleura owing to infection of a pleural effusion by gas-producing organisms. This is generally the result of wounds.

Sudden spontaneous pneumothorax in apparently healthy persons is not very unusual and is occasionally found in the course of routine radiography. It is usually known as *simple benign pneumothorax*. The causation is not certain, but it used to be regarded as tuberculous with the same significance as a pleural effusion; this belief has now been discarded. Brock performed thoracoscopy in some of these cases and in a proportion of them he was able to see ruptured vesicles in either generalised or localised *emphysematous areas*. In some he found ruptured *bullæ* in apical scars presumably tuberculous; in some a cystic appearance of the lung, and in others a peculiar "cuckoo-spit" appearance which leaked air. The probability is that, in the majority of cases, benign spontaneous pneumothorax is due to the rupture of an *emphysematous bulla* however caused. In most cases the lung rapidly re-expands, although there is a tendency to recurrence usually on the same side but occasionally on the opposite side. Complete recovery is the general rule although in rare cases re-expansion takes a long time and may not occur. Very occasionally spontaneous *hæmopneumothorax* occurs. The symptoms are usually more severe and a fatal result is not uncommon.

The exciting cause of pneumothorax may be physical strain or violent cough, but many cases occur while the patient is at rest or even during sleep.

**Pathology.**—The entrance of air between the layers of the pleura disturbs the pressure relations in the thorax in a similar way to the effusion of fluid; but whereas with the latter the process is gradual, in pneumothorax it is rapid, and the pressure within the pleura changes from the normal negative figure to that of the atmosphere, often in a few minutes or less. Mediastinal and cardiac displacements like those in pleural effusion, and due to the unopposed traction of the sound side, are also rapidly produced. The subsequent pressure relations depend upon the source of the air. If the opening is in the chest wall, the intrapleural pressure will remain equal to the atmospheric, until the opening becomes closed. If the opening is in the lung, three varieties occur: (1) the opening may remain patent, when the pressure keeps at atmospheric level; (2) the opening may be valvular, permitting the entry of air into the pleura during inspiration, but preventing its escape during expiration. In this case the pressure in the pleura rises above that of the atmosphere, and the air within it is at a positive pressure, causing further cardiac and mediastinal dislocation with downward displacement of the diaphragm; (3) the opening becomes sealed, and there is a condition of closed pneumothorax in which the pressure may be equal to, greater or less than, that of the atmosphere.

To demonstrate pneumothorax *post mortem*, the necropsy may be performed under water, or by a flap being made of the skin and muscles at the side of the thorax, this being filled with water before puncturing the intercostal spaces. A third method is to dissect carefully through an intercostal space down to the pleura, when the lung will be found to be retracted. On opening the thorax the appearances vary. If the air entering the pleura is sterile, no inflammatory reaction occurs, the pleura

remains shiny and no fluid is formed, the condition being one of simple pneumothorax. If bacteria have gained access to the pleura with the ingoing air, or subsequently through the opening when this remains patent, either serous fluid or pus collects. In the former case the condition is described as hydro-pneumothorax, in the latter as pyo-pneumothorax. The appearances of the pleural membrane are similar to those found in serofibrinous pleurisy and empyema respectively. The lung is collapsed in every case of pneumothorax, and lies retracted towards the hilum and the spine. In tuberculous disease, a caseous focus or small cavity just under the pleura is the most frequent cause. The perforation may be a large circular rent or a small pin-hole, but multiple apertures may occasionally be present. The opening can usually be found, even if small, by submerging the lung under water while pumping air down the trachea. When extensive adhesions are present, the collapse of the lung is largely prevented and the pneumothorax is only partial. In such cases the perforation is frequently near the adhesions. In cases where fluid is present the diaphragm may be seen to be depressed on the affected side and its curvature lessened or reversed.

**Symptoms.**—In a considerable proportion of cases the onset is sudden and the condition of the patient becomes alarming at once. On the other hand, pneumothorax may develop insidiously, with surprisingly little pain and dyspnœa, so that its occurrence may be overlooked or only discovered on routine physical and radiographic examination, including a lateral film. This is more likely to be the case when perforation occurs in a lung extensively diseased or when the aperture is small, and the leak of air is slow. In the acute form of onset the patient is seized with severe pain while coughing or engaged in some extra exertion. There is often a feeling of "something having given way", and at once great dyspnœa develops with signs of collapse and severe mental anguish. The patient may appear blue, cold and clammy, breathing is rapid and shallow, the temperature falls to subnormal, the heart beats quickly and the pulse becomes small and weak. The patient is often restless, very alarmed and unable or afraid to speak. Occasionally death occurs in a few minutes. As a rule, the more acute symptoms subside in a few hours, but the temperature rises and the rapid breathing usually persists for some time. On examination the patient will usually be found sitting up, with *alae nasi* working and with rapid shallow breathing. The affected side is almost or entirely immobile and is usually bulged. The displacement of the cardiac impulse towards the unaffected side is generally obvious, and is almost immediate. Palpation confirms the absence of movement, and vocal fremitus is found to be absent, except where the collapsed lung remains in contact with the chest-wall, over which area it may be increased. The exact position of the cardiac impulse should also be determined: in right-sided cases it will be found in the left axillary region; in left-sided cases it may be under or beyond the right nipple. The liver may be felt much depressed in right-sided cases. The note over a pneumothorax is characteristically tympanitic or drum-like, as a rule, but in cases with positive pressure the tympany may be flat and muffled. The tympanitic area should be carefully mapped out; it may be found to extend across the middle line, or to encroach on or obliterate the liver dullness in right-sided cases. On the other hand, in partial pneumothorax, the area may be small and easily escape recognition. In left-sided cases, the cardiac dullness may be completely wanting on that side, and a dull area found to the right of the sternum. This may give a useful hint as to the diagnosis. On auscultation, the breath-sounds are often absent, but they may be present at the apex, although weak. In other instances distant tubular breathing may be audible from the collapsed lung; in cases with a large patent opening hollow cavernous breathing may be heard. The voice sounds have an amphoric or metallic quality, and an amphoric echo may occur with any sound produced near the pneumothorax. Metallic tinkling is an example of this, being the quality conveyed to *râles* or other adventitious sounds produced in breathing. The bell-sound or *bruit d'airain* is a



valuable sign, but is not invariably present. It is elicited by listening to the chest, near where a coin is placed flat on it and tapped with another. Where the acoustic conditions are right for the production of these musical sounds, all sounds which produce rhythmic vibrations in the pneumothorax cavity will have a ringing quality, whether they are râles, voice-sounds, breath-sounds, coin-sounds or even heart-sounds. The displacement of the heart can be confirmed by auscultation, and the heart-sounds may be found to have a metallic character. When air and fluid are present in the pleura the signs are somewhat modified. There is dullness at the base, which shifts its level with the patient's movements, the upper limit being straight, in contrast with the curved line of ordinary effusions. A marked succussion splash may be heard and felt on shaking the patient, or the patient may demonstrate the sign by a sudden shake or jerk.

**Complications and Sequelæ.**—Cardiac failure and rapid death occur occasionally. The chief complications are due to the entry of infective organisms into the pleura, leading to pleurisy and the effusion of sero-fibrinous fluid or pus. The sequelæ may be pleural adhesions in cases that recover, especially if effusion occurs. There may be also permanent collapse of the lung in long-standing cases, and in pyo-pneumothorax a fistula, either pleuropulmonary or external, may remain in spite of treatment.

**Diagnosis.**—The recognition of a large or of a complete pneumothorax is easy as a rule, the signs being characteristic. When a large quantity of fluid is present in an open pneumothorax, the presence of air may not be recognised until after paracentesis and radiographic examination. The latter gives information of the greatest value and sometimes demonstrates the presence of local pneumothorax where it has not been suspected. The air space between the lung and pleura shows most clearly in radiograms, and if fluid is present as well, the dead level of the upper border of the shadow, varying with position, is most characteristic. Diagnosis is more difficult in cases where pleural adhesions exist, or where the pneumothorax is small and localised. Sometimes very careful positioning of the patient and very close scrutiny of the radiographic film may be necessary before the slight collapse can be seen. The following conditions may give rise to difficulty and should be considered in doubtful cases. (1) Total excavation of a lung, or a large pulmonary cavity, in either of which the note may be boxy or even tympanitic, the breath-sounds amphoric and the râles metallic or tinkling, while the coin-sound may be obtained. These conditions can usually be distinguished by the flattening and retraction of the chest-wall over them, and the absence of cardiac displacement, or if it exists, the traction of the heart towards the affected side by fibrosis. (2) Advanced emphysema, with complete obliteration of the cardiac dullness, may be confused with pneumothorax. Large bilateral bullæ may be mistaken for bilateral pneumothorax. (3) Massive collapse of one lung, with compensatory emphysema of the opposite side, may also be mistaken for it. In both these conditions careful examination will establish the real nature. (4) A subphrenic abscess containing gas (subphrenic pyo-pneumothorax); in this condition the diaphragm may be displaced upwards, and the note over the lower ribs may be markedly tympanitic. These signs are more suggestive when right-sided. Succussion splash and bell-sound may be elicited. The heart, if displaced, is pushed upwards. The history of previous abdominal disease may be helpful, and a radiogram may give conclusive evidence of the subphrenic origin of the condition. (5) A hernia of the stomach or bowel through the diaphragm, or eventration of the diaphragm, all rare conditions, may simulate pneumothorax, but in all there is generally abdominal flattening and little if any cardiac displacement. A barium meal examination will, as a rule, establish the nature of the condition.

**Course and Prognosis.**—The course and prognosis of pneumothorax are profoundly influenced by the cause. In cases due to rupture of an emphysematous vesicle, or of a small localised healed tuberculous focus, where the pleura remains sterile and the aperture of entry closes, the air is usually completely absorbed in a

**Treatment.**—(See p. 196.) The pultaceous pleural contents should be removed as far as possible by operation. Penicillin should be given as for actinomycosis of the lung and injected intrapleurally.

## SIMPLE TUMOURS OF THE PLEURA

These are very rare and are, as a rule, only discovered after death. They are almost invariably of extrapleural origin and their presence in the pleura is due to the direction taken by the growth. Lipoma of the subpleural or of the mediastinal fat may occur as small pedunculated tumours or very rarely as a large mass. They can be differentiated from tumours of the lung by radiographic examination after a diagnostic pneumothorax.

## MALIGNANT TUMOURS OF THE PLEURA

Primary malignant disease of the pleura is rare, and may take the form of endothelioma, carcinoma or sarcoma. Secondary carcinoma and sarcoma are more common.

**Ætiology.**—Primary endothelioma of the pleura is more common in late adult life and in the male sex. Sarcoma is more likely to occur in children and in young adults. Secondary growths may occur at any age, but more commonly in later life.

**Pathology.**—Endothelioma of the pleura is a growth of obscure origin. It has not been conclusively established that it is derived from the pleural endothelial cells, and by some writers it is classed as a carcinoma. It is at first unilateral, but it involves the affected pleura over a wide area, sometimes universally. The membrane appears to be overlaid with an irregular, rough hard covering, sometimes nodular. In other cases there is more thickening and the condition may be localised. There is nearly always a large amount of blood-stained serous effusion. The condition may spread to the bronchial or supraclavicular glands, the lung, the spine, the diaphragm and the peritoneum.

Primary carcinoma of the pleura has also been described, but is very rare. Primary sarcoma is also extremely uncommon, but the round-celled and spindle-celled varieties may occur, and angio-sarcoma, fibro-sarcoma, myxo-sarcoma and chondro-sarcoma have all been recorded.

Secondary carcinoma and sarcoma of the pleura are relatively common, and may occur from direct extension in growths of the lung, bronchi and mediastinum, by *metastases* of growths in almost any distant part, or by *lymphatic permeation* in mammary carcinoma. In the last-named condition pleural and pulmonary growths are a not infrequent form of recurrence, sometimes occurring months or years after removal of the primary growth.

expectoration, often blood-stained, or it may involve the chest-wall. Metastases sometimes develop along the course of the needle track after aspiration of the fluid. The secondary growths, especially those in the glands, may exert pressure, e.g. the axillary glands may cause oedema and swelling of the arm. A primary growth of the pleura may cause intense pain as it may split the costal cartilage from the sternum and invade the periosteum.

**Diagnosis.**—A chronic pleural effusion in a middle-aged man, not associated with fever, and not due to tuberculosis, should arouse suspicion of malignant disease of the lung and pleura. Evidence of fluid in one pleura, at an interval after excision of the breast for malignant disease, is very suggestive of secondary pleural growth. A hæmorrhagic effusion, not due to tuberculosis or renal disease, should also arouse suspicion of malignancy, especially if reaccumulation after tapping is rapid, and if the subsequent tapplings show increasingly hæmorrhagic characters. When aspiration of a considerable quantity of fluid gives little relief to symptoms, or when irregular dull areas remain where resonance might be expected, the probability of growth must be borne in mind. Growth involving the chest-wall, or the presence of cervical or axillary glandular metastases render it certain. Radiological examination after removal of some of the fluid may show characteristic plaques on the pleura.

**Course.**—This is almost invariably progressive, the duration being rarely more than 2 years, and occasionally much less.

**Prognosis.**—Malignant growth of the pleura is invariably fatal unless removal is possible.

**Treatment.**—From the nature of the condition this can only be palliative. Analgesic drugs may be given freely for the relief of pain, morphine being reserved for the severe forms and later stages, as far as possible. Repeated tapplings may be almost compulsory, if there is much distress from the reaccumulation of the fluid, but it must be remembered that in hæmorrhagic effusions the loss of blood by this means is considerable. Air replacement may sometimes give relief for a longer period than simple aspiration. In rare cases, removal by operation may be practicable if the diagnosis is made early and the growth is localised in an accessible position. Deep X-ray therapy may relieve the pain.

## INJURY

Injury to the pleura may occur in fracture of the ribs, the fragments piercing or tearing it. Similarly in penetrating wounds of the chest, the pleura may be extensively lacerated. It may also be torn by direct violence without breaking of the ribs, and in rare cases a hernial protrusion of lung may occur, forming a small swelling in an intercostal space, protruding with inspiration and emptying with expiration.

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## DISEASES OF THE DIAPHRAGM

### SPASM OF THE DIAPHRAGM

Diaphragmatic spasm may be either clonic or tonic, the former being termed *hicough*.

**Clonic spasm.**—This may be due to a variety of causes, namely: (a) Alimentary:

from irritation of the œsophagus or stomach by pungent or irritant substances such as pepper, pickles or tobacco. It occurs also as a symptom in gastritis, dilatation of the stomach, enteritis, intestinal obstruction, tympanites and peritonitis, and in the late stages of debilitating disease. (b) Nervous: as in hysteria, cerebral tumour, meningitis, hydrocephalus, epilepsy and alcoholism. It may also result from peripheral nerve irritation, in such conditions as mediastinal tumour, mediastinitis, enlarged thoracic glands, diaphragmatic pleurisy or pericardial effusion. During epidemics of encephalitis lethargica, hiccough has occurred as a symptom. There is usually some slight pyrexia, and the condition may persist without intermission for several days. (c) Renal: as in chronic nephritis and uræmia.

*Tonic spasm.*—This may be met with in tetanus, strychnine poisoning, laryngismus stridulus, eclampsia, epilepsy and hydrophobia. If there is associated intercostal or laryngeal spasm, there is grave risk of death from asphyxia.

*Treatment.*—Simple hiccough may often be relieved by holding the breath, pressure on the chest or by simple inhalations, such as of ammonia, ether or spirits of chloroform. Hiccough due to organic disease or to peripheral irritation may only be relieved by removal of the cause. In epidemic hiccough, in obstinate cases of hiccough due to other causes and in the tonic form of spasm, various antispasmodic measures may be tried, such as trinitrin, bromides or phenobarbitone, by the mouth; adrenaline, or adrenaline and pituitary (posterior lobe) extract, hypodermically; or the inhalation of chloroform. In some cases relief may be obtained by spraying the skin above the clavicle with ethyl chloride. Injection of the phrenic nerve with procaine has been used with success when all other methods have failed.

## DIAPHRAGMATIC PLEURISY

This condition is described on p. 1065 under the heading of Pleurisy.

## PARALYSIS OF THE DIAPHRAGM

*Definition.*—Paralysis and inactivity of either leaf of the diaphragm, or of both.

*Ætiology.*—Paralysis of the diaphragm may be caused by disease damaging the centre in the spinal cord, by conditions affecting the phrenic nerve in its course, or by reflex inhibition of the centre. Causes involving the centre include poliomyelitis, hæmorrhage into the spinal cord and tumours of the spinal cord or its membranes, or of the spine itself. The phrenic nerves may be affected by diphtheritic neuritis. Either or both of the nerves may be compressed by mediastinal tumours, or by inflammatory exudates. They may be severed or injured by wounds in the neck. Evulsion or crushing of the phrenic nerve is now frequently employed therapeutically, in order to promote collapse of the base of one lung and closure of cavities in cases of tuberculosis and in bronchiectasis. Occasionally no cause for the paralysis may be found.

*Symptoms.*—Diaphragmatic paralysis results in the affected leaf of the diaphragm becoming immobile and remaining at a higher level in the thorax than normal, or showing paradoxical movement, *i.e.* ascending with inspiration. This can easily be seen on radiographic examination. Sometimes this is noted as a reversal of the ordinary abdominal movements during respiration, with the result that there is epigastric recession during inspiration. In elderly patients the diaphragmatic paralysis sometimes causes dyspnoea on exertion and some discomfort after meals.

*Treatment.*—This is, in general, that of the condition causing the paralysis.

## EVENTRATION OF THE DIAPHRAGM (see p. 647)

## DISEASES OF THE MEDIASTINUM

The mediastinum is the interpleural space, and occupies the median part of the thorax, from the superior aperture above to the diaphragm below. Strictly speaking, any affection of any of the important structures occupying this space, such as the pericardium, heart, great vessels, air passages and the thymus, might be included under this heading. They are, however, more conveniently grouped under the various systems to which they belong, and diseases of the mediastinum are commonly restricted to conditions arising in, or affecting the connective tissue and glands found in this space.

### MEDIASTINITIS

Mediastinitis or inflammation in the mediastinal connective tissue, may be acute or chronic. In the acute forms there may be an inflammatory serous exudate causing œdema, or the inflammation may progress to abscess formation. The chronic forms are indurative or fibroid in character, although chronic abscess may occur.

#### ACUTE SIMPLE MEDIASTINITIS

**Ætiology.**—Acute mediastinitis without suppuration may result from injuries to the chest-wall or sternum, and from lacerating wounds of the œsophagus or trachea. It is sometimes secondary to inflammatory processes in the lungs, pleuræ, pericardium or peritoneum, and to periostitis of the sternum or vertebræ. Pneumonia is a not uncommon cause.

**Pathology.**—There is a hyperæmia of the mediastinal connective tissue with inflammatory œdema. Mediastinal serous effusions have been described, but these are, without doubt, encysted pleural effusions encroaching on the mediastinum.

**Symptoms.**—The clinical manifestations of acute mediastinitis are vague and not characteristic. There is a mild pyrexia, the temperature reaching 99° or 100° F. Pain under the sternum may be complained of, and on auscultation over it a few fine crepitations may be heard on deep breathing, or they may occur synchronously with the heart beats.

**Diagnosis.**—Mediastinitis is often not recognised or suspected, since it is masked or overshadowed by the clinical manifestations of the primary condition.

**Course.**—The affection may subside or proceed to abscess formation. It may result in fibroid thickening or adhesions.

**Treatment.**—No special treatment is required, apart from that appropriate to the condition inducing it.

#### ACUTE SUPPURATIVE MEDIASTINITIS

**Ætiology.**—Acute suppurative mediastinitis or mediastinal abscess is more common in males and may occur at any age, although it is more frequently seen in early adult life than at other periods. Some cases are of traumatic origin, and follow perforating wounds or blows on the sternum, not necessarily causing fracture. Perforation or injury of the œsophagus is a comparatively frequent mode of access of pyogenic organisms to the mediastinum. This may occur from ulceration of an œsophageal new-growth, from injury due to a swallowed body such as a tooth-plate, or from the passage of an œsophagoscope or bougie. Perforation of the trachea or main bronchi by an inhaled foreign body is sometimes the cause of mediastinal suppuration. Various

pulmonary conditions may lead to pyogenic infection of the mediastinum, such as pulmonary abscess or gangrene, pneumonia and bronchiectasis. Periostritis or osteomyelitis of the sternum, vertebræ or ribs, suppuration in the mediastinal glands, or tracking down of deep cervical abscesses may all lead to mediastinal abscess. Extensions of pyogenic processes from the pericardium, pleura or peritoneum may also be causes. A suppurating hydatid or dermoid cyst may rupture into the mediastinum, and, lastly, the infection is blood-borne in some cases from infective endocarditis, pyæmia, erysipelas or enteric fever. Dieulafoy pointed out that certain cases of empyema, originating near the mediastinum, may, by encroaching on this region, induce predominating mediastinal symptoms, which he described as the "mediastinal syndrome". Such cases, although abscesses encroaching on the mediastinum, are not mediastinal abscesses, but are in reality special instances of encysted empyema.

**Pathology.**—The suppuration may be limited to any part of the anatomical subdivisions of the mediastinum, or may spread from one compartment to another. The pus sometimes tracks in various directions, *e.g.* upwards to the neck, downwards to the abdomen, or it may point in the chest-wall. The abscess may rupture into the œsophagus, trachea, aorta, pleura or pericardium.

**Symptoms.**—The onset may be insidious or acute. In the latter case it may be ushered in by severe pain under the sternum, radiating to the back and shoulders. The symptoms may be divided into those due to the inflammatory process, and those resulting from the pressure exerted by the collection of pus. The former comprise malaise, fever and sometimes rigors, while blood examination may demonstrate a leucocytosis of 10,000 per c.mm. or over. The pressure symptoms vary according to the amount of pus produced and its situation. They include dyspnœa and paroxysmal or brassy cough, from compression of the vagus nerve or direct pressure on the trachea. There may also be dysphagia from obstruction of the œsophagus, and hoarseness from pressure on the left recurrent laryngeal nerve. Pressure on the spinal nerve roots, intercostal nerves or brachial plexus may lead to severe neuralgic pains. Partial or complete obstruction of the great veins may be apparent from distension of the superficial thoracic veins or of those in the neck. Oedema of the chest-wall is sometimes seen from this cause, or it may result from the inflammatory process extending to the chest-wall. The signs in severe cases will be those caused by the pressure effects just described. The patient looks ill, distressed, dyspnœic and more or less cyanosed. The respirations may be noisy, as there is sometimes inspiratory dyspnœa with stridor, this being known as the *bruit de cornage*. The dilated veins may be apparent and the direction of the current may help to localise the seat of the obstruction. There is sometimes local redness and œdema from pointing of the abscess near the sternum, in the neck or in the interscapular region on either side. Palpation may reveal local tenderness and even fluctuation in any of these areas. There is often dullness over the sternum, sometimes extending to one or other side, or the dullness may be found in the interscapular region. It is said that the dullness may shift with the position of the patient in some cases. Breath-sounds are distant, and weak or bronchial over the dull area, except when it is behind the sternum, when they are harsh.

**Complications and Sequelæ.**—The important complications are those due to rupture of the abscess. If this occurs into the lung or the œsophagus pus is expectorated, or passes into the stomach. Gangrene of the mediastinum may follow, or death may occur from suffocation or hæmorrhage. Extension of the abscess may lead to purulent pleurisy, pericarditis or peritonitis, or to suppuration in the neck. In cases that recover, chronic mediastinitis with matting together of the mediastinal contents may be a sequel.

**Diagnosis.**—The "mediastinal syndrome" of dyspnœa, stridor, paroxysmal cough, hoarseness and dysphagia with signs of pressure on arteries, veins and nerves is common to many conditions causing mediastinal pressure, notably mediastinal

new-growth, enlarged mediastinal glands, aneurysm and pericardial effusion. The differential diagnosis of these is more fully considered under mediastinal new-growth. The occurrence of fevers and rigors, the presence of a pointing swelling, and the demonstration of a leucocytosis may give strong suggestion as to the inflammatory origin of these symptoms and signs. The radiograph may reveal a localised mediastinal shadow, often non-pulsating, although it must be remembered that in rare cases a mediastinal abscess may pulsate.

**Course.**—The disease is acute and rapidly progressive, unless relieved by operation or by spontaneous external drainage in a few fortunate cases.

**Prognosis.**—This is very grave, and the majority of cases die unless recognised and treated early. If gangrene develops, a fatal result is inevitable. The outlook is more hopeful when the anterior mediastinum alone is involved.

**Treatment.**—**PROPHYLACTIC.**—Foreign bodies in the œsophagus and trachea should be removed as soon and as gently as possible. The utmost care should be exercised in the passage of a bougie or the œsophagoscope in cases of œsophageal stricture.

**CURATIVE.**—As soon as mediastinal suppuration has been diagnosed and localised, surgical measures should be adopted. The mediastinum can be reached by resection of pieces of costal cartilage or by trephining the sternum; appropriate antibiotic treatment should be given.

#### CHRONIC MEDIASTITIS

This also occurs in two forms, chronic indurative mediastinitis and chronic abscess.

**CHRONIC INDURATIVE MEDIASTITIS.**—This may occur as a sequel of any form of acute mediastinitis. The best known is that associated with chronic adhesive pericarditis, and usually known as chronic indurative mediastino-pericarditis (pp. 77, 883). Other forms include the chronic inflammation and thickening which occur around enlarged, sclerotic and pigmented mediastinal glands, and around the same glands when affected by caseous or calcareous tuberculous lesions.

**CHRONIC MEDIASTINAL ABSCESS** is generally of tuberculous origin, arising from breaking down caseous bronchial or mediastinal glands, or from tuberculous disease of the spine or ribs. A chronic abscess may, however, be caused by a foreign body, such as a bullet.

**Symptoms.**—Simple indurative mediastinitis may give rise to practically no symptoms or signs. Chronic abscess may cause symptoms of ill-health and of mediastinal pressure, or may only become apparent when it points superficially.

**Treatment.**—The treatment of chronic mediastinal abscess is practically the same as that for other "cold" abscesses due to tuberculosis, incision and drainage being avoided if possible in favour of aspiration and chemotherapy. Other cases may require operation.

#### EMPHYSEMA OF THE MEDIASTINUM

In performing tracheotomy, the pretracheal layer of deep cervical fascia is of necessity incised. If difficulty arises in inserting the tube into the tracheal incision, air may be drawn deep to this fascia by the vigorous attempts at respiration and thus pass into the superior mediastinum, or superficial to it into the anterior mediastinum. Rupture of the trachea, bronchi or œsophagus, or rupture of air vesicles or pulmonary lesions where the pleura is adherent, may also cause it. In acute interstitial emphysema of the lungs, the escaped air may track along to the root and reach the mediastinum.

**Symptoms.**—Emphysema of the mediastinum may give rise to very indefinite

indications. A few fine crackling sounds may be heard on listening over the sternum, sometimes varying with respiration or with the heart movements. The percussion note over the præcordium may be hyper-resonant, and the heart sounds may be distant and muffled. Small quantities of air escaped into the mediastinum can be rapidly absorbed and may not be of serious import.

**Diagnosis.**—This is often a matter of speculation, unless the air spreads upwards to the neck and causes superficial surgical emphysema.

**Prognosis.**—This depends entirely on that of the underlying cause, which is often of serious nature.

**Treatment.**—No special treatment is required, as a rule, apart from that of the primary condition, except that pain may necessitate the use of analgesic drugs at the onset.

## ENLARGED MEDIASTINAL GLANDS

The mediastinal lymphatic glands are arranged in groups. A few small ones are found in the anterior compartment, another group is situated in the posterior mediastinum. The most important of these is the tracheo-bronchial group, situated around the bifurcation of the trachea and extending along the bronchi. It is enlargement of this group that most often gives clinical manifestations.

**Ætiology and Pathology.**—A simple inflammatory enlargement of these glands may occur in many acute affections of the bronchi and lungs, and in certain acute specific fevers, notably influenza, pertussis and measles. A more chronic enlargement, associated with indurative changes, results from chronic respiratory diseases, such as chronic bronchitis and the pneumoconioses. In the latter case, considerable pigimentary changes may be found, from deposition of the particles derived from the dusty inspired air. In town-dwellers, these glands are often grey or black in colour from deposited carbon. Tuberculosis is the commonest cause of enlargement of the mediastinal glands, particularly of the tracheo-bronchial group, those about the right bronchus being most affected as a rule. This is a frequent early localisation of tuberculous disease in children. The infection spreads from the lungs in the majority of cases (Ghon), but in some instances the path of infection is from the tonsils through the cervical lymphatics and glands, while in others the mode of entrance is from the intestines through the mesenteric glands. The lesions may be miliary tubercles, or small caseous nodules which calcify subsequently, or which may soften and lead to local spread or generalisation. In other cases a fibroid hyperplasia of the gland results.

Enlargement of the mediastinal glands due to sarcoidosis is now realised to be a common condition as a result of routine radiography. It is often asymptomatic.

In syphilis, mediastinal adenitis may occur in the secondary or tertiary stages. In Hodgkin's disease and in lymphatic leukaemia, the mediastinal glands may share in the general adenopathy, and in the former the condition may be primary in these glands. Enlargement due to malignant disease is of great importance and receives separate consideration.

**Symptoms.**—These may be slight and escape notice, unless the enlargement is sufficient to produce pressure or irritation. Cough is the commonest symptom; it is usually dry, irritative, noisy and ineffective. It may occur in paroxysms, somewhat suggestive of those of whooping-cough. Dyspnoea and dysphagia occur only when the enlargement is considerable. Vomiting sometimes develops, probably reflexly from vagal stimulation. Pain behind the sternum or in the upper thoracic region posteriorly may be complained of. In children with tuberculous disease in these glands, there is often languor, anorexia, anæmia and wasting, sometimes with slight irregular fever and night sweats. Such symptoms in a child of 5 to 12 years of age are very suggestive. The signs are also variable and frequently inconclusive.



In glandular enlargement from any cause, there may be dilated veins over the front or back of the chest, especially in the upper part, and a "hilum dimple" has been described as appearing in the second intercostal space beside the sternum, on holding the breath at the end of inspiration. One pupil may be larger than the other, owing to sympathetic stimulation. Small areas of dullness may be found at the back, near the upper thoracic spines, or in front close to the manubrium. Breath-sounds over these areas may be bronchial or harsh. Occasionally the enlarged glands impede the air entry to a lower lobe, generally the right, in which case breath-sounds are notably weakened over this area, while the percussion note may be impaired. Normally, whispering pectoriloquy ceases at the seventh cervical spine; with enlarged mediastinal glands it may be heard along the middle line or close beside it, in the upper thoracic region from the first to the fifth thoracic spines. This is known as d'Espine's sign or tracheophony. It is a confirmatory sign, when other indications are present. Eustace Smith's sign is of little value. It consists in a venous hum, audible over the manubrium sterni, when the child's head is thrown back as far as possible. Most of these physical signs are of historical interest only as diagnosis is unreliable without radiological information. Occasionally pressure on the recurrent laryngeal nerve may lead to an abductor paralysis of one vocal cord. In cases of tuberculosis, syphilis, Hodgkin's disease or leukaemia, enlarged glands may be present in other parts of the body, and may thus assist in diagnosis.

**Complications.**—A caseous gland may ulcerate into a bronchus or into the trachea, and death has resulted from glottic impaction of a portion of the gland. Ulceration into the œsophagus has been described. Rupture into the mediastinum may lead to mediastinal abscess. Invasion of the pleura, lung or pericardium may occur, or generalisation causing widespread miliary tuberculosis. Compression by tuberculous glands may lead to lobar collapse and bronchiectasis may follow.

**Diagnosis.**—Whenever the condition of mediastinal glandular enlargement is suspected, radiographic examination should be made if possible. It may help to distinguish between other conditions causing mediastinal pressure, such as aneurysm, abscess and malignant growth. Unfortunately in tuberculous disease, it shows best the condition of least importance, namely, the old healed calcified glands. The Mantoux test should be used to differentiate between tuberculosis and sarcoidosis.

**Prognosis.**—This varies with the cause, being serious in Hodgkin's disease and leukaemia. In tuberculous cases, the prognosis is, as a rule, good, apart from complications, provided treatment is prompt and adequate. The prognosis of this form of sarcoidosis is excellent.

**Treatment.**—In tuberculous adenitis, the general condition should be improved by every possible means. The child should be taken from school, rest and exercise are to be carefully graduated, and a liberal diet supplied, with extra milk, cream and butter. Cod-liver oil and malt extracts are useful. In glandular enlargements due to syphilis, Hodgkin's disease and leukaemia, the treatment appropriate to these diseases should be employed and symptoms due to pressure relieved as far as possible. Opinions differ as to whether tuberculous adenitis and the primary lesion which gives rise to it should be treated with antibiotics. Undoubtedly most cases recover without, but treatment with streptomycin and isoniazid should be given in very young children, or where there are complications such as bronchial ulceration or compression, or any suggestion of post-primary spread, or where the severity of symptoms suggest any doubt as to the usually favourable outcome.

## MEDIASTINAL TUMOURS OR NEW-GROWTHS

Routine radiology and thoracic surgery have enlarged our knowledge of mediastinal tumours.

NEUROGENIC TUMOURS, divided into neurofibromata and ganglio-neuromata, are

found mainly in the posterior mediastinum. Simple tumours often reach a considerable size before giving rise to any symptoms but about 15 per cent. undergo malignant changes. Occasionally they are associated with von Recklinghausen's neurofibromatosis.

**DERMOIDS** and **TERATOMATA** are congenital cysts which are usually found in the anterior mediastinum. They often give rise to no symptoms but they have a definite tendency towards malignant change.

**LYMPHOBLASTOMA** and **LYMPHOSARCOMA** produce considerable mediastinal enlargement with pressure symptoms. They are usually very sensitive to radiotherapy and their disappearance after a few exposures is almost diagnostic, but they soon recur and eventually fail to respond to radiotherapy.

**LYMPHADENOMA** or **HODGKIN'S DISEASE** causes mediastinal tumours similar to those of lymphosarcoma. They also respond to radiotherapy but not quite so quickly or completely, although the effect often lasts longer.

**THYMOMA**.—This tumour is found usually in the anterior and upper part of the chest but they may occur over the pericardium or even on a level with the diaphragm. Their presence is sometimes associated with myasthenia gravis and they sometimes become malignant.

**INTRATHORACIC GOITRE**.—Colloid goitre sometimes descends into the anterior mediastinum behind the upper end of the sternum where it may cause pressure symptoms. It can sometimes be felt from above on deep inspiration or during swallowing, and it often causes deviation of the trachea with respiratory symptoms.

**PLEURO-PERICARDIAL CYSTS** are simple cysts lined by flattened epithelial cells and filled with a clear colourless liquid from which they get the name "Spring water cysts". In origin they are congenital arising from the pleural cavity at the 15 mm. embryonic stage. They are found lying in the cardio-phrenic angle, usually on the right side, and may be circular or lobulated in outline. They seldom give rise to any symptoms unless they become very large. This is unusual, and their chief importance clinically is due to the errors in diagnosis that may arise when they are seen in a radiograph of the chest.

**MEDIASTINAL GLANDS** may become very massive in bronchial carcinoma so that they overshadow the primary lesion, and in primary tuberculosis in children and non-immune native races they may give rise to mediastinal symptoms.

**HYDATID CYSTS** of the mediastinum are rare in this country although they arise in the more primitive agricultural countries of the Continent, the Americas and Australia.

**OTHER TUMOURS** occasionally occur: lipomata, meningocele, hæmangioma and chondromata are worthy of mention.

**Pathology**.—The morbid appearance depends upon the situation of origin, the directions of growth and the nature of the tumour. Sarcomata are generally soft, pinkish in colour and vascular, while carcinomata are paler and firmer. There may be one large mass weighing several pounds, or there may be multiple growths. When the tumour reaches a considerable size it may infiltrate, surround, compress or displace contiguous structures. This is particularly the case in the lympho-sarcomata. The trachea, œsophagus and large vessels may be surrounded, the pericardium and heart may be extensively infiltrated, and the nerve trunks may be enclosed and compressed. Secondary deposits are common in other glands, but not infrequently the pigmented bronchial glands may be seen entirely enclosed in growth without being infiltrated.

**Symptoms**.—The onset is often insidious, and the condition may not be suspected until cachexia and pressure signs develop. Malaise, weakness, shortness of breath, cough and pain are often early symptoms, which become more pronounced as the case progresses. The pressure symptoms and signs constituting the "mediastinal syndrome" comprise—

1. *Pressure on the air passages*, giving rise to dyspnoea, cough and expectoration.

The dyspnoea may be inspiratory and associated with stridor, or expiratory and paroxysmal. The cough is harsh and may be "brassy"; it is often associated with mucoid, blood-stained or even "prune juice" sputum. Bronchiectasis may result in some cases.

2. *Pressure on or infiltration of the lung*, leading to collapse and sometimes breaking down of lung tissue. If the pleura is reached or invaded, pleural effusion, often blood-stained, may result.

3. *Pressure on arteries*.—Compression of branches of the pulmonary artery may lead to local gangrene, or in other cases the growth may ulcerate into a larger vessel and cause fatal hæmorrhage. Pressure on the subclavian artery may cause inequality of the radial pulses, and, according to Ekgren, this may only be present when the patient is lying and not when he is standing.

4. *Pressure on veins*.—Dilated tortuous veins may be seen over the front of the chest and abdomen, or in the neck. The flow of blood in these superficial veins may be reversed in direction, owing to the obstruction of the superior vena cava or its main radicles. The current then runs from above downwards, instead of from below upwards, as normally. There may be œdema of the chest-wall or of the face and neck from the same cause.

5. *Pressure on nerves*.—The vagus may be compressed, causing paroxysmal dyspnoea and cough. Laryngeal paralysis or spasm may result from involvement of the recurrent laryngeal nerve. Dilatation of the pupil, followed later by constriction, drooping of the upper lid and enophthalmos, occurs when the sympathetic is involved (Horner's syndrome). Paralysis of the diaphragm on one side from compression of the phrenic nerve, and pain from involvement of the intercostal nerves, may be present.

6. *Pressure on the œsophagus* may lead to dysphagia of increasing degree.

In addition to the signs afforded by these various conditions, there may be glandular enlargements in the neck, the suprasternal notch or in the axillæ. The growth may invade the chest-wall at any spot, and in rare cases it may cause visible or palpable pulsation. The pulmonary physical signs are dyspnoea, sometimes orthopnoea and cyanosis. In some instances the patient prefers to lean forward; this is said to be due to the fact that in this position the antero-posterior diameter of the mediastinum is increased, and the tension caused by the growth is thereby lessened. There may be dullness over the sternum or over the upper thoracic spines, and over any part of the lung invaded or compressed by the growth. The breath-sounds heard over the dull area may be harsh, bronchial, tubular, weak or absent. The signs due to any secondary condition, such as bronchitis, bronchiectasis or a pleural effusion may be found in addition.

**Complications.**—These include the secondary conditions just mentioned. Others are due to ulceration of the growth through the chest-wall, or into the trachea, bronchi, œsophagus or aorta. Pericarditis may occur if the growth invades the pericardium, and hæmopericardium may result from ulceration of a vessel.

**Diagnosis.**—When signs of mediastinal pressure become apparent, new-growth should be suspected, in common with aneurysm, mediastinal abscess or cyst, enlarged mediastinal glands and pericardial effusion. The history, the general condition of the patient, the physical signs, blood examination and the radiograph may all help in distinguishing between these conditions. The evidence afforded by the radiograph may be of the utmost value. The pulsating shadow of an aneurysm, the large area of a pericardial effusion, the indefinite edge of an infiltrating growth extending into the lung, may be shown clearly, but the appearance should always be interpreted in the light of the other clinical features, and a diagnosis should not be made on radiographic findings alone, since a growth may pulsate, or may give rise to an effusion, while a mediastinal abscess or a cyst may give a sharp shadow. An œsophageal new-growth can sometimes be differentiated by the œsophagoscope, but this should only

be employed when aneurysm can be excluded. Diagnosis from bronchial new-growths may be almost impossible. Before the onset of pressure symptoms, growth may be suspected from the cough and emaciation, and here again the radiograph may give valuable indications. Chronic tuberculous disease should always be excluded by repeated sputum examinations. The diagnosis of mediastinal growth may sometimes be obscured by some of the complications it induces, notably pleural effusion and bronchiectasis. The rapid onset and progress of these conditions and the blood-stained character of an effusion may all suggest the possibility of a malignant cause. The presence of enlarged glands in the neck or axillæ, or of nodular growth in the chest-wall or episternal notch, may afford almost conclusive evidence of malignancy.

**Course.**—Malignant growths enlarge and the course is often rapid, particularly in lympho-sarcoma. Fulminating cases lasting only a few weeks occur; more commonly the patients live from 6 months to 2 years from the onset, rarely more. Simple tumours often give rise to no symptoms and are discovered as a result of routine radiological examination.

**Treatment.**—Since simple tumours may grow in size and cause pressure symptoms or become malignant they are better removed if this is possible, although if left they do not necessarily cause death or disability. The treatment of inoperable malignant tumours is that of inoperable malignant disease elsewhere. Deep X-rays or radium treatment in some form may be tried. Otherwise treatment is symptomatic and palliative. Pain may be relieved by aspirin, codeine or morphine. Sleep may be induced, if there is insomnia, by chloral hydrate, papaveretum (Omnopon) or other hypnotics. If effusion is causing dyspnœa it may be tapped, but the fluid usually collects again rapidly.

## DIAPHRAGMATIC HERNIA

**Definition.**—Protrusion of an abdominal viscus, usually the stomach, through the diaphragm into the thorax.

**Ætiology.**—The condition may be congenital or acquired, some of the latter being due to trauma or inflammatory necrosis. The majority of cases result from a congenital defect in the development of the diaphragm. Congenital herniæ are usually "false", there being no covering sac as a portion of the diaphragm is missing. They occur dorso-laterally, through the foramen of Bochdalek, posteriorly through the œsophageal hiatus or parasternally through the foramen of Morgagni. The stomach, omentum, colon, small intestine, liver, duodenum, pancreas, cæcum or kidney may protrude into the thorax.

The acquired variety, when not due to trauma or necrosis, constitutes the par-œsophageal hernia. A portion of the stomach passes through the œsophageal hiatus, and being enclosed in a sac constitutes a "true" hernia. This may be due to delay in descent of the stomach, constituting a congenital short œsophagus, so that the œsophageal gap around the cardiac end of the stomach is larger than that which normally occurs around the narrow lower end of the œsophagus. The difference in pressure between the abdomen and thorax, which is accentuated by muscular strain, atrophy of the diaphragmatico-œsophageal membrane which fixes the diaphragm to the lower end of the œsophagus and the cardiac end of the stomach, and the fact that the œsophageal opening is lax so that it may distend when the œsophagus is filled with food, are further factors which may lead to the development of a hiatus hernia. Traumatic herniæ are due to wounds or crushing injuries of the thorax or abdomen which involve the diaphragm. They are more common on the left side owing to the protection afforded by the liver on the right side. Subphrenic abscess, empyema or abdominal carcinoma may lead to inflammatory necrosis and herniation of the diaphragm. The hiatus type of hernia is by far the most common clinically.

**Symptoms.**—The symptoms of congenital diaphragmatic hernia are dyspnoea, cyanosis, abdominal pain and distension, and vomiting. In many cases of hiatus hernia there are no symptoms, the condition being revealed by barium meal examination. In others the patient complains of dysphagia, eructations, hiccough, abdominal pain, vomiting or hæmatemesis. Some of the symptoms are due to the ulceration which is sometimes found in the herniated viscus. An otherwise inexplicable secondary anæmia may be due to bleeding from such a lesion.

**Diagnosis.**—The diagnosis is established by barium meal examination of the patient lying in the Trendelenberg position. In some cases of hiatus hernia the symptoms may suggest disease of the gall-bladder, in others angina pectoris or organic lesions of the œsophagus may be simulated.

**Prognosis.**—Death often occurs in the congenital type within a few days of birth. Better results are obtained by operation within 48 hours than by waiting for a week or 10 days. In some series a 50 per cent. cure has been obtained.

**Treatment.**—Medical treatment consists in small and frequent feeds and avoidance of lying down shortly after a meal. In the majority of cases giving rise to symptoms surgery is required, various types of repair operation being performed according to the nature of the lesion.

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## SECTION XIV

### DISEASES OF THE KIDNEYS

#### THE CHARACTERS OF NORMAL URINE

NORMAL urine is a clear, amber-coloured fluid. A slight gelatinous mucoid deposit, called the nubecula, settles out of it on standing. The quantity of urine secreted in 24 hours is about 50 oz. or 1500 ml.; it depends on the amount of food eaten and fluid drunk, and on the amount of fluid lost by the skin, lungs and bowel. Solid food accounts for 33 to 50 per cent. of the total fluid intake. About 75 per cent. of the total intake is excreted by the kidneys, but on any one day the variation may be 50 to 95 per cent. of the intake. The specific gravity usually varies between 1.015 and 1.025. Individual specimens may be 1.005 or less if much fluid has been drunk; or 1.035 on a dry diet, or as the result of much fluid being lost through the skin or bowel. The concentration of chlorides and phosphates has more effect in raising the specific gravity than has urea. The presence of glycosuria may make the specific gravity still higher. The reaction is generally acid, due to acid sodium phosphate. The total acidity is such that about 650 ml. of decinormal caustic soda will neutralise the daily output, but in acidosis the total acidity may be doubled, even despite large doses of alkalis. The pH of individual specimens varies between 4.7 and 10. Urine is more acid during fasting than during digestion while hydrochloric acid is being secreted in the gastric juice. Protein food tends to make the urine acid, but fruit and vegetables tend to make it alkaline, because the organic acids in these foods are converted into alkaline carbonates, which are excreted in the urine. It may be alkaline after rising in the morning, due to increased activity of the respiratory centre, the so-called alkaline tide. On decomposition, either in the bladder or after evacuation, the urine becomes alkaline from the conversion of urea into ammonium carbonate.

The constituents of urine are partly derived from the food (exogenous) and partly from the katabolism of the tissues (endogenous). We may briefly consider the source and significance of the principal constituents.

*Nitrogenous constituents.*—The total nitrogen excreted each day on an ordinary mixed diet is about 18 grammes. Of the various nitrogenous constituents urea is by far the most abundant, its output being 33 g., which contains 15.4 g. of nitrogen, or 85 per cent. of the total nitrogen. As so much of the urea comes directly from the food, the amount of urea falls both absolutely and relatively in starvation; the total nitrogen drops to 5 g. or even less, of which urea nitrogen forms about 60 per cent. On a diet rich in carbohydrates and fat, but containing hardly any nitrogen, these figures may fall still lower, as the assimilation of other foodstuffs reduces the waste of tissue nitrogen to a minimum. This is often forgotten, and in nephritis undue importance is attached to a drop in the output of urea, which is simply due to the diet prescribed being poor in nitrogen.

The purine bodies are next in importance. The best known is uric acid (tri-oxy-purine). A small quantity of the less oxidised purines, xanthine and hypoxanthine, is also excreted. Uric acid is only excreted as such when the urine is concentrated and highly acid; it normally appears as acid-sodium urate (see Gout, p. 444).

Creatinine, the anhydride of creatine, is in some way related to muscle metabolism; 1 to 1.5 g. are excreted daily. It is unimportant in relation to kidney disease, but endogenous (i.e. fasting) creatinine clearance roughly parallels inulin clearance and provides a relatively simple indication of glomerular filtration rate. It is curious that the urine of the adult male contains no creatine, or only traces of it, whereas children

excrete both creatine and creatinine, and in the female the excretion of creatine is intermittent. It is, however, continuous in pregnancy.

Ammonia is normally excreted to the extent of 0.5 to 1 g. daily. The kidney conserves plasma sodium by forming ammonia from protein breakdown products. The increased excretion of ammonia is, therefore, to some extent a measure of acidosis.

The pigments of urine are nitrogenous. The principal one, urochrome, to which urine normally owes its colour, though closely related to urobilin, has an independent origin. Even when all the bile escapes from the body through a biliary fistula the excretion of urochrome is unaltered. Urobilin, on the other hand, is a reduction product of bile pigment. The reduction is effected by bacterial action in the bowel, when it is reabsorbed by the blood and excreted by the kidney. Normally it is excreted as a colourless chromogen. The excretion of urobilin as such may result from increased hæmolytic or from large extravasation of blood, and in diseases of the liver, and with intestinal putrefaction or obstruction. Urobilin gives urine an orange tinge. Urobilinogen changes to urobilin on exposure to light and air, and this partly accounts for the higher colour of urine on standing. The chief interest of uroerythrin, of which normal urine contains only a trace, is that it gives the urine a reddish orange colour when excreted in appreciable amount as a result of gross liver disease (new-growth or cirrhosis) and congestive heart failure. It is responsible for the pink colour of urates deposited from concentrated urines in these diseases. Traces of two other pigments, urochrome and hæmatoporphyrin, are present in normal urine.

Other nitrogenous constituents of the urine are hippuric acid, the purine bases guanine and adenine, aminoacids and peptides, and traces of basic substances including trimethylguanidine, putrescine and cadaverine.

*Non-nitrogenous constituents.*—These are principally salts. Sodium chloride is the most abundant, averaging from 10 to 13 g. a day. It is retained whenever the body retains excess of fluid. This explains the reduced output of sodium chloride in such conditions as œdema and serous exudation. Reduced salt intake or loss through excessive vomiting are other causes. On the other hand the output is much increased in Addison's disease. A simple test for chloride is made by adding 10 drops of concentrated nitric acid to 5 ml. urine, and then add 5 ml. 3 per cent. silver nitrate solution. In normal urine there is an abundant curdy precipitate of silver chloride, but if the chlorides are diminished the solution merely appears milky or opalescent. Urinary sulphates, which are chiefly derived from the sulphur of the protein molecule, are excreted in the urine as inorganic sulphates (about 90 per cent.), and the remainder as ethereal sulphates and neutral sulphur. Indican (an ethereal sulphate, potassium indoxyl sulphate) is present in traces in normal urine; it is excreted in excessive quantity in intestinal putrefaction and in simple constipation. Less importance is now attached to indicanuria than formerly, but it is of interest as an example of a means, namely that of conjugation, by which the body renders a toxic substance innocuous. The phosphates are excreted half as acid phosphates of sodium and potassium, and half as earthy phosphates of calcium and magnesium. The former are not precipitated on neutralisation, while the latter are; they come down as amorphous debris which settles as a white deposit. If amorphous phosphates separate from the urine before it is passed they make it opalescent or milky (phosphaturia). The amorphous deposit of urates is distinguished from that of earthy phosphates by the fact that it occurs in acid urine, is dissolved by heat (about 60° C.) and is often stained pink by the adsorption of urochrome and uroerythrin.

Crystalline deposits are of varied kind, and are briefly as follows: Crystals of ammonium magnesium phosphate (triple phosphate crystals), found in urine which has undergone ammoniacal decomposition, are described as coffin-lids or knife-rests. Crystals of calcium hydrogen phosphate are uncommon, and have the form of simple needles, or occur as clusters or rosettes. Calcium oxalate crystals are octahedral (envelope crystals), or they may be dumbbell shaped. These crystals deposited in

the urine before its passage may cause irritation of the renal pelvis with pain and hæmaturia. Uric acid crystals to naked-eye examination are distinctive. They appear like grains of cayenne pepper at the bottom of a urine glass, and under the microscope assume varied forms like barrels, prisms, needles or rods. Their colour is due to adsorption of urinary pigments. Other crystals to which reference may be made are the thorn apple crystals of sodium or ammonium urate, the hexagon crystals of cystine, the sheaves of tyrosine and the rare yellow spherical masses of leucin. Urinary deposits often contain starch granules (extraneous origin). These may be either recognised by their form or by the fact that they stain deep blue with iodine.

Diastase is the only other substance of importance in the urine. Ten to 30 units of diastase (the urinary diastatic index), are normally present, but less will be found in some forms of impaired renal capacity and a great deal more in most pancreatic diseases. A diastatic index of 50 units suggests a pancreatic lesion, while 100 or more make this certain. In severe pancreatitis 300 to 500 may be found.

## THE ESTIMATION OF RENAL FUNCTION

Renal excretion is the most important mechanism by which the body maintains its remarkably constant chemical composition in varying conditions of nutrition and metabolism. Thus renal function includes not only the concentration and elimination of metabolic waste products such as urea, but also the regulation of body water and electrolytes by controlled absorption of these substances from glomerular filtrate and in some instances by tubular excretion. A full assessment of renal function would involve examination of all these separate mechanisms. The development of renal clearance tests has made it possible to investigate separately changes in glomerular filtration and in the tubular reabsorption and excretion of the various urinary constituents. In addition, abnormal excretion of a substance is often reflected in alteration of its concentration in the plasma. Thus renal function may be studied by investigation of glomerular and tubular "handling" of any blood constituent or by estimation of this substance in the body fluids.

The choice and practical value of tests of renal function depends on a variety of circumstances. In organic renal disease failure of tubular concentration is usually the earliest indication of impairment of function and may be detected by examination of the specific gravity of the urine or by the urea concentration test. Creatinine clearance is the most practicable test for recognising early impairment of glomerular filtration. The urea clearance test gives a good indication of progressive impairment of renal function but requires special precautions for accurate results and does not discriminate between organic renal insufficiency and extrarenal (circulatory) nitrogen retention. The blood urea level is of obvious value in recognising more advanced failure of glomerular filtration leading to nitrogen retention, but again concentration tests are necessary to exclude purely circulatory causes of reduced filtration. The specific clearance tests, such as inulin clearance for measuring glomerular filtration and Diodrast or *p*-amino-hippurate clearance for measuring renal blood flow and maximum tubular excretion, are of great value in studying variations in renal function in normal subjects, but their interpretation in patients with severe renal disease is often doubtful. The same applies to clearance measurements of individual normal constituents of the urine. Such tests are rarely indicated in the common forms of kidney disease but may be of value in the occasional cases where specific anomalies of tubular function occur in the absence of serious organic renal damage. Detailed description of clearance tests is therefore not included here but some practical information on the simpler tests of renal function is given below.

*Urine Specific Gravity.*—If the patient is under observation in hospital, daily examination of the first specimen of urine passed on waking provides a series of



specific gravity values which gives a useful indication of tubular concentrating power. A more accurate test is performed by withholding fluids after breakfast on one day, emptying the bladder last thing at night, and measuring the specific gravity of the first three specimens passed at hourly intervals after waking next morning. If the specific gravity does not exceed 1.020 in any specimen there is definite impairment of tubular function. The presence of 1 g. per 100 ml. albumin in the urine raises the specific gravity 3 points. A negative error may be introduced if the specific gravity is measured when the urine is still warm, the values then being 3-4 points below readings taken at room temperature.

*The Urea Concentration Test.*—Fifteen grammes of urea dissolved in 100 ml. water are taken in the fasting state after the bladder has been emptied. The urine urea concentration at the end of 1, 2 and 3 hours is then estimated (if the blood urea is considerably elevated urea need not be administered). When the urea concentration of the urine exceeds 2 g. per 100 ml. tubular concentrating power may be taken as unimpaired. Values below this level may, however, be obtained in normal subjects if absorption of urea is delayed or if the urine volume exceeds 100 ml. per hour during the test.

*Creatinine Clearance.*—At low blood levels creatinine clearance is a fairly accurate measure of glomerular filtration. This test requires only estimation of the creatinine concentration in the blood and in a 3-hour specimen of urine.

*Phenol Sulphonephthalein (P.S.P.) Excretion.*—This dye is partly excreted by the renal tubules and gives a rough indication of tubular dysfunction. The percentage excretion of the dye is estimated 2 hours after intramuscular injection, or for more accurate information, 30 minutes after intravenous injection; during this period 60-70 per cent. of the injected dye should be excreted in normal subjects. The interpretation of results is doubtful if low urine volumes are excreted and occasionally normal figures are obtained when other tests are grossly impaired.

In conclusion renal function is influenced by a wide variety of circumstances, and changes in glomerular and tubular activity are so diverse that, on the one hand, no single test can be expected to give an accurate indication of renal impairment, and, on the other, most tests are subject to wide normal variations and errors of interpretation. From the practical point of view, however, the creatinine clearance test gives early evidence of impaired glomerular filtration, whilst elevation of the blood urea indicates a more severe degree of glomerular impairment. Whether this is due to organic renal damage or extrarenal (circulatory) factors can only be decided by other tests. Tubular concentration is usually normal in conditions producing extrarenal nitrogen retention, an important exception being severe sodium deprivation. Thus it is essential in all patients with elevation of the blood urea to look for clinical and biochemical evidence of extrarenal causes. The urine specific gravity gives valuable information on tubular concentrating power, but after the specific gravity becomes fixed, further deterioration in tubular function can be followed only by quantitative tests such as urine urea concentration. At this stage, however, the blood urea level is probably a more reliable index of progress and is more easily determined.

#### ESTIMATION OF FUNCTION OF KIDNEYS SEPARATELY

This can only be approximately determined but is a necessary preliminary to nephrectomy, since it is essential that the opposite kidney shall be functioning normally. Some evidence of impaired function may be obtained on intravenous pyelography, when it may be seen that concentration is impaired or absent on one side. Further evidence may be obtained by observing on cystoscopy the time taken for indigo-carmin to appear at the ureteric orifices after intravenous injection of 5 to 10 ml. of the dye. If more exact information is required, urine should be collected from the kidney by ureteric catheterisation. The specimen can then be examined for specific gravity, albumin, pus and bacterial culture.

## ABNORMALITIES OF THE URINARY SECRETION

## 1. POLYURIA

Polyuria implies an increased volume in the output of urine, without reference to mere increased frequency of micturition. It may be due to :

1. Increase in the quantity of fluid imbibed.
2. Increase in the molecular concentration of the glomerular filtrate as in diabetes mellitus. Less water is thereby reabsorbed by the tubules from the glomerular filtrate.
3. Elimination of sodium from the body, *i.e.* saline diuresis as after administration of salt or cortisone.
4. Incapacity of diseased kidneys to excrete a concentrated urine, as in chronic nephritis.
5. Diabetes insipidus may arise without any discoverable cause or may be due to disease of the pituitary gland or of the overlying hypothalamus, or to damage in this neighbourhood of syphilitic meningitis of the base of the brain.

## 2. ANURIA

This means suppression of the secretion of urine as opposed to retention and may be due to :

1. Acute nephritis or nephrosis, whether the result of an infection or of drugs, such as sulphonamides, especially sulphathiazole and sulphapyridine, turpentine, cantharides and mercuric salts.
2. Bilateral obstruction to the ureters.
3. Traumatic causes, such as operations on the kidney or trigone of the bladder, crushing injuries of the limbs, obstetric shock.
4. Severe infections such as malaria, Weil's disease, infected abortion.
5. Incompatible blood transfusion.
6. Peripheral circulatory failure (shock). Here both low blood pressure and oligæmia reduce glomerular filtration.

## 3. ALBUMINURIA

Albuminuria should be more correctly termed proteinuria—since blood serum contains two proteins—albumin and euglobulin—and either may appear in the urine, though search is seldom made for the latter. The ordinary tests of heat coagulation, nitric acid or salicyl-sulphonic acid give positive results with either. The presence of euglobulin may be shown by the addition of dilute acetic acid (33 per cent.) to urine in the cold. The acid is added drop by drop, and the precipitation of globulin is shown by an opalescence in the urine to which the acetic acid is added. Mucin is also deposited by the addition of acetic acid, but it is not redissolved by an excess of acid. A more distinctive test is the precipitation of globulin in distilled water. Single drops of urine are dropped into a glass vessel containing distilled water. As the drop of urine falls through the water it assumes a ring form, and the ring has a milky appearance due to precipitated globulin when the latter is present. The globulin can be precipitated for quantitative examination by making the urine alkaline with ammonia, and then half saturating it with ammonium sulphate.

Proteinuria may be classified thus :

## I. WITHOUT ORGANIC DISEASES OF THE KIDNEYS, as in—

1. *Functional or orthostatic proteinuria.*—This is common in males between puberty and adolescence; it is much less common in females of the same age. Dukes found it in 16 per cent. of all boys entering Rugby School. Protein appears in the urine

secreted in the upright posture, and is absent from the urine passed on first rising; but it may be present in the urine secreted during the first hour of recumbent posture. There is no evidence that the amount of protein in the food influences it. Severe physical exercise may excite proteinuria in healthy young adults. Collier found it present in every one of the Oxford crew of 1906 after rowing a course; to such a condition the term "physiological" proteinuria may fairly be applied. When the protein appears apart from exertion, the subject is often an anæmic weedy youth with a dull heavy aspect and a tendency to fainting. The heart is irritable, and the blood pressure unstable, and fluctuates with change of posture. There may also be a few hyaline casts, and frequently calcium oxalate crystals. In any case of proteinuria, less than 0.1 per cent. in amount, in a boy or young man the diagnosis of a kidney lesion should not be made unless casts other than hyaline are discovered and unless the blood pressure is definitely and permanently raised. If the urine passed on first rising in the morning is albumin-free the albuminuria is almost certainly functional.

2. *Febrile*.—Any acute specific fever may be accompanied by proteinuria due to cloudy swelling of the kidney. It should subside soon after the temperature falls to normal. This type of albuminuria is referred to again under the heading of Toxæmic Kidney, to which it more properly belongs.

3. *Congestive*.—In heart failure there is usually proteinuria from venous congestion of the kidneys. Hyaline casts may also be found. Unlike the urine of nephritis the urine is loaded with urates. After an epileptic fit there is often a transitory proteinuria, probably due to the congested condition of the veins during the fit. For a similar reason protein is apt to be present in the urine of any unconscious person.

## II. WITH ORGANIC DISEASES OF THE KIDNEYS AND URINARY TRACT—

1. Nephritis, acute and chronic, including acute suppurative nephritis, focal nephritis, periarteritis nodosa and pyelonephritis.

2. Acute and chronic ischæmic renal disease, including malignant hypertension, diabetic glomerulosclerosis, severe renal arteriosclerosis and renal infarction.

3. Toxæmia of pregnancy and tubular nephroses.

4. Amyloid disease of kidney.

5. Renal tuberculosis, Grawitz tumour and congenital cystic kidneys.

6. All conditions of the urinary tract characterised by hæmaturia and pyuria.

## 4. ALBUMOSURIA

Albumose, or more correctly proteose, may be found in urine during autolysis of the tissues. It is not of clinical importance except to distinguish it from Bence Jones proteinuria. Bence Jones protein, which is found in considerable amounts in the urine of sufferers from multiple myeloma, is not a true proteose, though possessing similar solubilities. It has affinities with native proteins. It begins to be precipitated at 40° to 55° C., but on approaching boiling-point most of the precipitate is redissolved. This is probably due to the influence of certain salts in the urine, and is not a property of the isolated protein. Since organic renal disease may complicate myelomatosis the heat test may be masked by the presence of albumin. If present, this should be precipitated and the heat test repeated on the filtrate. Bence-Jones protein also gives a ring of coagulum on contact with strong hydrochloric acid. Its recognition is of great diagnostic value, as it is pathognomonic of multiple myeloma (see p. 1184). Sometimes the Bence Jones protein is spontaneously precipitated, causing the urine to appear milky. Considerable excess of phosphates may be found in this milky precipitate, probably derived from the autolysis of the surrounding bone.

True peptone is exceptionally found in the urine in pneumonia and phthisis, but is of no clinical importance.

## 5. HÆMATURIA

When blood is intimately mixed with the urine it is held to be in favour of its renal origin. Bleeding from the bladder is more apt to occur into the last part of the urine voided, while urethral bleeding is said to occur chiefly into the first part. When the quantity of renal bleeding is not great, it imparts a smoky appearance to the urine, owing to the conversion of some of the hæmoglobin into methæmoglobin. On spectroscopic examination methæmoglobin gives an absorption band in the red in addition to the two bands in the green characteristic of oxyhæmoglobin. The chief causes of hæmaturia are best classified as follows :

1. *Prerenal*.—The altered condition of the blood which occurs, for instance, in scurvy, purpura hæmorrhagica and certain hæmorrhagic fevers, leads to the escape of some of the blood through the kidney without any evidence of a definite kidney lesion.

2. *Lesions of the kidney*, due to (a) Nephritis, both acute and chronic. Hæmaturia is a constant feature of acute nephritis and of exacerbations of chronic nephritis. In acute focal nephritis (*e.g.* complicating subacute bacterial infection) hæmaturia may be the only sign of renal disease.

(b) Malignant hypertension.

(c) Local lesions of the kidney, *e.g.* tuberculosis, Grawitz tumour, congenital cystic kidney, epithelioma of the renal pelvis, calculus.

(d) Renal trauma.

(e) Infarction of the kidney.

(f) Drugs such as sulphonamides, mercury.

3. *Local lesions of the urinary tract*, *e.g.* ureteric calculus, papilloma and carcinoma of bladder, prostatic enlargement.

## 6. HÆMOGLOBINURIA

This is due to some hæmolytic agent. It may be—

1. *Paroxysmal*, as in Raynaud's disease and in syphilis. Most cases are syphilitic. The corpuscles are broken down by a hæmolysin which is present in the blood of 5 to 10 per cent. of cases of tertiary syphilis. Those who suffer from paroxysmal hæmoglobinuria are presumed to have some constitutional peculiarity which renders them susceptible to this hæmolysin. The hæmolysin acts as an amboceptor, unites with the red corpuscle in the cold and on return to warmth the normal complement in the plasma causes hæmolysis. In addition to this there are some rare forms of non-syphilitic paroxysmal hæmoglobinuria.

2. *Toxic*.—In this group the toxic agent produces the hæmoglobinuria without an additional factor. Striking examples of this are blackwater fever (*q.v.*) in which the hæmoglobin is actually excreted as methæmalbumin, poisoning by arseniuretted hydrogen, and transfusion of incompatible blood. Hæmoglobinuria may also occur in Lederer's anaemia. The chemical tests for hæmoglobinuria are the same as for hæmaturia, but the microscope will fail to reveal red corpuscles. Some of the pigment is excreted as methæmoglobin, especially after drugs of the aniline group, nitrites or potassium chlorate.

## 7. PORPHYRINURIA and PORPHYRIA (See p. 452)

## 8. BILIRUBINURIA

Another derivative of hæmoglobin, bile pigment, appears in all forms of jaundice due to obstruction of the main or intrahepatic ducts. In hæmolytic jaundice, such as acholuric family jaundice, as the name implies, bile does not appear in the urine.

Bile pigment can often be recognised by noting the tingeing of the froth caused by shaking the urine, but is best detected by the green colour given on addition of a solution of iodine to the urine. Hunter's diazo reaction is a more delicate test for bilirubin. Bile-salts are often absent from the urine when bile pigment is present.

### 9. MELANURIA

Melanin only appears in the urine in melanotic sarcoma. Garrod has shown that in all other diseases in which melanuria has been recorded the test employed has been unsatisfactory. The melanin is excreted as melanogen which darkens on standing, and gives a black precipitate on addition of ferric chloride, which is soluble in excess of the reagent, yielding a black solution. A more delicate test is made by the addition of sodium nitro-prusside and sufficient caustic soda to render the urine alkaline. The ordinary ruby-red colour, due to creatinine, is developed. The urine is now made acid with acetic acid, and if melanogen is present a prussian-blue colour appears.

### 10. ALKAPTONURIA

Alkaptonuric ochronosis is an inborn error of metabolism (Garrod). It is hereditary and scarcely affects health. The individual cannot complete the katabolism of the amino-acids phenylalanine and tyrosine; as a result, 2, 5-dehydroxyphenylacetic acid or homogentisic acid appears in the urine. The urine reduces Benedict's solution on boiling, but it does not ferment. It darkens on standing, or at once on the addition of alkalis. It may stain the linen brown. When a dilute solution of ferric chloride is allowed to fall drop by drop into urine, each drop produces a transitory deep blue colour. The urine reduces ammoniacal silver nitrate in the cold, giving a silver mirror on the sides of the test tube. The black pigment in ochronosis is noticed clinically in cartilaginous tissue. An early sign of the disorder is a blue discoloration of the ears, especially of the concha and antihelix, and later the tragus and antitragus. Triangular brown pigmentary deposits with their bases towards the cornea are noted in the sclerae. Bluish discoloration of the tendons of hands also occurs. In long-standing alkaptonuria a peculiar "goose-gait", kyphosis and a stooping posture are characteristic features. These changes are due to osteoarthritis, especially of the vertebral joints.

(For other reducing substances in the urine, including sugar, see p. 425).

### 11. KETONURIA

Ketonuria is a term used loosely to include the appearance in the urine of diacetic acid and its derivatives, acetone and  $\beta$ -oxybutyric acid. Acetone, however, being merely a decomposition product of diacetic acid, is relatively unimportant;  $\beta$ -oxybutyric acid, formerly regarded as the source of diacetic acid, is more saturated and less toxic and has been shown by Hurlley to be formed out of diacetic acid by the liver, as an attempt at detoxication. Diacetic acid is derived from the incomplete oxidation of fats or of the fatty acid groups in protein. It is probably always made in small quantities, but when there is an abundant consumption of carbohydrate, it is completely oxidised. In starvation the store of glycogen is quickly exhausted and the body chiefly lives on its fats; hence ketonuria. Vomiting, whether persistent or cyclical, will excite ketonuria, though without such a degree of intoxication as to cause symptoms. Any disturbance of health in infancy and childhood, especially a febrile state, is liable to cause ketonuria. In conditions where the liver is thrown out of gear, such as post-anæsthetic poisoning, ketonuria may occur with toxic symptoms, because of the severe disturbance of all metabolic processes. But there are other

agents at work besides diacetic acid which may be responsible for those symptoms. Only in advanced diabetes do we find toxic symptoms directly due to diacetic acid. Here there may be complete inability to utilise carbohydrates, so that the body perforce lives on protein and fats. If these are freely given in the food the amount of diacetic acid produced may be very large. But if a diabetic be starved there is a great drop in ketonuria, showing that most of this is exogenous in origin (see Diabetes). The test used for diacetic acid is the mahogany red colour given on the addition of ferric chloride. This has the disadvantage of being masked if the patient is taking salicylates. The nitro-prusside test was formerly regarded as showing the presence of acetone, but Piper demonstrated that it is really a much more sensitive test than ferric chloride for diacetic acid. A crystal of nitro-prusside of soda is dissolved in the urine, and then a strong solution of ammonia is poured on the top. A ring, the colour of Condyl's fluid, speedily develops at the junction of the liquids and spreads upwards. The intensity of colour is a rough measure of the degree of ketonuria. The reaction is made still more sensitive by previous addition of crystals of ammonium sulphate to saturation (Rothera).

## 12. DRUGS WHICH ALTER THE COLOUR OF URINE

Methylene-blue is used as a colouring matter of sweets and also as an ingredient of certain proprietary pills. It used to be given for *Bact. coli* infections of the urinary tract, gonorrhoea and bilharzia, or less commonly as an analgesic in rheumatism, sciatica and migraine. In small quantities it imparts a green colour to the urine, when it may be precipitated with the mucin. In larger doses it turns the urine blue. It can be recognised by simple filtration because it is adsorbed on the filter papers. It can be dissolved from the filter paper by chloroform, and is turned pink by the addition of alkalis. Its identity is best proved by loss of colour on adding glucose and alkali. Eosin may be used in sweets and turns the urine a fluorescent pink. Prontosil and pyridium turn the urine a reddish-orange colour, though, if the urine is alkaline, this may not appear until it is acidified. Amidopyrine may have a like effect. Rhubarb and senna may turn the urine reddish-brown from the chrysophanic acid they contain. The urine turns pink on the addition of an alkali. Santonin turns the urine a vivid yellow, which becomes rose-pink with alkalis. Carbolic acid may turn the urine greenish-black on standing, from the formation of hydroquinone. In carbolic acid poisoning the urine withdrawn by a catheter may even be found olive-green without exposure to the air. Other drugs, which may have this effect are salol, creosote, naphthalene and uva ursi. In chronic carboloria, ochronosis may occur as in alkaptonuria.

Certain drugs can readily be recognised in the urine by some colour reaction. Thus, salicylates are excreted as salicyluric acid, which gives a violet colour on the addition of ferric chloride. Copaiba, which is precipitated by nitric acid, can be distinguished from albumin by the solubility of the precipitate in alcohol. On the addition of hydrochloric acid a urine containing copaiba turns cloudy, the cloud soon becoming rose pink. Iodides in urine give a blue colour with guaiacum, and on the addition of hydrochloric acid impart a violet colour to chloroform shaken up with the urine.

## 13. PYURIA

Pus may come from the urethra, prostate, bladder or kidney. The diagnosis of the source is discussed under septic diseases of the kidney. The best test for pus in the urine is the microscope. If the amount of pus be considerable it will yield aropy mass on the addition of liquor potassæ. If ozonic ether is shaken with the urine, bubbles of oxygen are evolved. With tincture of guaiacum a blue colour may be given even without the addition of ozonic ether.

## 14. CHYLURIA

True chyluria is due to blocking of the thoracic duct, most commonly by *Filaria bancrofti*, but sometimes the result of inflammatory or neoplastic conditions, with consequent rupture of lymphatics of the bladder through back pressure. Fat may be found in the urine in the lipæmia of diabetes, in growths of the kidney and after fracture of long bones, when fat may be liberated into the circulation. Accidental contamination by an oily lubricant for a catheter and fraudulent addition of milk to the urine must be excluded. Pseudo-chyluria is due to a lecithin compound of globulin, and is sometimes found when there is a great excess of globulin in the urine. Unlike true fat, this substance is not extracted by shaking up with ether.

## 15. PNEUMATURIA

Osler gives the following causes for gas in the urine: (1) Mechanical introduction of air in vesical irrigation or cystoscopic examination in the knee-elbow position. (2) Infection of the urine as by *Clostridium welchii*. (3) Vesico-enteric fistula. An additional cause is infection with yeasts in diabetes.

## 16. CRYSTALLINE DEPOSITS IN URINE

The chief factors in the deposit of uric acid crystals as such are high acidity, high percentage of uric acid and poverty in mineral salts. The first two are the most important, especially the first. Deposits of urates are usually amorphous. These have already been briefly described (see p. 1099). Calcium oxalate crystals may cause bladder irritability with increased frequency of micturition, and occasionally albuminuria and hæmaturia. They may arise from ingested oxalates. Rhubarb, spinach, asparagus and sorrel are the foods most likely to produce oxaluria sufficient to excite symptoms, for each contain more than 2 g. of oxalic acid per kilogram, though many other articles of diet contain some oxalates. Some individuals seem sensitive to strawberries which, however, only contain 0.06 g. per kilogram.

## 17. AMINO-ACIDURIA

Recent light has been thrown on the significance of amino-acid excretion by paper chromatography. Amino-acids may appear in the urine in excess, either due to an abnormally high plasma level as in liver disease or due to low renal threshold as in Fanconi's syndrome and familial cystinuria. In severe liver disease such as acute yellow atrophy, gross amino-aciduria occurs and there may be an excess of all the common amino-acids in high concentration. In chronic liver disease an excess of cystine is commonly found. In hereditary (familial) cystinuria, cystine is continuously excreted in large quantities, crystals may appear in the urine, and cystine calculi tend to form; in these cases lysine and arginine are also excreted in increased amount. In Fanconi's syndrome the cystinuria is part of a generalised disturbance of urinary amino-acid excretion, and abnormal amounts of other amino-acids appear in the urine. Resistant rickets and deposition of cystine in the tissues (cystinosis) occur in the Fanconi syndrome but stone formation does not occur.

## CIRCULATORY DISTURBANCES

1. *Passive congestion*.—Anything which raises the pressure in the renal vein must produce a passive congestion of the kidney. Failing compensation in heart disease

and hypertension is the commonest cause; but it may also be brought about by respiratory diseases or by pressure on the renal vein by abdominal tumours or ascities. A transient congestion may result from an epileptic fit.

The cardiac kidney, as it is called, is the most typical example of passive congestion. The organ is firm and dark in colour, especially the pyramids. The capsule strips normally. The stellate veins are engorged. The kidney may drip with blood on section, and if placed in a dish after section soon exudes œdematous fluid.

The urine is scanty, high-coloured and of high specific gravity. Unlike the urine of chronic nephritis it is loaded with urates. It contains a variable amount of albumin and hyaline casts, with a few red blood corpuscles, if the congestion is at all considerable. A moderate degree of nitrogen retention may result (up to 100 mg. per cent. blood urea) but tubular concentrating power is unaffected. The prognosis and treatment are those of the cardiac condition causing it. Stimulating diuretics are of much more service than in nephritis, since there is no primary disease of the secreting structures. Organic mercurial preparations are especially effective.

2. *Infarction*.—This may be due to embolism, e.g. in rheumatic carditis or infective endocarditis, or to thrombosis in an atheromatous renal artery. Obstruction of large arteries leads to anæmic infarcts, "map-like" areas of coagulation necrosis, roughly wedge-shaped, but with irregular edges and with the base reaching the surface of the organ. Their formation may cause a sudden pain in the loins if they are large. Either of these conditions will cause both albuminuria and hæmaturia.

3. *Thrombosis of the renal vein*.—This is rare, and is usually significant of a terminal infection, as in a marasmic infant. In thrombosis of the inferior vena cava the process may reach as high as and spread into the renal vein. This would produce the same effects as the cardiac kidney, but in a much more intense form. Bilateral renal vein thrombosis may arise from no apparent cause and may produce a picture indistinguishable from that of nephrosis.

## URÆMIA

Uræmia literally means retention of urine in the blood, so that by derivation, the principle features should be due to failure of excretion of waste products of metabolism. The functional disturbance in renal failure is, however, much more complex than this. Excretion of waste products by the kidney is only a small part of its total function, and renal failure can only be fully understood when the kidney is considered as the chief executive organ of the homeostatic mechanism of the body. That is, acting under the influence of the adrenal and pituitary glands and other controlling factors not yet elucidated, the kidney plays a vital part in maintaining the various body equilibria. These include total water content of the body, sodium and potassium regulation, acid base balance and, in all probability, maintenance of normal blood pressure. It is obvious, therefore, that renal failure will produce complex and varied symptoms related to these functions. The picture is further complicated by the fact that renal efficiency is itself considerably affected by disturbance of these body equilibria. Thus salt deficiency, alkalosis and hypotension all have a serious effect on the process of urine formation. At the outset therefore, it is necessary to distinguish between *extrarenal uræmia* due to these factors and *primary renal failure* due to organic disease of the kidneys, and further to appreciate that the latter may be complicated by the former.

**NORMAL KIDNEY FUNCTION.**—(1) *Excretion of waste products*.—These are almost entirely the end-products of protein metabolism, urea, uric acid, creatinine and ammonia. In addition, organic acids may be excreted either alone or after being conjugated with other substances by the liver.

(2) *Acid base balance*.—The cations excreted by the kidney are sodium, potassium,



ammonium, calcium and magnesium. The anions are chloride, phosphate, sulphate and organic acid radicals. The kidney compensates for changes in the acid base balance of the blood largely by conservation of base. This it performs, e.g. in severe acidosis, by increase in the reabsorption of sodium, in the excretion of hydrogen ions and in the elaboration and excretion of ammonia by the renal tubule cells.

(3) *Body water*.—Excessive water drinking leads to water diuresis whilst excessive loss of fluid due to vomiting, sweating or diarrhœa leads to oliguria. This compensatory process is due to the action of the posterior pituitary anti-diuretic hormone, which decreases or increases reabsorption of water by the renal tubules. Disorder of this mechanism is illustrated by the gross polyuria of diabetes insipidus.

(4) *Electrolyte control*.—Conservation of body sodium is a priority function of the kidney and the absorption of sodium by the tubules is under the direct control of the salt hormone of the adrenal cortex. Breakdown of this control occurs in Addison's disease and leads to excessive sodium loss in the urine with consequent reduction in the volume of extracellular fluid. The mechanism by which the renal tubules regulate potassium excretion is not fully understood. Phosphate reabsorption is controlled by the parathyroid glands; excessive elimination in hyperparathyroidism leads to the gross disturbance of calcium metabolism which characterises this disorder. Other rare functional tubular anomalies of electrolyte control occur in nephrocalcinosis and the Fanconi syndrome.

(5) *Maintenance of the arteriolar resistance* which determines diastolic blood pressure is in some way related to kidney function, since diastolic hypertension is a common feature of renal disease and experimental interference with renal blood flow in animals regularly produces high blood pressure. That this is not due to renal failure in the ordinary sense of the term is shown by the fact that unilateral renal artery constriction can lead to sustained hypertension. There is a possibility that the adrenal cortex is also concerned in this function of the kidney, since such experimental hypertension is abolished by adrenalectomy.

**MECHANISM OF URINE FORMATION.**—There are roughly one million nephrons in each kidney and the renal blood flow through the glomeruli is about 1.3 litres per minute, i.e. one-third of the cardiac output. Urine is formed by a combination of glomerular filtration with selective tubular absorption. Glomerular filtration is purely physical and is brought about by an effective filtration pressure which is the resultant of the blood pressure and osmotic pressure in the glomerular capillaries. The glomeruli filter about 170 litres per day and the filtrate contains all the constituents of blood plasma except that protein is present in only minute amounts; the specific gravity of glomerular filtrate is approximately 1.010. Clearance of substances from the blood is almost entirely a function of glomerular filtration. Selective tubular reabsorption is responsible for changing the glomerular filtrate into urine. It therefore involves the reabsorption of all the water in the glomerular filtrate except some 1,500 ml. together with the greater part of the useful substances such as sugar and chloride. By this massive reabsorption of water the tubules concentrate waste products, particularly urea, about one hundred times. Since the urine is normally hypertonic (S.G. 1.020 to 1.030) compared with glomerular filtrate, it is obvious that the fluid absorbed by the tubules must be hypotonic, i.e. in health the renal tubules do osmotic work in concentrating the urine. Even when tubular function is impaired and no osmotic work is done (i.e. when the urine specific gravity is fixed at 1.010), there is still a selective reabsorption of useful substances which permits considerable concentration of urea.

**PRIMARY RENAL FAILURE.**—Primary renal failure is due to destruction of nephrons by organic kidney disease. At the outset two main types must be recognised. The more common is chronic uræmia due to progressive Bright's disease or other destructive lesions. Less common is acute uræmia to which reference is made under the heading of Traumatic Anuria.

## (A) CHRONIC URÆMIA

In this form of uræmia impairment of tubular function precedes and exceeds impairment of glomerular filtration, since the epithelial cells of the tubules are more susceptible to noxious agents than is the vascular structure of the glomerulus. Furthermore the kidney has a very considerable physiological reserve so that considerable organic damage may occur before the usual tests of tubular or glomerular function can be shown to be impaired. We must therefore recognise three stages of renal failure :

(1) *Reduction of renal reserve.*—In this stage the blood urea and urinary concentrating power are both normal, but tests devised to measure the total excretory mass, such as diodone clearance may indicate a reduction below the normal. This is found, for example, in severe benign essential hypertension and in renal arteriosclerosis. The practical point here is that if a severe strain is imposed on the kidneys, for example, by a surgical operation or the onset of heart failure or hæmorrhagic shock, it may lead to a severe and sometimes fatal uræmia.

(2) *The stage of impaired tubular concentrating power.*—The earliest clinical symptoms of renal inefficiency appear at this stage and consist of nocturnal frequency with, later, polyuria and thirst. The limits of specific gravity of the urine are narrowed and there is eventual fixation around 1.010. The urine urea concentration falls below 2 g. per cent., and this test is a useful measure of subsequent deterioration after the urine specific gravity is fixed. This intermediate stage of renal impairment may persist for many years before the blood urea starts to rise. Nevertheless polyuria has in most cases of chronic renal disease a limited duration owing to the progressive destruction of glomeruli. Persistent polyuria is usually observed only in forms of nephritis in which the tubules are primarily or predominantly involved, e.g. ascending pyelonephritis with congenital dilatation of the urinary tract.

(3) *Failure of glomerular function.*—In this final stage the glomerular filtrate volume falls below the limiting value at which the blood can be cleared of urea. The symptoms of uræmia which follow are not, however, solely attributable to elevation of blood urea, but are referable to a complex disturbance of function which has already been discussed.

**THE CLINICAL SYNDROME OF CHRONIC URÆMIA.**—The clinical syndrome of chronic uræmia results from a combination of excretory failure, disturbance of body equilibria and hypertensive manifestations. In general, those symptoms which are due to excretory failure appear late, and may be seen only in the terminal stages, whilst hypertensive symptoms are often amongst the earliest manifestations of the disease. Elevation of blood urea in itself is not responsible for the variety of symptoms since patients with gross nitrogen retention but without hypertension may be free from symptoms. The real cause of the varied manifestations which are often attributed to the retention of waste products is quite obscure. Most prominent amongst these are digestive symptoms—*anorexia*, *nausea*, *vomiting* and *hiccough*; *diarrhœa* is infrequent. *Anæmia* is a common complication and is refractory in type. *Acidosis* due to failure of ammonia formation by the kidney leads to the classical, usually terminal, harsh, deep, regular, acidotic breathing first described by Kussmaul in diabetic acidosis. Severe dehydration and sodium deficiency may be due to polyuria and vomiting, and these in turn may greatly aggravate the renal failure. Increased muscular irritability leading to cramps and twittings, and occasionally to tetany, are due to a complex disturbance in the ionic balance which regulates nervous and muscular excitability; no uniform abnormality of blood calcium is found. Irritation of the skin is common and so-called “urea frost” may sometimes be observed on the face. There is an increased tendency to hæmorrhage which may cause purpura, bleeding into joints or gastro-intestinal hæmorrhage. A sterile pericarditis is a not uncommon terminal complication. Ultimately excretory failure results in drowsiness,

disorientation and fatal coma. In the very chronic uræmia which occurs in patients with little or no hypertension, disturbance of calcium and phosphate excretion leads to decalcification of bone and deposition of calcium in other tissues such as the arterial walls, muscles and kidneys. Decalcification of the bones in young children may lead to a picture indistinguishable from vitamin D deficiency rickets, while in older subjects there may be multiple cystic degeneration of bone such as occurs as a result of hyperparathyroidism; marked hyperplasia of the parathyroid glands occurs in chronic uræmia.

The hypertensive manifestations of chronic uræmia are referable to the heart, the brain and the retina. Heart failure is common in hypertensive Bright's disease and predominantly affects the left ventricle with consequent pulmonary congestion and œdema. "Renal asthma" is the same as cardiac asthma, and consists of attacks of paroxysmal, usually nocturnal, dyspnoea, due to pulmonary œdema. The development of heart failure further aggravates the renal dysfunction. Organic cerebral vascular lesions occur as in any other form of hypertension. If the malignant phase develops, there may be attacks of encephalopathy consisting of disorientation, headaches, convulsions, transient blindness and coma. Exudates and hæmorrhages appear in the retina and when these affect the macula, impairment of vision results. The development of papilloedema is diagnostic of the malignant hypertensive phase. Added to this picture of excretory failure and hypertension are the effects of general malnutrition and hypoproteinæmia due to anorexia, vomiting and albuminuria. It is not surprising therefore that in the terminal stages many patients with uræmia develop generalised œdema, the mechanism of which may be partly cardiac, partly renal and partly nutritional.

#### (B) ACUTE URÆMIA

Acute uræmia is described under Traumatic Anuria (p. 1128). It is characterised by a total failure of the nephron leading to suppression of urine. This form of uræmia is also seen in acute nephritis when anuria occurs in the early stage.

**EXTRA-RENAL NITROGEN RETENTION.**—This term is preferable to "extra-renal uræmia" since the disturbance is usually limited to a moderate elevation of blood urea (rarely over 100 mg. per cent.), unassociated with the various complex disorders described above. The immediate cause of extrarenal nitrogen retention is some impairment of the renal circulation leading to diminished renal blood flow, or lowered filtration pressure, or both. Such disturbances arise in oligæmic states such as result from hæmorrhage or from severe dehydration. The latter may be due to repeated vomiting, diarrhoea, massive œdema formation, or salt deficiency as in Addison's disease. A similar degree of nitrogen retention is produced by severe heart failure. Glomerular filtration pressure is lowered by shock or by other causes of low blood pressure such as Addison's disease. In all these circulatory disturbances the effect is primarily on glomerular filtration so that the blood urea is often found to be elevated whilst tubular concentrating power is normal; the urine is highly coloured and the urine output greatly diminished. If the circulatory disturbance is severe and very prolonged tubular function is affected and concentrating power is diminished. Epithelial cell damage may occur and a tubular nephrosis results which may resolve but leave behind calcification of the epithelium. It is important to realise that primary renal failure may be aggravated by extrarenal factors and that correction of the latter may greatly improve renal function.

**Treatment of Uræmia.**—This is fully discussed under the treatment of chronic Type 1 and Type 2 nephritis (chronic uræmia) and of traumatic anuria (acute uræmia).

#### RENAL HYPERTENSION

The occurrence of high blood pressure in some cases of kidney disease was known to Bright. The subject has in recent years gained steadily in importance as

experimental evidence has revealed the close relationship between hypertension and development of organic renal damage. Goldblatt's experiment, in which sustained hypertension was produced in dogs by renal artery occlusion, first suggested a mechanism by which renal disease might elevate the blood pressure. It has subsequently been shown that many types of experimental renal damage in different species of animals will give rise to hypertension. Although it seems probable that some form of circulatory restriction is common to all, the exact nature of the haemodynamic disturbance which leads to elevation of blood pressure is not yet understood. Some important relationships have, however, been established. The work of Wilson and Byrom showed that sustained hypertension could be produced in rats by incomplete occlusion of one renal artery without interfering with the opposite kidney, so that renal insufficiency in the usually accepted sense of the term is not necessary for the development of hypertension. Furthermore, organic renal damage is not a necessary pre-requisite since high levels of blood pressure were produced although the ischaemic kidney remained histologically normal. It was also demonstrated in these experiments that arteriolar necroses with associated glomerular and tubular lesions found in malignant hypertension were produced in the opposite kidney but were absent from the clamped kidney. From this it was deduced that the renal lesions which characterise malignant hypertension are in fact the result and not the cause of the high blood pressure in this disorder. The common occurrence of similar hypertensive lesions in primary renal disease was also thereby explained. Wilson and Byrom went on to postulate that since hypertension can produce occlusive renal vascular lesions a vicious circle may be established which leads to progressive renal damage and further hypertension. Such a vicious circle would account for the rapidly progressive course of malignant hypertension, whether renal or essential in origin, and the dramatic manner in which progressive deterioration may be checked when the blood pressure is lowered, for example, by removal of a single diseased kidney, indicates the possibility and importance of breaking the sequence. More recent experiments have shown that renal hypertension persists after total nephrectomy so that an extra-renal mechanism is in some way involved. It seems probable that the adrenal cortex plays a rôle in this mechanism since adrenalectomy abolishes experimental renal hypertension. Moreover administration of salt hormone or increase in sodium chloride intake can act as an effective substitute for the adrenal cortex in maintaining the hypertension. A tentative hypothesis is put forward, therefore, that normally the kidneys inhibit or inactivate an extrarenal pressor mechanism which depends on electrolyte distribution in the arterioles. Damage to the kidneys or their removal interferes with this renal inactivation and leads to a rise in blood pressure. Much further evidence is required before this hypothesis can be regarded as established but there are many clinical observations, such as the well-known effect on the blood pressure of sodium restriction on the one hand or increased salt intake on the other, which have an obvious relevance to this hypothesis.

The varieties of high blood pressure encountered in different forms of renal disease cannot yet be fully related to the underlying lesion. Chronic renal disease progressing to renal failure without hypertension is rare but may be encountered in chronic Type 2 nephritis (chronic nephrosis), amyloid disease, chronic pyelonephritis and congenital lesions, particularly those associated with dilatation of the urinary tract. Renal hypertension becomes malignant, *i.e.* papilloedema develops, in about a third to one-half of all cases, *i.e.* much more commonly than is observed in essential hypertension. Development of the malignant phase is usually followed by rapid deterioration of renal function and death in 6 to 12 months. Nevertheless a temporary remission with subsidence of papilloedema may occasionally occur spontaneously or after reduction in the blood pressure level by sympathectomy, hexamethonium drugs or salt restriction.

**HYPERTENSION DUE TO UNILATERAL RENAL DISEASE.**—Many cases have been

reported in which unilateral renal disease has led to the development of severe hypertension, and this may be of the malignant type. Secondary hypertensive changes may occur in the contralateral kidney and the histological picture of malignant nephrosclerosis is sometimes found post mortem in such kidneys. It is therefore important, especially in young subjects presenting with hypertension but without impairment of renal function, to search for a possible unilateral lesion. Intravenous pyelography may reveal a nonfunctioning kidney, or unilateral hydronephrosis, or gross contraction on one side with a hypertrophied kidney on the other. In such cases nephrectomy may bring about prompt reversal of papilloedema and restoration of blood pressure to the normal level even after many years of severe hypertension. A great variety of lesions may be found in the diseased kidney, the most common being chronic pyelonephritis in a congenitally abnormal kidney. Other causes of unilateral renal disease which may lead to hypertension are atheromatous obstruction of a main renal artery, tuberculosis, hydronephrosis, renal cysts and tumours.

### RENAL ŒDEMA

Anasarca was the main clinical feature described by Bright in patients with organic kidney disease. Nevertheless our knowledge of the mechanism of renal œdema is no more exact than our understanding of hypertension. While in the majority of patients more than one factor is involved, it must be recognised that there is a form of fluid retention directly attributable to kidney disease and it is this factor which is still obscure.

**Pathology of Oedema.**—Oedema of all forms is the result of water and sodium retention in the tissues. In health the extracellular fluid volume is maintained constant by a balance of physical and chemical forces. The physical component is the resultant of the hydrostatic pressure of the blood and plasma protein osmotic pressure and these forces control the tissue circulation; *i.e.* the circulation of fluid from the arterial end of the capillary into the tissues and back from the tissues into the venules. Increase of hydrostatic pressure as in right heart failure, or lowering of osmotic pressure due to hypoproteinæmia, will favour accumulation of fluid in the tissues. The chemical factors are those responsible for the maintenance of a constant extracellular fluid volume and the most important of these is the salt hormone of the adrenal cortex which directly influences reabsorption of sodium by the renal tubules. Administration of the hormone in excessive doses will produce œdema as will failure of tubular function in anuria, unless salt and water intake are restricted. This hormonal control thus maintains a balance between intake of sodium and water, tissue fluid content and excretion by the kidneys.

**RENAL ŒDEMA.**—*Characteristics.*—Anasarca occurs only when both kidneys are diseased. In the absence of complicating factors, *e.g.* in acute nephritis, œdema is sudden in onset and has a generalised distribution, affecting the face, trunk and legs. It tends to be most marked in the early morning and diminishes with activity, in contrast to cardiac œdema. In severe cases serous effusions and pulmonary œdema may be produced. Clinically, the œdema can be recognised by pitting on pressure, although there may be in adults retention of half a stone of excess fluid before pitting œdema is demonstrable.

**Causation.**—In many patients with Bright's disease several secondary factors play a part in the development or maintenance of œdema. These are hypoproteinæmia, heart failure and anæmia.

**HYPOPROTEINÆMIA.**—In the nephrotic syndrome the plasma proteins fall to a low level as a result of heavy albuminuria. More albumin than globulin escapes in the urine owing to the smaller size of its molecule; thus the lowering of the protein osmotic pressure of the blood is chiefly due to a fall in its albumin content. It is usual to find œdema when the total proteins fall below 5 g. per cent. or the albumin

below 2 g. per cent. It is probable that hypoproteinæmia contributes to the generalised œdema of many patients with Bright's disease, not only those with the nephrotic syndrome, but also in the early and late stages of Type 1 nephritis when protein loss may lead to considerable lowering of plasma proteins. Nevertheless even in Type 2 nephritis hypoproteinæmia is not the primary cause of œdema, since in the early stages generalised œdema may be present with a normal plasma protein level, and in any patient massive diuresis with disappearance of œdema may occur without any significant elevation of the blood protein level.

**INCREASED VENOUS PRESSURE.**—This factor may contribute to œdema in chronic hypertensive Bright's disease with manifest heart failure, and in the occasional cases of acute Type 1 nephritis where heart failure is a complication. It cannot however be held accountable for the generalised œdema which occurs in the majority of patients with nephritis. Anæmia may contribute to œdema, especially in the uræmic stage of chronic nephritis, when hæmoglobin levels may fall very low. The effect is probably attributable to aggravation of myocardial failure.

**SODIUM RETENTION.**—Sodium and water retention are manifestly present in renal as in other forms of œdema; restriction of salt in the diet may produce some improvement while increase in sodium intake may increase it. We have at present no reason to incriminate either the adrenal cortical hormone or renal retention of sodium due to diminished glomerular filtration or increased reabsorption by the renal tubules. In fact glomerular filtration tends to be high in nephrotic œdema and there is no evidence in any form of Bright's disease of inability to excrete sodium unless there is suppression of urine. When renal insufficiency develops the tendency is towards excessive sodium loss due to acidosis and failure of ammonia formation by the kidney; in occasional cases this may progress to gross salt deficiency. There is no justification for the idea that increase in capillary permeability is a factor in salt retention since the capillaries are completely permeable to electrolytes in health and disease. Increase in permeability to protein in acute nephritis has not been satisfactorily demonstrated, but it is unlikely that this could play a rôle in œdema formation, since the proteins themselves are in a state of dynamic equilibrium between blood and tissues.

**Treatment.**—The treatment of renal œdema is described under Acute and Chronic Glomerulo-nephritis.

## BRIGHT'S DISEASE

Bright's "Disease" is in fact a syndrome, consisting of albuminuria, œdema and (usually) high blood pressure associated with organic kidney disease. The majority of patients presenting with this clinical picture are suffering from glomerulo-nephritis in its acute or chronic forms. Other diseases which may produce the syndrome are amyloid nephrosis, chronic pyelonephritis, malignant hypertension and diabetic glomerulosclerosis.

### *Classification of Bright's Disease*

#### A. NEPHRITIS.

##### I. Glomerulo-nephritis.

Type 1 (synonym: acute hæmorrhagic nephritis).

Type 2 (synonym: parenchymatous nephritis, including lipoid nephrosis).

##### II. Pyelonephritis.

#### B. RENAL VASCULAR DISEASE.

The kidney in essential hypertension—(1) benign; (2) malignant.

Senile arteriosclerosis.

Diabetic glomerulosclerosis.

## C. MISCELLANEOUS CONDITIONS.

Amyloid nephrosis.

Traumatic anuria.

Toxæmia of pregnancy.

Toxic nephrosis.

## GLOMERULO-NEPHRITIS

In describing glomerulo-nephritis most of the confusion in the past has arisen because names have been given to cross-sections of the disease at different stages. Hence glomerulo-nephritis running a continuous course in the same patient might at different times be labelled acute hæmorrhagic nephritis, subacute parenchymatous nephritis, chronic interstitial nephritis, azotæmic nephritis. This cross-sectional terminology can only be avoided by a long-term study of nephritis from both its clinical and pathological aspects. When this approach is followed we arrive at a classification of the *courses* of nephritis such as was introduced by Volhard and Fahr in 1914. In addition, recent information derived from experimental pathology and physiology of the kidney has made it possible to relate various disorders of function such as hypertension, œdema and uræmia to different organic lesions of the kidney. A long-term clinical and pathological study of some 600 cases of Bright's disease by Ellis and his colleagues at the London Hospital showed that the many clinical syndromes of glomerulo-nephritis were related to two main types of pathological process which were termed Type 1 and Type 2 nephritis. Type 1 is usually preceded by a streptococcal infection. Its onset is acute, with hæmaturia as a prominent feature. The prognosis is good, 80 to 90 per cent. of patients recovering completely. In the remainder, according to the severity of the glomerulo-nephritis, death may occur in the acute stage or after a rapidly progressive course running a period of months, or a slowly progressive course lasting from years to decades. Type 2 nephritis has an insidious onset with œdema, which tends to increase and persist for months or even years. Hæmaturia is not a prominent feature, but albuminuria is severe and is associated with gross depletion of plasma proteins. Recovery is rare and is practically limited to cases without hypertension. The great majority of patients continue with albuminuria and recurrent œdema for many years before renal failure develops. The morbid anatomical changes correspond closely with these clinical courses. In Type 1 nephritis the lesion is diffuse and severe at the onset, but in most cases resolves completely. In Type 2 nephritis there is a less intense diffuse glomerulo-nephritis which gradually progresses in severity and at all stages presents a characteristic involvement of the glomerular capillaries.

## TYPE 1 NEPHRITIS

**Synonyms.**—Acute Hæmorrhagic Nephritis; Acute Diffuse Nephritis.

Most cases of nephritis presenting with acute onset are of this type. The disease is commonest in children and adolescents, but may occur at any age.

**Ætiology.**—Scarlet fever and streptococcal tonsillitis are the common preceding infections. Sometimes the patient complains of a "cold" or a chill without sore throat. Less frequent preceding infections are otitis media, pneumonia, peritonitis, erysipelas, impetigo, boils and pyogenic dermatitis. Severe burns may be followed by nephritis, possibly due to secondary infection. In time of war nephritis may occur in epidemic form, for example, the "trench nephritis" of the War of 1914-1918. In these outbreaks the nature of the primary infection may be obscure.

**Pathology.**—Microscopically the characteristic feature in the acute stage is increase in cellularity of the glomerular tufts due to proliferation of endothelial cells and infiltration with polymorphonuclear leucocytes. Hæmorrhage into Bowman's capsule

is common, and collection of red cells and leucocytes may be seen in the tubules. In severe cases, fibrinoid necrosis of the glomerular arterioles and even of the glomerular capillaries occurs. In the rapidly progressive course the main feature is epithelial crescent formation (proliferative capsulitis). Vascular necroses are common and the tubules may show hyaline droplet degeneration; the interstitial tissue is infiltrated with acute inflammatory cells. In the slowly progressive course, damaged glomeruli become organised and disappear, interstitial fibrosis is extensive and in the later stages acute and chronic lesions of the glomeruli and vessels are found—focal necroses, capsular adhesions, necrotising arteriolitis—which are the result of severe hypertensive damage. This ultimately leads to focal scarring of the kidney with marked tubular atrophy, dilatation of the intervening tubules and hyaline cast formation. The final stage is sometimes termed secondary contracted kidney or chronic interstitial nephritis.

**Symptoms.**—The onset is usually acute, though occasionally it may be insidious. In the latter instance the patient may complain of biliousness, nausea, vomiting and abdominal pain, with headache and sometimes diarrhoea before the onset of renal symptoms. In the cases with acute onset, there may be more or less severe pain in the back, and œdema soon develops. It usually starts in the face; the legs and scrotum are generally involved next, and the swelling soon spreads all over the body. Occasionally the dropsy is curiously localised and fugitive. Though dyspœa is not regarded as a common feature of acute nephritis most patients admit to it on direct questioning, and if cardiac failure occurs it may be a prominent symptom. There is usually only slight fever, though occasionally a temperature of 102° or 103° F. may be reached; this may be due to persistence of the original infection. The pulse rate is increased and the blood pressure is generally raised. The skin may be dry and itching, with occasionally a papular or erythematous eruption. Retinal hæmorrhages may occur, but very rarely.

The urine is greatly reduced in volume, and may be entirely suppressed; 8 to 12 oz. would be an ordinary figure. It is dark in colour and usually contains obvious blood. This may render the urine as dark as porter, but it may be bright red or merely smoky. Sometimes the blood forms a flocculent, reddish-brown precipitate. The urine is usually loaded with albumin, and casts will be found on microscopical examination. At first blood casts and epithelial casts will alone be found; but at a later stage, granular and hyaline casts appear. Leucocytes are present, often in large numbers. Isolated renal cells, transitional epithelium and squamous cells from the lower urinary tract are also commonly found. The urine is sterile on culture. A sudden increase in urine output after a few days is a sign of definite improvement due to elimination of œdema fluid.

Slight impairment of renal function is common, the blood urea being moderately raised. Some degree of impaired concentrating power is found in the more severe cases.

**Complications.**—(1) *Acute heart failure.*—Shortness of breath may be a presenting feature, and in severe cases acute pulmonary œdema may occur. This complication is found in patients who have a marked rise in blood pressure and demands urgent treatment.

(2) *Hypertensive encephalopathy.*—The symptoms are sudden in onset and include convulsions, blindness, mental excitement, severe headache, vomiting and transient palsies. Coma sometimes develops. Severe hypertension is present but the renal function in these patients is good. With adequate treatment recovery is the rule.

(3) *Infections.*—Not infrequently a flare-up of the primary infection or the incidence of a new infection may produce a recrudescence of the nephritis. Modern therapy has lessened the risk of these infections which were previously often fatal.

(4) *Oliguria.*—Diminution in the urine output may be due to (1) actual suppres-



sion in severe cases, or (2) extrarenal factors such as vomiting, gross œdema, acute heart failure or therapeutic fluid restriction. Marked oliguria occurs when there is severe kidney damage and most frequently when there is no hypertension.

**Diagnosis.**—The combination of dropsy, hypertension, albuminuria, hæmaturia, casts and scanty urine usually makes the diagnosis quite easy. The differential diagnosis of acute nephritis from an exacerbation of chronic nephritis may be difficult. Definite evidence of cardiac hypertrophy and arterial changes are in favour of the latter. An infarct in the kidney which causes a pain in the back and hæmaturia may simulate nephritis, but there is no œdema, nor are casts present in the early stages. Great reduction in the volume of urine is not usual. Signs of septic endocarditis would suggest infarction. In malignant nephrosclerosis there may be a smart hæmorrhage, but the presence of papillœdema and the cardiovascular signs would lead to a correct diagnosis. The renal hæmorrhage in the early stage of new-growth of the kidney is so profuse that confusion with acute nephritis is not likely to occur. Moreover, epithelial casts would not be found, though a large blood cast from the pelvis of the kidney is a very characteristic feature. Pyelitis may give rise to some confusion, as there may be small hæmorrhages, especially at the beginning. The presence of micro-organisms in a catheter specimen and abundant pus cells, in the absence of casts, will generally make the diagnosis clear. Moreover, general dropsy does not occur in pyelitis unless it sets up severe nephritis as a sequel. In any cases of hæmaturia, especially when it is associated with profound constitutional disturbance, loss of weight, tachycardia, continued fever and peripheral neuritis, the diagnosis of periarteritis nodosa must be considered (*q.v.*).

**Prognosis and Progressive Courses.**—The prognosis in Type 1 nephritis is good and 80 to 90 per cent. of patients recover completely. Second attacks after complete clinical recovery are extremely rare. In the early stage, suppression of urine is the most serious prognostic symptom and death in the acute stage is most commonly due to persistent anuria. If this lasts more than a week the outlook is very grave, but recovery has been known to occur after 14 days' anuria. In such severe cases hypertension may be absent and persistent vomiting may lead to extrarenal uræmia, the blood urea rising as high as 300 mg. per cent. Severe hypertension (around 200 mm. mercury systolic) may also be a bad prognostic sign in the acute stage in terms of immediate complications, *i.e.* left ventricular failure and hypertensive encephalopathy. Heart failure as a complication has a much more serious significance than encephalopathy. Persistent hæmaturia is usually evidence of a progressive lesion, but recovery has occurred in cases where visible blood persisted in the urine for three months. Microscopic hæmaturia has a less serious significance particularly in younger subjects since it may be orthostatic in origin, and complete recovery may occur after red cells have persisted in the urine for a year or more. The same is true of a persistent trace of albumin in the urine. Recrudescences, usually marked by return of hæmaturia during the first few weeks, often following recurrence of the initial infection, may greatly prolong convalescence or lead to chronic nephritis. Recovery tends to be slower in the elderly than in young subjects. About 5 per cent. of patients with acute nephritis die in the acute stage, *i.e.* the first 2 or 3 weeks, the causes being anuria, pulmonary œdema due to heart failure or infection.

(1) *Rapidly progressive course.*—This occurs in about 5 per cent. of patients and is due to a severe irreversible glomerulo-nephritis characterised by epithelial crescent formation. Clinically there is persistent hæmaturia, hypertension and œdema which is often severe and generalised. Progressive renal failure occurs over a period of 6 months to 2 years and there may be a malignant hypertensive termination with papillœdema, encephalopathy and left ventricular failure.

(2) *Slowly progressive course.*—In a series of cases of acute nephritis studied by Ellis only about 5 per cent. followed this course. Nevertheless in any clinic there

will be a large proportion of patients with chronic Type 1 nephritis, since the disease may last for decades. Moreover, about half these patients will give no history of acute nephritis, but first present with symptomless albuminuria or hypertension often discovered on routine examination, or with hypertensive symptoms or uræmic manifestations later in the disease. The natural history and prognosis is decided by two factors, the severity of the residual nephritic lesions and the incidence of hypertension. Where the nephritic damage is severe there is no hard-and-fast demarcation from cases running a rapidly progressive course. There is severe destruction of the kidney, and uræmia may develop insidiously in 5 to 10 years, with or without marked hypertension. Polyuria may appear when tubular concentrating power becomes impaired, but as destruction of nephrons progresses, urine output returns to normal and in the final stages there is usually oliguria. Anæmia is often found long before the onset of uræmia and is probably due to malnutrition. In chronic renal failure refractory anæmia develops and this is in some patients the presenting feature of the disease. Further symptoms are described under uræmia (p. 1010). With less severe degrees of residual renal damage the patient may continue for 30 years or more and during this stage may be free from symptoms, but regular examination of the urine shows persistent albuminuria. During this long stage, inflammatory elements are usually absent from the urine and acute recrudescences of nephritis are rare. At any time, however, and more commonly in males the blood pressure may be observed to rise, often over a period of months, and rapid deterioration in renal function may then occur. About 50 per cent. of patients develop the malignant hypertension syndrome. This complication may be the first manifestation of renal disease and it may be very difficult, if there is no past history of acute nephritis, to decide whether the hypertension is nephritic or essential. In general, patients with malignant essential hypertension are found to have only slight impairment of renal function when papilloedema is first discovered, whereas in chronic nephritis renal failure is usually advanced at this stage. Although the ultimate prognosis is poor in both conditions the results of treatment by sympathectomy or hexamethonium compounds are somewhat better in malignant essential than in malignant renal hypertension. The clinical features of the malignant termination in chronic Type 1 nephritis are identical with those of malignant essential hypertension (p. 914) except that symptoms of renal failure are more pronounced. Attacks of hypertensive encephalopathy, producing headaches, blindness, convulsions, disorientation and coma may occur; as in acute nephritis this condition is reversible and improves after the blood pressure is lowered by hexamethonium drugs. In chronic nephritis, however, the improvement is usually short-lived because of the associated irreversible uræmia.

**OTHER FORMS OF ACUTE NEPHRITIS.**—*Acute focal nephritis* is characterised clinically by an attack of hæmaturia occurring in the course of an acute infection, such as otitis media. Hypertension, œdema and renal failure are absent and recovery usually takes place after a few days. Occasionally, however, attacks of focal nephritis recur at long intervals and in such patients albuminuria may persist, indicating residual renal damage. If the attacks continue, hypertension and renal impairment eventually appear and the histological picture in this late stage is indistinguishable from that of chronic Type 1 nephritis.

*In subacute bacterial endocarditis nephritis*, when it occurs, is characteristically focal but may be diffuse. Histologically the focal lesion consists of glomerulitis with hæmorrhage into Bowman's capsule, which leads to epithelial crescent formation and later to characteristic "boat-shaped" collagen crescents. Although this lesion was at one time thought to be embolic, it is doubtful whether there is any ætiological difference between the focal and diffuse forms of glomerulo-nephritis in bacterial endocarditis. A similar state of affairs occurs in *Henoch-Schönlein purpura* where renal involvement may take the form of hæmaturia alone or the full picture of nephritis may develop with hypertension, œdema and renal failure. In the latter case the prog-

nosis is usually poor. This form of nephritis is probably allied to that occurring in *periarteritis nodosa*, which may present with a typical attack of acute nephritis and purpura. In both conditions acute necrotising arteriolitis may be found in the kidney and in other organs. Acute nephritis is occasionally seen in patients with acute rheumatic carditis but so rarely that the association may be fortuitous.

**Treatment.—ACUTE STAGE.**—In the acute stage the patient should be put to bed and kept completely at rest as in a case of acute carditis. Daily observations of the blood pressure should be made, the fluid intake and urine output recorded and the urine examined for specific gravity, albumin and blood. Microscopic examination of the deposit for red cells, leucocytes and casts should be made twice weekly. Renal function tests and plasma protein examination should be made. It is important to search for any residual primary infection such as tonsillitis and to treat such infection with the appropriate dose of penicillin according to age. In this way it may be hoped to avoid recrudescences which may otherwise lead to serious relapse of nephritis during the recovery period. A low protein, low salt, high carbohydrate diet should be given to minimise protein breakdown and sodium retention. In children and in co-operative adults this can be very simply provided by restricting the fluid intake to 1 or 2 pints of orange juice daily, with a carbohydrate diet until the acute stage of the disease has passed. Diuretics, and particularly potassium salts, should not be given. The patient must be kept in bed until pitting œdema has disappeared, the blood pressure has returned to normal and the urine is free of albumin. If, after a period of at least 4 weeks from the onset, the only residual urinary abnormalities are a faint trace of albumin and a few red cells per high power field on microscopic examination of the deposit, the patient may be allowed up, but periodic examination of the urine deposit for erythrocytes is advisable until these disappear; in children, particularly adolescents, this may take up to 12 months. Tonsillectomy is not advised until the nephritis has resolved and should then only be undertaken if the tonsils are obviously chronically inflamed or there is a past history of repeated sore throats.

**Complications.**—Secondary infection should be treated with an appropriate antibacterial agent, penicillin being the most useful. Heart failure is a definite risk when there is marked hypertension. In severe cases with acute pulmonary œdema venesection is the treatment of choice. If the blood pressure is very high, reduction with hexamethonium salts may be worthy of trial, although experience in this connection is still limited. Digitalis is of questionable value and in the majority of patients spontaneous improvement occurs as the nephritis subsides. The most serious complication is anuria. If this persists uræmia rapidly develops and may be complicated by extrarenal nitrogen retention due to vomiting. The essence of treatment is to maintain the electrolyte and fluid balance, keeping a careful watch on the serum potassium, as described under the treatment of traumatic anuria. No attempts should be made to force diuresis by intravenous infusions and potassium salts should never be administered.

Hypertensive encephalopathy occurs with about the same frequency as heart failure in patients with very high blood pressure. Recent experimental work indicates that the syndrome is due to cerebral vascular spasm, and in the later stages this may lead to cerebral œdema. Prompt venesection with removal of 1 pint of blood will sometimes produce dramatic improvement. Failing this, attempts should be made to reduce the blood pressure by intramuscular injection of hexamethonium salts. The cerebrospinal fluid pressure is not usually raised in the early stages, but lumbar puncture should be carried out and if the pressure is high, an intravenous injection of 100 ml. 50 per cent. sucrose solution should be given in an attempt to reduce cerebral œdema. Alternatively 4 to 6 oz. 25 per cent. magnesium sulphate may be given per rectum, but this is a less effective measure. Hypertensive encephalopathy and heart failure may occur together, but, fortunately, reduction of the blood pressure

will usually relieve both conditions. There is often a slight to moderate degree of anemia in acute nephritis, probably due to the initial streptococcal infection, and it should be adequately treated by iron preparations.

*Rapidly progressive course.*—In these patients the nephritis is severe, and hæmaturia, hypertension and oedema persist. Treatment is continued as in the acute stage, and complications such as heart failure and hypertensive encephalopathy should be dealt with promptly. The patient should be kept at rest in bed for at least 3 months, since complete recovery may occur even after this prolonged course. Diuretics must not be given nor fluids restricted if renal failure is present. Tonsillectomy is to be avoided as it may aggravate the nephritis in this active stage.

*Slowly progressive course (chronic Type 1 nephritis).*—In the long intermediate stage before the development of renal failure and severe hypertension, it is most important that the patient should not be made an invalid by unnecessary or even harmful treatment. There are frequently no symptoms during this time, the only findings being residual albuminuria and perhaps slight variable hypertension. The old practice of protein starvation is thoroughly bad as it leads to protein deficiency, iron deficiency, anemia, malnutrition and the conviction of invalidism. A normal diet should therefore be allowed so long as the renal function tests are normal. Iron should be prescribed if there is any degree of anemia, and the only necessary medical attention is a periodic examination at 3 to 6-monthly intervals, when the urine and blood pressure should be tested and renal function tests occasionally carried out. In the later stages the blood pressure tends to rise progressively and renal impairment develops. Headache and breathlessness may be presenting symptoms and should be treated as in benign hypertension. When other analgesics fail, ergotamine tartrate sometimes relieves hypertensive headaches, especially if these are migrainous in character. If left ventricular failure is severe, rest in bed, digitalis and mercurial diuretics are indicated. The appearance of retinopathy probably justifies an attempt to reduce the blood pressure by hexamethonium derivatives. When renal impairment appears, the fluid intake should under no circumstances be restricted; protein in the diet should be reduced only when the blood urea rises considerably above the normal, e.g. to 100 mg. per cent.

Anæmia should be treated by iron preparations, but when uræmia is present the anæmia is usually refractory and the only beneficial treatment is blood transfusion. It is well to remember that some degree of uræmia may be due to heart failure or anemia or even to severe hypertensive crises and some improvement may be expected if these complications are adequately treated.

#### TYPE 2 NEPHRITIS

**Synonyms.**—Subacute and Chronic Parenchymatous Nephritis; Nephrotic Nephritis; Hydropigenous Nephritis; Lipoid Nephrosis.

Type 2 nephritis is less common than Type 1 nephritis, but its incidence ranks high in a clinic for renal diseases since in the majority of patients it follows a chronic course of many years' duration. The incidence is more uniformly distributed over the first six decades of life than that of Type 1 nephritis. In young children and occasionally in adults, hypertension and hæmaturia may be absent, so that the condition is indistinguishable from so-called lipoid nephrosis. Long-term clinical and histological study of such cases reveals, however, no clear demarcation from Type 2 nephritis, and it would seem reasonable in the great majority of instances to regard lipoid nephrosis as a mild form of the latter.

**Ætiology.**—In most cases no ætiological factor is established and it is unusual to obtain a previous history of acute streptococcal infection. This is no doubt partly due to the fact that albuminuria (and therefore the onset of disease) may precede the onset of oedema by months or years. The development of oedema, which in most cases first brings the patient to the doctor, may be precipitated by severe intercurrent

infection or by pregnancy, the common factor presumably being a lowering of the plasma proteins which upsets the balance between loss of protein in the urine and new protein formation.

**Pathology.**—The kidney is large and pale and may or may not be œdematous. The kidney pattern and the demarcation of cortex from medulla are blurred, and fatty changes in the tubules and interstitial tissue may appear as white streaks on the cut surface. The microscopic picture depends on the stage of the disease and the severity. In cases with little or no hypertension the picture resembles that described in nephrosis, i.e. there are minimal changes in the glomeruli, consisting of bland focal necroses, together with deposition of lipid in the tubular epithelium and interstitial tissue; slight interstitial cellular infiltration may be present. In more severe cases there is a diffuse proliferative glomerulitis with accentuated lobulation of the tufts and swelling of the capillary basement membrane. As this lesion progresses, deposits of hyaline material appear in the glomerular tufts and the glomerular capsule undergoes fibrous thickening, but epithelial crescent formation is almost always absent. Glomerular hyalinisation gradually and very slowly increases so that even after 10 years the characteristic glomerular lesion may still be recognisable. The tubules undergo fairly diffuse atrophy and a uniform interstitial fibrosis develops, but it is unusual for more than a moderate degree of renal contraction to result. Vascular lesions are not conspicuous although occasional arteriolar necroses may be observed in those cases with a malignant hypertensive termination.

**Symptoms.**—It has already been stated that albuminuria, discovered on routine examination, may provide the first indication of the disease, months or years before the appearance of œdema or other symptoms. In most patients, however, Type 2 nephritis presents with gradual or rapid onset of œdema, which steadily increases and tends to become massive. The œdema may be generalised, affecting the face, hands, trunk and legs. It is often first noticed as puffiness of the eyelids, or it may first appear as a swelling of the feet and ankles extending up the legs. The patient may feel quite well apart from the disability caused by œdema. On the other hand, there is more usually complaint of malaise and fatigue, loss of appetite and nausea, and sometimes of epigastric pain. There may be cough and slight shortness of breath due to slight bronchial catarrh, œdema of the lungs or hydrothorax. A pericardial effusion may develop. Swelling of the abdomen may be the result of œdema of the abdominal wall or ascites. The face is pale and the eyelids and cheeks are puffy, but the mucous membranes are of a good colour, and the blood count is usually normal. The urine is reduced in quantity, its specific gravity is normal, it contains a large amount of albumin, often amounting to 0.5 or even 1 per cent., and readings of 4 per cent. or even more have been recorded. In mild cases the urinary deposit contains only a slight excess of cells and few or no casts, while red blood corpuscles are generally absent. In the more severe cases leucocytes, red blood cells and granular casts are regularly found in the urine deposit. The blood pressure may be normal or moderately raised. There is no retinitis in the early stages. Characteristic changes are found in the blood. The plasma albumin falls more considerably than in other forms of Bright's disease. Approximate normal figures are plasma albumin 4 g. per cent., globulin 2.5 g. per cent., total protein 6.5 g. per cent., which gives an albumin-globulin ratio of 1.6 to 1. In Type 2 nephritis plasma albumin may be 1 to 2 g. per cent., globulin 2.5 to 3.5 g. per cent., so that albumin-globulin ratio is often less than unity. The blood cholesterol may be 300 to 800 mg. per cent. (normal 130 to 250 mg. per cent.). The blood urea is often raised, especially in patients with gross œdema and oliguria, but concentration tests are unimpaired.

**Complications.**—These are :

(1) Pulmonary œdema and cerebral œdema which occur only in cases with gross anasarca. Cerebral œdema is very rare but has been observed in children after rapid generalised increase in swelling.

(2) Pyogenic infection—the common ones being pneumococcal peritonitis, pneumonia and erysipelas.

(3) Hypertensive encephalopathy. Owing to the moderate degree of blood pressure elevation, this complication is not often seen, but it may develop in the subacute stage when, especially in adult males, severe hypertension is sometimes encountered. The symptoms are identical with those described under Type 1 nephritis.

**Diagnosis.**—The insidious onset with œdema, gross albuminuria and hypoproteinæmia is so characteristic of Type 2 nephritis that there is usually no problem of diagnosis. There may be some difficulty in the early stages in distinguishing it from Type 1 nephritis running the rapidly progressive course. Here also there is often gross generalised œdema and heavy albuminuria, but the acute onset and greater depth of hæmaturia, hypertension and renal impairment enable the separation to be made in most cases. Amyloid disease of the kidney also produces generalised œdema, albuminuria and hypoproteinæmia. Some obvious primary infection such as bronchiectasis, osteomyelitis or tertiary syphilis is usually present, the spleen may be enlarged and the Congo Red test is of particular value. The nephrotic syndrome occasionally arises in the later stages of diabetic glomerulosclerosis. Although Type 2 nephritis may occur in the diabetic, the appearance of œdema and albuminuria in the course of chronic diabetes is usually due to this specific form of glomerular hyalinisation. Disseminated lupus erythematosus may produce a glomerulo-nephritis in which swelling of the capillary basement membrane resembles that seen in some cases of Type 2 nephritis, and clinically the nephrotic picture may develop. The associated features of disseminated lupus are, however, diagnostic. Another rare cause of generalised œdema with gross albuminuria is bilateral renal vein thrombosis, but, as a rule, this diagnosis is only made post mortem. It is possible that the nephrotic syndrome may arise from other causes, including chemical poisons and secondary syphilis; cases of obscure origin have been described in several members of the same family.

**Course and Prognosis.**—Complete recovery is rare in Type 2 nephritis, particularly in adults. Clinical resolution does, however, occasionally occur, sometimes after many years of persistent or recurrent œdema. In children, recovery is not uncommon, particularly when the features are those of nephrosis, *i.e.* when hypertension and hæmaturia are absent. In the great majority of patients, however, the disease runs a steadily progressive course and the prognosis is closely related to the degree of hypertension which develops. With no hypertension or a moderate degree which subsides under treatment, good health often continues for many years, whereas with marked elevation of blood pressure the course may be rapidly progressive. Hypertension is generally more severe, and the course correspondingly shorter, in men than in women. Thus in men, Type 2 nephritis usually continues with variable œdema, moderate hypertension and considerable albuminuria; after 2 or 3 years progressive renal impairment sets in and leads to uræmia 3 to 5 years from the onset of œdema, often with the development of the malignant hypertension syndrome. In less severe cases (more commonly women) the disease runs a slower course; œdema may subside very gradually over the course of months or may recur at intervals, but in the absence of hypertension the patient may lead a useful and symptom-free existence for 10 or 20 years. In this group the degree of albuminuria tends to diminish, and the plasma proteins to rise, at a variable interval after the onset. Intercurrent infection may occur at any time and this is particularly serious in children with generalised œdema, the common infections being pneumococcal peritonitis, pneumonia or erysipelas. Occasionally intercurrent infection is associated with an exacerbation of the nephritis and there may be frank hæmaturia during such episodes; in other patients infection may precipitate a massive diuresis with subsequent reduction in the degree of albuminuria.

**Treatment.**—In the early stages, particularly if examination of the urinary deposit

reveals evidence of active nephritis (i.e. red cells, leucocytes and granular casts), treatment should follow the régime advised in acute Type 1 nephritis. As a rule, however, the disease is in its subacute or chronic stage when the patient is first seen. Even then it is advisable to insist on rest in bed so that a full assessment of the condition can be obtained. Observations on the blood pressure, urine, renal function and plasma proteins should be made as in Type 1 nephritis and it is of value to record the patient's weight daily as this gives a useful index of changes in œdema. The objectives are to rest the patient, treat or prevent secondary infection, counteract plasma protein depletion by a high protein diet and encourage the removal of œdema fluid. Very severe generalised œdema may present an urgent problem since, particularly in children, fatal pulmonary œdema or cerebral œdema may result. In the average case, however, no heroic measures are required, and since the œdema is a manifestation of nephritis it cannot be expected to resolve completely until the nephritis subsides. It is wise, therefore, to maintain complete rest, and during the first week or two treatment should consist in restriction of salt intake, the sodium content of the food being reduced to 0.5 g. daily. The diet should otherwise be adapted to please the patient. Under this régime œdema will gradually diminish in most instances. Rest in bed should be continued so long as red blood cells and leucocytes persist in the urine. Heavy proteinuria may continue for many months; after the first few weeks, therefore, and when œdema is no longer severe, it is wise to give a high protein diet (up to 200 g. daily) in an attempt to restore the depleted body protein. No considerable rise in plasma proteins must be expected for 1 or 2 months or even longer. If the above treatment does not succeed in reducing œdema, mercurial diuretics should be given intramuscularly (Mersalyl 1 to 2 ml.) twice or three times weekly at the start, and once a week subsequently. If the diuretic response is poor, ammonium chloride may be given before the injection. If salt restriction and mercurial diuretics both fail to promote diuresis acupuncture of the legs, under cover of adequate doses of penicillin, will always produce an effective reduction in œdema. The patient should be placed in Fowler's position before this is carried out to allow the œdema fluid to gravitate to the legs. When subcutaneous drainage is under way it may be found that mercurial diuretics will now produce a better response. If, as is frequently the case, ascites and pleural effusions are present, paracentesis may be necessary and again mercurial diuretics may give an improved response after this has been performed. It is a common observation that massive diuresis may occur in refractory cases after an infection such as measles or pneumonia. Attempts to reproduce such a response has therefore been made by T.A.B. injections or even malaria therapy, but the results are not impressive and the use of direct subcutaneous drainage, under antibiotic cover, has made this rather drastic therapy unnecessary.

**Complications.**—Pulmonary œdema and the much rarer complication of cerebral œdema occur only when subcutaneous swelling is gross, and both should be avoidable if the measures outlined above are employed in good time. Should either of these complications develop, direct subcutaneous drainage should be started immediately. Infections such as pneumonia, pneumococcal peritonitis or erysipelas should be treated by appropriate doses of penicillin. In the subacute stage of the disease hypertensive encephalopathy occasionally occurs in the rare case with severe hypertension and should be treated as in acute nephritis. Iron preparations should be given if anaemia develops.

**Chronic Type 2 nephritis.**—After the initial stage, continued supervision is necessary. When the patient first becomes ambulant it is common for some œdema of the legs to return and this can usually be controlled by fitting full-length elastic stockings, which should be worn only during the day. In some cases œdema continues for many months and can only be satisfactorily controlled by weekly or twice weekly injections of mercurial diuretics. The high protein, low salt diet should be continued;

salt-free bread and a substitute for table salt which does not contain sodium can now be purchased. Iron should be prescribed for anæmia and any devices which may improve the patient's sense of well being, including a stimulating tonic, alcohol in moderation, or a seaside holiday are to be commended. The main point, however, is to encourage the patient to lead a normal life and return to work, with the obvious precautions of avoiding chills and excesses of any kind. It is in the nature of the disease that relapses tend to occur. If these are mild, and unaccompanied by more than slight œdema, rest in bed at home is often sufficient, but if œdema increases, the patient should be admitted to hospital and treated as described above. In the later stages of the disease when hypertension and uræmia develop, treatment is the same as in chronic Type 1 nephritis.

## RENAL VASCULAR DISEASE

### BENIGN ESSENTIAL HYPERTENSION

**Synonym.**—Benign Nephrosclerosis.

In this form of hypertension, renal vascular changes rarely produce clinical symptoms, the disorder being one of chronic arterial and arteriolar degeneration, and it will be necessary to make only a brief reference to it here.

**Pathology.**—The chief kidney changes are in the smaller arteries and arterioles. They are described in detail on p. 909. In contrast with malignant nephrosclerosis, there is only hyaline and fatty degeneration of the arterioles. There may be renal ischæmia and consequent irregular contraction and fibrosis of the renal parenchyma. In some cases this condition is marked and a granular contracted kidney results. There is then a patchy fibrosis of glomeruli with tubular atrophy and secondary interstitial changes. This fibrotic atrophy is secondary to the arterial narrowing, and it is because of its patchy distribution that renal function is not impaired.

**Symptoms.**—See Benign Essential Hypertension (p. 909). In some cases the urine contains a trace of albumin, but this is confined to long-standing cases with severe ischæmic fibrosis. Given this clinical picture, the differential diagnosis from chronic nephritis is made on the absence of a past history of acute nephritis and of renal failure. There are occasional cases presenting with the clinical features of benign hypertension in which intravenous pyelography reveals unilateral renal disease. If this is discovered in childhood or early adult life removal of the diseased kidney may be followed by recovery from the hypertension. In a small proportion of cases (probably not more than 5 per cent.) benign hypertension may progress to malignant hypertension and terminate in uræmia.

**Treatment.**—See that of Hypertension (p. 911), the Heart in Hypertension (p. 851) and Uræmia.

### MALIGNANT ESSENTIAL HYPERTENSION

**Synonym.**—Malignant Nephrosclerosis.

As in benign hypertension, the renal changes are secondary to the vascular lesions. This disease is called malignant nephrosclerosis because the kidneys are severely affected, so severely in fact that fatal uræmia is the usual outcome.

**Pathology.**—The chief kidney changes are in the smaller arteries and arterioles. They are described on p. 913. In contrast with benign nephrosclerosis, there is, in addition, fibrinous necrosis, especially of the arterioles.

**Symptoms.**—These are described on p. 914.

**Diagnosis.**—The differential diagnosis of malignant nephrosclerosis from chronic nephritis depends on the fact that in the former there is no past history of acute or chronic nephritis, nor is there renal œdema. Further, in malignant nephrosclerosis



papillœdema usually appears whilst renal function is fairly good; in fact it may be normal and there may be no albuminuria. In chronic nephritis, however, renal failure is usually advanced by the time papillœdema develops.

**Treatment.**—See that of Hypertension (p. 911), the Heart in Hypertension (p. 851) and Chronic Uræmia (p. 1122).

### NEPHROSCLEROSIS WITHOUT HYPERTENSION

**Synonym.**—*Senile or Atheromatous Kidney.*

In this form of kidney disease also the vascular changes are of greater importance than the renal, and it is only necessary to deal briefly with the affection.

**Pathology.**—The kidneys show depressed red areas, which are due to contraction of fibrous tissue along the distribution of particular interlobular arteries and, therefore, tend to be conical in form, with their base to the surface of the organ. There is an absence of cardiac hypertrophy. The glomeruli in scarred areas shrink, and the connective tissue around them becomes condensed and thickened. The degenerate glomerulus and its capsule fuse together and undergo fatty and fibrotic changes. The atheromatous kidney is, therefore, contracted, due to atrophy following insufficient circulation, with consequent fibrosis.

**Symptoms and Diagnosis.**—There may be gradual failure of the physical and mental powers—described by Allbutt as “contraction of the spheres of bodily and mental activity”—rather than the more dramatic events of malignant nephrosclerosis. There is a trace or more of albumin in the urine. The radial artery is thickened and tortuous. The blood pressure is not high, and there is an absence of cardiac hypertrophy. Death by cardiac failure or intercurrent affections is the commonest ending, while cerebral hæmorrhage and uræmia are unlikely.

### RENAL LESIONS IN DIABETES

Renal disease is now one of the commonest fatal complications of diabetes. This is due to the fact that control of hyperglycæmia and ketosis by insulin has greatly prolonged life so that the vascular complications are becoming increasingly prominent. The gradual change in the natural history of diabetes over the past 20 years has brought to light a specific form of renal involvement which is closely related to chronic vascular degeneration in other organs. This condition, first described by Kimmelstiel and Wilson in 1936 and named by them *intercapillary glomerulosclerosis*, is the commonest renal lesion in diabetes. Secondly, ischæmic atrophy of the kidney tends to be very severe in the diabetic; thirdly, ascending pyelonephritis may occur in a particularly intense form leading to medullary necrosis. The diabetic patient is therefore particularly liable to these three forms of renal damage. In addition, other types of renal disease such as glomerulo-nephritis are occasionally encountered.

#### DIABETIC GLOMERULOSCLEROSIS

**Incidence.**—It is probable that diabetic glomerulosclerosis occurs in 10 to 20 per cent. of all cases. In long-standing diabetes, starting before the age of 15, the incidence is much higher and may reach 50 per cent. Its occurrence is related to long duration of diabetes rather than to the age of the patient. Although it may be discovered within a few years of the onset of glycosuria, the average duration of diabetes when the renal lesion first appears is about 10 years. Thus the majority of patients first present evidence of this renal disorder in middle age. The incidence is higher in females than in males. Neither severity of diabetes nor insulin treatment play any essential rôle in its pathogenesis, since the lesion is found in patients who have never received insulin, and it is not uncommon in those who have a mild, easily

controlled diabetes with little or no tendency to ketosis. It would thus appear that, as with the other vascular complications of the disease, there is little relation between the incidence and severity of diabetic glomerulosclerosis on the one hand and the disturbance of carbohydrate metabolism on the other. Apart from these factors, nothing is known about the aetiology of the process.

**Pathology.**—As its name implies, diabetic glomerulosclerosis consists of a degeneration of the glomerular tuft. This takes the form of progressive hyalinisation, but it is possible to recognise several distinct histological features. The first is a nodular deposit of hyaline material in the glomerular tuft which resembles amyloid material but does not take amyloid stains; this lesion is peculiar to diabetes. In addition the majority of affected glomeruli show a diffuse hyaline change which is seen to be an extension into the glomerular tufts of a similar hyaline degeneration in the afferent arterioles. An identical, but much less conspicuous hyaline degeneration may result from senile atherosclerosis of the kidney. Thirdly, lipo-hyaline deposits and occasional capillary aneurysms occur within the glomerular tuft and contribute to its disorganisation; focal glomerular necroses may also be found, particularly if the blood pressure has been very high. It will be seen, therefore, that diabetic glomerulosclerosis is closely associated with severe degenerative changes in the arterial system of the kidney; furthermore, the association is equally close with severe atheromatous change elsewhere in the body, especially in the heart, brain and retina. Because of the severe ischaemic atrophy the kidney is usually considerably contracted and the arteries are seen to be extremely prominent.

**Clinical Features.**—Albuminuria may for a period of many years be the only manifestation of diabetic glomerulosclerosis. It is variable in amount and is not usually accompanied by inflammatory elements in the urinary deposit. The further development of the clinical syndrome is due not so much to the specific diabetic lesion, but to other complications resulting from generalised arterial degeneration. Hypertension, heart failure and progressive ischaemic damage to the kidney are the most important of these. Impairment of renal function is the rule, although its development is very gradual. In the later stages albuminuria increases to a degree which leads to a considerable reduction in the plasma protein level. When this occurs, and particularly when myocardial failure due to coronary disease supervenes, severe generalised oedema may appear. Hypertension is usually, but not invariably, present and is moderate in degree; malignant hypertension is only rarely encountered. The final picture is one of combined heart failure and renal failure, and there is often severe mental disturbance due to cerebral vascular degeneration. Diabetic retinopathy will be found in practically all patients with diabetic glomerulosclerosis, and diabetic peripheral neuritis, usually mild in degree, is also commonly present. During the later stages of the disease it is not infrequently found that the insulin requirement falls. This is probably accounted for by the diminished food intake and restricted activity of the patient due to increasing incapacity.

**Diagnosis.**—When the usual investigations have excluded focal lesions such as calculus, tuberculosis, neoplasm, cystitis and pyelitis, chronic albuminuria in a diabetic patient is almost certainly due to intercapillary glomerulosclerosis with associated renal ischaemic damage. The presence of retinopathy strongly supports the diagnosis as does evidence of arterial degeneration in other organs. There is no specific test for the disease. The association with retinopathy is so close that if renal failure is discovered in a diabetic patient in the absence of retinal changes it is highly probable that some other form of kidney disease is the cause.

**Prognosis.**—As already indicated, glomerular hyalinisation and ischaemic atrophy develop very slowly and albuminuria may be present for 10 years before the late complications supervene. The prognosis in fact depends rather more on the extent of vascular degeneration elsewhere in the body than on the presence of glomerulosclerosis.

**Treatment.**—Apart from control of the diabetes, treatment is the same as in other patients with chronic hypertensive renal disease (see Chronic Nephritis, p. 1122)

#### ACUTE MEDULLARY NECROSIS

This is a severe suppurative pyelonephritis which leads to zonal necrosis of the renal medulla.

**Pathology.**—This is the same as in pyelonephritis, except that necrosis of parenchymal tissue occurs and multiple small abscesses may be formed. Severe active pyelitis is present. The necrosis is obvious to the naked eye as yellowish-white areas lying between the base of the renal pyramid and its papilla. There may be multiple necroses in different pyramids and one or both kidneys may be involved. Inter-capillary glomerulosclerosis is sometimes associated with medullary necrosis.

**Symptoms.**—The symptoms may be those of acute pyelitis, but more commonly the condition will be found in an elderly patient who becomes severely ill and is found in what appears to be diabetic coma. The condition should indeed be suspected in any patient, especially a woman, who fails to recover from coma after diabetic ketosis is controlled. In such circumstances the urine should be examined for pus and organisms. Renal calculus or urinary obstruction may be the underlying cause of ascending infection. Unless the condition responds to treatment oliguria develops and death occurs in uræmia.

**Treatment.**—Prophylaxis consists in dealing with renal calculi or any obstructive lesion of the renal tract which may be discovered in the diabetic patient. The presence of pyuria in a severely ill or comatose diabetic, calls for prompt and effective antibiotic therapy. Sensitivity tests should be carried out on the organisms cultured from the urine and streptomycin, chloramphenicol or oxytetracycline should be given according to the results. General therapeutic measures are the same as for acute pyelitis.

#### THE CONTRACTED KIDNEY

In the past, various terms have been applied to the contracted kidney but the ætiology and natural history of the process have often been obscure. Contraction of the kidney is due to destruction of nephrons and the development of interstitial fibrosis. It will be obvious from the conditions already discussed that these changes may arise in many ways; nevertheless there may be no previous history of renal disease. The clinical manifestations are those of renal failure and there are often no distinguishing features to indicate the nature of the primary lesion. The following are the common causes of contracted kidney.

**CHRONIC TYPE 1 NEPHRITIS.**—Some of the smallest contracted kidneys result from the slowly progressive course of Type 1 nephritis. The disease may have been present for 30 or 40 years and in about half the cases there is no history of acute nephritis. The renal contraction is due to a combination of the original nephritis and of subsequent hypertensive damage. The former produces diffuse fibrosis and the latter focal scarring. The number of surviving nephrons may be extremely small so that only occasional hypertrophied glomeruli with greatly dilated tubules are seen in each low power field.

**CHRONIC TYPE 2 NEPHRITIS.**—Renal contraction in this form of Bright's disease is usually only slight or moderate and is limited to those cases which run a slow course of 10 to 20 years. Renal failure is slow in development and may be present as long as 5 years before symptoms of uræmia appear. A malignant hypertensive termination is common in these cases.

**CHRONIC PYELONEPHRITIS.**—Some of the most contracted kidneys fall into this group. Broad zones of interstitial scarring lead to a coarse irregularity of the kidney. Contraction often affects the two kidneys unevenly and one kidney may be reduced

to a fibrous remnant whilst the other is greatly hypertrophied. In such cases of unilateral renal disease severe hypertension may be present and may progress to a malignant termination. The hypertrophied kidney may then show the characteristic histological changes of malignant nephrosclerosis.

**CONGENITAL RENAL LESIONS.**—Here again the kidneys may be extremely small due to a failure of development (hypoplasia) as well as to fibrotic contraction usually attributable to ascending pyelonephritis. This "ascending contraction" is particularly prominent in cases of idiopathic dilatation of the renal tract. An unexplained feature of congenitally small kidneys (described by Rose Bradford) is the absence of associated hypertension and cardio-vascular hypertrophy. Nevertheless severe hypertension occasionally occurs.

**MALIGNANT ESSENTIAL HYPERTENSION.**—As a rule, the kidneys are not contracted in this disorder owing to the rapidly progressive course. Occasionally, however, and particularly in older subjects, the disease may progress relatively slowly over the course of 3 or 4 years. There is often in these patients a preceding history of long-standing benign hypertension and a moderate to severe degree of renal contraction takes place.

**BENIGN ESSENTIAL HYPERTENSION.**—Renal contraction in this disorder is unusual but is seen in moderate degree when atheroma of the renal arteries is severe. The mechanism of contraction only differs from that of the senile arteriosclerotic kidney in the more extensive fatty hyaline degeneration of the arterioles, which gives a finely granular appearance to the surface due to subcapsular scarring. Obstruction of one renal artery by an atheromatous plaque may reduce the affected kidney to a fibrous remnant and this is one of the unilateral lesions which may lead to hypertension. In diabetes arterial degeneration is severe in the kidney, as in other organs, and some contraction of the kidney is likely. This will be all the greater if diabetic glomerulosclerosis is also present.

**HYDRONEPHROSIS.**—Obstructive lesions of any kind lead to pressure atrophy of the renal parenchyma and the renal substance may be reduced to a thin layer of fibrotic tissue surrounding the hydronephrotic sac. Where chronic ascending infection has been present in the early stages, as in many cases of renal calculus, the kidney may be small and contracted with a minor degree of hydronephrosis.

### TRAUMATIC ANURIA AND ALLIED CONDITIONS

**Synonyms.**—Acute Cortical Ischæmia; Acute Tubular Necrosis; Lower Nephron Nephrosis; Crush Kidney; Acute Focal Interstitial Nephritis.

The clinical manifestations and renal histological changes in this disorder were first adequately studied in patients who received crushing injuries to the limbs during air-raids on London in the War of 1939-1945. The characteristic clinical feature is suppression of urine, and little structural damage may be found in the kidney except for focal areas of tubular necrosis. Since its first description the syndrome has been recognised as a sequel of a variety of widely differing aetiological factors. Apart from crushing injuries it may follow prolonged application of tourniquet to a limb, any form of major surgical trauma, especially gall-bladder operations, obstetric shock, retroplacental hæmorrhage, infected abortion, other severe infections such as Weil's disease and blackwater fever, incompatible blood transfusion; sulphonamide therapy and perhaps acute poisoning with heavy metals such as mercury and bismuth.

**Pathology.**—There is a severe dysfunction of the whole nephron, glomerular filtration being inhibited or grossly diminished whilst tubular reabsorption is in abeyance. Histologically the only findings are occasional foci of epithelial necrosis in the distal convoluted tubules associated with slight inflammatory infiltration. Blood pigment casts may be present in the tubules.

**Symptoms.**—Suppression of urine is the primary disorder and this leads to acute uræmia with vomiting, drowsiness, muscular twitching and coma. Purpura

may appear, hypertension is slight or absent, but may develop in the later stages during recovery. Restoration of renal function may occur after severe oliguria lasting up to 3 weeks. If the patient survives the acute stage, copious polyuria develops. This may, however, give a false impression of recovery of renal function, for the urine at first approximates in composition to glomerular filtrate. Since tubular reabsorption is in abeyance, an output of many litres of urine may therefore correspond to only a fractional recovery of glomerular filtration and the blood urea may still continue to rise. There is a danger in this stage of excessive electrolyte depletion due to failure of tubular reabsorption; restoration of tubular concentrating power may not be complete for many months.

**Treatment.**—During the stages of anuria and subsequent polyuria it is essential to maintain electrolyte and fluid balance, since over-hydration in the anuric stage carries a grave risk of fatal pulmonary oedema. Electrolyte depletion due to lack of tubular reabsorption in the polyuric stage can be equally serious. Endogenous protein breakdown leads to accumulation of extracellular potassium in the absence of urinary excretion, and if this is excessive, death may occur from cardiac arrest. Potassium salts must therefore under no circumstances be administered at this stage. Protein breakdown can be reduced by high carbohydrate diet and the extracellular potassium can, if necessary, be reduced by intravenous insulin or sodium loaded ion-exchange resin. The following régime of treatment should be followed: 1 litre of 40 per cent. glucose is given daily by intra-gastric drip. If any urine is passed, an equal volume of extra water is added. If vomiting occurs, saline solution equivalent to that lost in the vomit is added. If vomiting persists, oral treatment is discontinued and 1 litre of 40 per cent. glucose is given intravenously by catheter via the saphenous vein into the inferior vena cava. Half a million units of penicillin should be given daily intramuscularly. A rise of serum potassium above 6 m. Eq/litre may be dealt with in the first instance by the injection of insulin two to three times daily when the blood sugar is above normal. If the rise in serum potassium continues, sodium sulphonic ion-exchange resin should be given orally (15 g. t.d.s.) or if this cannot be tolerated, 30 g. daily per rectum. This form of conservative treatment has replaced the use of the artificial kidney. In the stage of polyuria sodium depletion may occur, so that the fluid and electrolyte intake must be increased to compensate for the amount lost in the urine.

### TOXIC NEPHROSIS AND RELATED DEGENERATIVE RENAL LESIONS

The term nephrosis means tubular epithelial degeneration; consequently many unrelated conditions are included under this heading. The types of tubular degeneration are albuminous, lipoid, hyaline droplet and necrotising or fibrinoid. Amyloid nephrosis is a special type which is dealt with elsewhere (p. 1131). Lipoid nephrosis has already been described under Type 2 nephritis, and one form of necrotising nephrosis has been dealt with under Traumatic Anuria.

**SIMPLE NEPHROSIS** in which there is albuminous degeneration of the tubular epithelium occurs in febrile states and toxæmias. From the renal point of view it is of no clinical significance except that mild albuminuria results. Sometimes heavy albuminuria is produced, for example, in hepatic failure due to acute yellow atrophy or Weil's disease; nitrogen retention may develop in such patients but is probably extrarenal in origin. The term "hepato-renal syndrome" has no specific meaning but is sometimes used for this combination of liver disease and renal tubular nephrosis.

**MERCURIAL NEPHROSIS** is a typical example of severe tubular degeneration associated with chemical poisoning. Ingestion of mercuric salts or even therapeutic use of mercurial lotions may, in patients with idiosyncrasy, produce fatty, hyaline droplet and fibrinoid necrosis of the tubular epithelium, which later undergoes calcification.

Oliguria and hæmaturia are produced, along with other manifestations of mercurial intoxication and fatal uræmia may result. In its clinical course and possibly in the development of the lesion this type of nephrosis is allied to that occurring in traumatic anuria. There is some evidence that organic mercurial diuretics may damage the renal tubules, but it is extremely rare. Bismuth poisoning may produce a similar picture to mercurial nephrosis but the renal damage is less severe. Other chemical poisons which affect the kidney are carbon tetrachloride and phosphorus; they cause severe fatty degeneration of the tubules but the whole nephron is probably affected since fatal uræmia may occur.

**ECLAMPTIC NEPHROSIS.**—In fatal eclampsia severe tubular damage, including fatty and hyaline droplet degeneration, is found post mortem. Although this is referred to as a "toxæmia of pregnancy" it is more probable that the lesion is an acute ischæmic one comparable to that seen in malignant hypertension or traumatic anuria. These changes, like other tubular degenerative lesions, are difficult to relate to the clinical features and it is doubtful whether chronic renal damage results from this form of nephrosis. Persistent hypertension and albuminuria following so-called toxæmia of pregnancy usually indicate pre-existing renal disease or hypertension. Any effect cyesis may have on the course of these disorders is probably due to exacerbation of the hypertension which so frequently occurs about the middle of pregnancy.

**BILATERAL CORTICAL NECROSIS** is a rare renal complication of pregnancy. Although it occasionally occurs in male subjects without any obvious cause, it may result from chemical poisoning or severe infections such as malaria. In pregnancy it is usually associated with eclampsia or retro-placental hæmorrhage. Its pathogenesis is probably related to that of acute tubular necrosis (traumatic anuria). The clinical picture is one of severe abdominal pain and anuria leading to rapidly fatal uræmia without hypertension.

**OTHER FORMS OF NEPHROSIS.**—Tubular degeneration occurs in gout secondary to deposits of sodium biurate crystals in the interstitial tissue. The common renal complication of gout is, however, a chronic "interstitial nephritis" probably due to associated essential hypertension.

Myelomatosis is not infrequently complicated by severe renal damage. The picture is often a mixed one due to ascending nephritis or ischæmic changes. There is, however, a specific lesion in myelomatosis consisting of tubular atrophy consequent on the formation of obstructive casts which are in some way related to Bence Jones protein. The glomeruli in such kidneys may be remarkably normal.

**NEPHROCALCINOSIS.**—It has already been stated that calcification of the tubular epithelium may follow necrotic changes such as result from mercury poisoning. Similar epithelial calcification may be a late sequel of alkalosis due to severe vomiting or may follow traumatic anuria, sulphonamide anuria and myelomatosis. An entirely different type of nephrocalcinosis, so-called metastatic calcification, occurs in hyperparathyroidism, large interstitial deposits being formed. Still another form is that occurring in hyperchloræmic acidosis in children in which the primary defect is a failure of the proximal tubule to reabsorb bicarbonate.

### CONGENITAL ABNORMALITIES OF THE KIDNEY

Many errors of development resulting in abnormalities of the shape or position of otherwise normal kidneys are of little clinical importance. They are unlikely to give rise to symptoms or to progressive renal impairment, although there is evidence that such kidneys have an increased tendency to infection. Maldevelopment of the kidneys leading to insufficient functioning nephrons may, without added infection, lead to renal failure. The pathological differentiation of such kidneys from those which are contracted as a result of chronic atrophic pyelonephritis, or of vascular or ureteric occlusion early in life, may be extremely difficult if not impossible. The

recognition of a congenitally absent or insufficient kidney is essential when nephrectomy is being considered as treatment of disease in the opposite kidney.

**RENAL AGENESIA.**—Agenesis implies the complete absence of a kidney. Bilateral agenesis is, of course, incompatible with survival.

**RENAL APLASIA.**—An aplastic kidney contains no renal tissue capable of normal function. Glomerular and tubular elements are contained, perhaps with cysts, within a dense stroma of fibrous tissue and scanty smooth muscle, and the ureter is often not patent. Owing to the difficulty of distinguishing such anomalous structures from secondarily contracted kidneys there is a lack of evidence whether they can be responsible for the development of hypertension.

**RENAL HYPOPLASIA.**—Truly hypoplastic kidneys contain virtually normal nephrons in markedly reduced numbers. They are miniatures with reduced function commensurate with their size and are therefore unable to maintain life indefinitely if the condition is bilateral. The renal failure which develops is analogous to that occurring in experimental animals in which a large part of the renal tissue has been removed. Histologically, hypertrophy of the individual nephrons and tubular dilatation are found.

Hypoplasia may be one cause of the so-called "Rose Bradford kidneys" in children or young adults, pyelonephritis or glomerulo-nephritis contributing to the picture of gross renal contraction in which areas of hypertrophied elements alternate with dense interstitial fibrosis. A closely related group of very contracted kidneys is characterised by idiopathic dilatation of the urinary tract. The condition may be unilateral or bilateral and the bladder may be dilated. No organic cause of obstruction is found in the majority of these cases but chronic pyelonephritis is an invariable complication. It is possible also that "Rose Bradford kidneys" may result from ascending infection of normal kidneys in early childhood or *in utero*. In all these groups of gross renal contraction renal failure is prolonged and the symptoms of polyuria and polydipsia are particularly prominent. Osteodystrophy (renal rickets and dwarfism) may occur in association with phosphate retention, acidosis, parathyroid hyperplasia and metastatic calcification. Hypertension is infrequent whilst very occasionally hypotension is associated with sodium depletion due to chronic acidosis.

**CONGENITAL POLYCYSTIC DISEASE.**—This condition is described on p. 1146.

## LARDACEOUS DISEASE

**Synonyms.**—Amyloid or Waxy Kidney.

**Definition.**—A pathological condition in which the blood vessels of the kidney, and in more advanced cases the tunica of the tubules and the interstitial tissue also, are the seat of waxy degeneration.

**Ætiology.**—This affection is now rarely met with. It attacks men more than women, and although occasionally seen in children it is more likely to occur in adolescence and earlier adult life, being uncommon after 50 years of age. It is usually due to chronic suppuration, especially in bone, chronic tuberculosis and syphilis. It rarely occurs in other chronic infections, but it has been described in severe rheumatic heart disease, and a certain amount of amyloid change has sometimes been found post mortem in patients suffering from chronic cardio-vascular disease and chronic nephritis in the absence of chronic suppuration. As it is a degenerative change it has, however, more affinity with nephrosis than with nephritis.

**Pathology.**—Amyloid material or lardacein is a product of protein degeneration, and consists of protein linked with chondroitin-sulphuric acid. The latter substance is a normal constituent of elastic tissue and cartilage. In uncomplicated cases the affected kidney has the appearance of a large white kidney with a smooth surface and a capsule that strips easily. The organ is firmer than it otherwise would be.

On section, the cortex is thicker than normal and has a yellowish white appearance; the glomeruli may be visible as minute translucent spots. The pyramids are dark red, in contrast to the pale cortex. If a solution of iodine in potassium iodide is poured over the surface, some of the glomeruli stand out as mahogany-brown spots and the vasa recta as brown streaks. In histological preparations stained with methyl-violet, amyloid material takes a pink colour. The disease tends to appear first in the capillaries of some glomeruli, while others are normal, and its incidence is often partial within a single glomerulus. The afferent arterioles, vasa recta and capillary plexus are next affected; in more advanced cases there is amyloid degeneration of the tunica propria of the tubules with amyloid deposits in the interstitial tissue. In most cases there is an associated nephritis. The kidney lesion is generally the most striking part of a widespread lardaceous degeneration which also involves the liver, spleen and intestine; less commonly the blood vessels of the thyroid, suprarenals, pancreas, heart and brain may be affected as well. Occasionally only the kidney is implicated.

**Symptoms.**—The onset is insidious and the symptoms are not likely to occur unless chronic suppuration has existed for at least 3 months.

The urine is copious, of low specific gravity (1.003 to 1.010). The amount of albumin is variable; when abundant, hypoproteinæmia may result. The amount of urine and its specific gravity may also be affected by the presence and degree of coincident nephritis, and the state of the heart. Hyaline and granular casts are present in the urine; casts staining brown with iodine are not evidence of amyloid disease, and may occur in other diseases of the kidneys. True waxy casts are not found. In later stages there is œdema, with diminished excretion of urine. The blood pressure is not raised, nor is the left ventricle hypertrophied, unless there is coexistent chronic nephritis.

**Diagnosis.**—The condition must be distinguished chiefly from Type 2 nephritis. The diagnosis of amyloid disease is made (1) when there is a sufficient cause in the past history or present condition, namely, chronic suppuration or syphilis; (2) on signs of lardaceous disease in other organs, such as enlargement of the liver or spleen and diarrhœa; (3) on confirmatory evidence from special tests. The Congo Red test is based on absorption of the dye by amyloid material and its consequent removal from the blood stream and failure to appear in the urine after intravenous injection of a known quantity of dye. The test is positive in 80 to 90 per cent. of cases. When it is essential to be certain of the diagnosis (e.g. when a decision on surgical treatment of the primary infection must be made) drill biopsy of the liver will afford histological proof.

**Course and Prognosis.**—This depends on that of the primary cause. If the latter is unchecked, the disease is slowly progressive and death occurs from exhaustion due to the original disease, or from uræmia. Where the original disease can be cured, recovery may occur. Complete recovery of the kidneys is less likely than is recovery of the liver, spleen and intestines. This is probably due to associated nephritis.

**Treatment.**—The treatment is that of the original disease. In suppuration of the bones or joints, empyema, etc., it is surgical; but it must be recognised that in advanced cases surgical treatment may be too late, even though it is successful in eradicating the septic focus. In all cases fresh air and sunlight and a nourishing diet are essential. Iron and cod-liver oil should be given. Cases of syphilitic origin should be treated with appropriate antisyphilitic therapy.

## PYELITIS

**Definition.**—Pyelitis is inflammation of the renal pelvis. When complicated by nephritis, the condition is termed pyelonephritis.



**Ætiology.**—Most cases are due to a blood-borne infection of the renal pelvis. The pelvis may also be involved by ascending infections—(a) via the lumen of the ureter when there is ureteral obstruction; it is probable that infection does not spread by this channel when the lumen is normally patent. (b) By way of the peri-ureteral lymphatics from local foci in lower parts of the urinary tract, such as the bladder, urethra, prostate, seminal vesicles and epididymis. Lastly, there is the possibility of direct spread of infection from the bowel, and by cross lymphatic channels from one kidney to the other. In those cases in which a pyelitis occurs secondary to appendicitis, cholecystitis, ulcerative colitis, etc., the spread of infection may be by the lymphatics or the blood-stream.

Pyelitis is more common in females than in males. Its age incidence depends on the determining cause. Thus, it is common in female infants, as a result perhaps of urethral infection, to which they are more liable than male infants. It is not an uncommon complication of pregnancy, occurring especially in the fifth month of gestation. It is common in males at a later age, associated with enlarged prostate and cystitis.

In general terms any injury or disease of the renal pelvis, or any condition which interferes with the normal flow of urine, may be the determining cause of pyelitis. Thus it is a common complication of hydronephrosis from whatever cause. It often complicates stone in a kidney, tuberculosis of the kidney and new-growths of the renal pelvis.

**Pathology.**—The mucous membrane of the pelvis is swollen, cedematous and hyperæmic, and the submucous venules are engorged. Where there is obstruction, the pelvis is dilated and contains a slightly turbid or opalescent fluid. In these circumstances the ureter above the obstruction is dilated and tortuous and its walls are thickened. The kidney is swollen and pale, from cloudy swelling, and in severe cases there may be multiple small abscesses in the renal parenchyma.

*Bact. coli* is by far the most common infecting micro-organism. Streptococci, staphylococci, gonococci and bacilli of the *Proteus* and typhoid groups may be found. The infecting micro-organism is readily recovered from the urine.

**Symptoms.**—The clinical types of pyelitis differ greatly from one another, and the condition may be responsible for an acute fulminating illness or for chronic malaise of indefinite nature.

**LOCAL SYMPTOMS.**—Pain is the most important, especially as a diagnostic indication in acute cases. It is a dull ache in the loin or flank, at first slight and intermittent, later, or in other cases at once, constant and sometimes intense. Occasionally it takes the form of renal colic. At its onset the pain may be diffuse and abdominal. Increased frequency and urgency of micturition is the most common symptom. There may be strangury.

**GENERAL SYMPTOMS.**—In acute cases there may be sudden onset with rigors, vomiting, headache and the general constitutional disturbance of profound toxæmia. These cases may simulate septicæmia (in fact there may be septicæmia), appendicitis, or, when associated with abdominal distension, constipation and vomiting may even simulate intestinal obstruction. In other cases, with cerebral symptoms, meningitis may at first be difficult to exclude.

In subacute cases, without marked pain or rigors, there is general malaise, fever, anorexia, wasting and a secondary anæmia associated with some degree of polymorphonuclear leucocytosis (white blood count=10 to 15,000).

In relapsing cases there are periods of exacerbation with acute symptoms, and intervening periods of fair health or general malaise. Fever is commonly present; in acute cases with rigors it may rise to 105° or 106° F. In general the temperature is irregular, remittent or intermittent, varying between 102° and 104° F. in acute cases, and 100° and 102° F. in subacute cases. The pulse is raised in proportion to the temperature, and there is a corresponding slight increase in the respiration rate.

Of other general symptoms constipation or diarrhoea frequently precedes the disease, and constipation generally accompanies it. Toxæmia is often marked.

Deep tenderness on palpation of the renal region and the presence of infected urine are the diagnostic signs of the disease. There is some degree of abdominal rigidity, and it may be possible to determine enlargement and tenderness of the kidney. The urine is passed in small quantities at frequent intervals. It has the usual characters of febrile urine and is turbid. The turbidity or an opalescence is still present after filtration. When an appreciable quantity of pus is present it settles at the bottom of a specimen glass in a thick whitish deposit. Examination of the deposit (catheter specimen in women) shows pus cells and epithelial cells from the urinary tract. There may be hæmaturia.

**Bacteriuria.**—In this condition bacteria are present in the urine in such quantity as to make it hazy to the naked eye, but there is little or no inflammatory reaction in any part of the urinary tract. Hence there are no localising symptoms and few pus cells. The urine when freshly passed has a hazy appearance. In a test-tube, when the tube is rotated, the urine has a "satiny" appearance or shimmer. It is not cleared by filtration. It often has a fishy smell in *Bact. coli* infection, and is ammoniacal in smell in *Proteus* infection. Its reaction is acid, unless due to staphylococcal or *Proteus* infection. It generally contains a trace of albumin, and often may contain a few white blood corpuscles and epithelial cells. A catheter specimen grown in broth, in dilutions of 1 ml.,  $\frac{1}{10}$  ml. and  $\frac{1}{100}$  ml. urine in 10 ml. broth, gives a growth in all dilutions, and in *Bact. coli* infections there is generally a growth in greater dilutions. Streptococcal and staphylococcal infections are less common, but even when present they are easily overlooked because the streptococci and some forms of staphylococci are liable to be overgrown by the *Bact. coli* on culture. Thus, an infection by *Streptococcus faecalis* may be first recognised only after the *Bact. coli* infection has been eradicated by treatment.

**Diagnosis.**—When there is fever and constitutional disturbance without localising signs or symptoms, the differential diagnosis is from those diseases which come in their early phases under the category of indeterminate fever. The diagnosis is established by examination of the urine. Pyonephrosis is diagnosed by the presence of a renal swelling. Calculus is recognised by its clinical features and by radiography. Perinephric abscess in its early stages is not accompanied by pyuria or increased frequency of micturition. Cystitis is generally afebrile; and it is accompanied by suprapubic discomfort and pain, particularly at the end of micturition; the diagnosis can be established by cystoscopy. Urethritis is recognised by local tenderness, urethral discharge and the appearances on urethroscopy, and prostatitis by swelling and tenderness on rectal examination.

**Prognosis.**—The usual outcome of uncomplicated pyelitis with efficient treatment is recovery in 5 to 10 days. Efficient treatment depends on the use of the drug, namely a sulphonamide or penicillin, to which the infecting micro-organisms are sensitive. When these remedies fail streptomycin may be effective within 24 or 48 hours even in the presence of a complication such as one or more stones in the kidney. These new remedies have greatly diminished the risk of ascending suppurative nephritis, pyonephrosis or chronic pyelonephritis.

**Treatment.**—Prophylaxis is important in nurseries and children's hospitals, since there is evidence of spread of infection via the urethra in females. Here it is a question of cleanliness. In general terms exposure to cold, over-fatigue and loose stools are to be avoided when there is susceptibility to *Bact. coli* infection of the urinary tract.

A patient suffering from an acute attack is treated with rest in bed, fluids in large quantity, bowel function is regulated and sufficient alkali is given by mouth to make the urine alkaline. In order to avoid chill the patient is nursed between blankets. Five to 6 pints of fluid are given in every 24 hours in the form of water,

barley water, imperial drink, weak tea and thin soups. Milk may be citrated, and as the temperature subsides diet is increased by the addition of starch, fruit and vegetables. Bowels are emptied with an initial laxative followed by an enema if necessary. After this the action of the bowels is regulated with paraffin, magnesia or mild laxatives, such as liquorice powder, rhubarb or aloes. It is important to avoid habitual loose stools because this predisposes to urinary infection. A mixture containing 30 g. each of potassium citrate and sodium bicarbonate is given 3-hourly until the urine is alkaline. Every specimen of urine passed is tested with litmus paper. When the urine is alkaline the mixture is given at 4 or 6-hourly intervals, that is to say, in sufficient quantity to keep every specimen of urine alkaline.

The alkali treatment of *Bact. coli* infections of the urinary tract is now only given in the initial stage of the more acute cases, and even in these with increasing experience of the efficacy of sulphonamide drugs in the treatment of urinary infections, one of these drugs is given as soon as the disease is diagnosed. Sulphacetamide is the drug of choice for *Bact. coli* infections, because of its low renal toxicity. It is readily absorbed, rapidly eliminated and is very soluble (much more so than sulphadiazine). Hence a high urinary concentration can be obtained with a relatively low blood level. In an acute case with high fever and a large fluid intake 1 g. is given 4-hourly. As soon as the temperature subsides and the fluid balance in the patient is restored to normal, the dose of sulphacetamide is reduced to one tablet 4-hourly and at the same time the fluid intake is limited to 2 pints in 24 hours. This treatment is given until the urine is perfectly clear when freshly passed: it is then continued for a further 48 hours. In a mild or chronic case the length of treatment is generally 5 to 6 days. In an acute case it may be considerably longer. Forty-eight hours after the drug is stopped the urine is again examined bacteriologically. If the urine is still infected the diagnosis should be reconsidered.

In the first place the infection may be a complication of concealed disease of the urinary tract, such as calculous disease, tuberculosis, neoplasm, enlarged prostate with residual urine or hydronephrosis. Chronic pyelonephritis, especially if of long standing, may resist sulphonamide therapy. Rarely a persistent infection may be a complication of organic disease of the digestive tract, such as chronic appendicitis, especially if the right ureter is involved, diverticulosis or even cholecystitis. In any case of urinary infection that is resistant to treatment or presents any unusual symptom, a detailed investigation of both urinary and digestive tracts is required in order to determine or exclude a change in structure which may be the underlying and determining cause of the urinary infection.

In the second place, when the *Bact. coli* infection has been cleared by sulphonamide treatment, a residual infection with *Str. faecalis* or staphylococcus may be found. It is important to clear the urine of these residual infections because they may determine a return of *Bact. coli* infection. Mandelix may be used for *Str. faecalis* infection. The routine is to give ammonium or calcium mandelate gr. 45 in solution (2 g.) with 2 oz. of water four times in 24 hours. Fluid intake is limited to 32 oz., which together with the medicine makes a total intake of 2 pints. Every specimen of urine passed is examined as to its pH, which must be 5 to 5.1, and sufficient ammonium chloride is administered by mouth to produce the required urinary pH.

Penicillin given intramuscularly is almost wholly excreted in the urine where a high concentration is therefore attained. Penicillin is now used for staphylococcal, *Str. faecalis* and *Proteus* infections of the urinary tract, as also in the unusual cases in which the *Bact. coli* is penicillin sensitive. Penicillin has therefore displaced sulphathiazole in the treatment of staphylococcal infections and mandelic acid in the treatment of *Str. faecalis* infections. An average dose is 20,000 units 6-hourly throughout the 24 hours. It is probable that the most effective treatment for Gram-negative bacillary infections of the urine will prove to be streptomycin, given intramuscularly

4-hourly in a dose of 0.5 g., namely 3 g. daily for 2 days. With further experience smaller doses may be found effective, and 2 days' treatment may prove sufficient.

In the uncommon fulminating cases with unilateral suppurative nephritis, nephrectomy may save the patient's life.

## CHRONIC PYELONEPHRITIS

It has already been stated that infection may spread from the renal pelvis into the kidney substance and produce pyelonephritis. The recognition of this extension is difficult in the early stages because renal involvement is focal so that the diagnostic signs of nephritis are absent. In severe cases of pyelitis, however, a slight degree of œdema and hypertension may be observed. A further pointer to the diagnosis is the persistence of albuminuria when the pyelitis has been effectively treated and pus and organisms are no longer found in the urine. In chronic pyelitis, particularly when there are recurrent attacks over a period of years, the presence of chronic pyelonephritis is strongly presumptive. An acute ascending infection, particularly when drainage is defective, as in neurogenic retention of urine, may lead to suppurative pyelonephritis with the formation of multiple small abscesses. Fever and toxæmia are severe, and in such cases pyuria may persist in spite of antibiotic therapy. A particularly intense and often fatal type of suppurative pyelonephritis occurs in diabetes and, especially in elderly patients, extensive medullary necrosis may be produced (see p. 1127).

The particular importance of chronic pyelonephritis lies in the fact that it may persist and progress after the pelvic inflammation has subsided. Gradual destruction of the renal parenchyma continues over a period of many years, usually in the absence of symptoms, and the clinical course resembles very closely that of chronic Type 1 nephritis. The similarity is further enhanced by the observation that a large proportion of patients presenting with this condition in its late stages give no history of acute pyelitis. The incidence of this form of the disease is much higher in women than in men, which suggests that sub-clinical pyelitis may possibly have occurred during pregnancy at some time in the past.

**Pathology.**—Pyelonephritis is an interstitial inflammation of the kidney which leads to focal scarring and destruction of nephrons extending upwards from the medulla to the cortex. Involvement of the kidney may be irregular, so that scarring may be confined to a single area, or may involve broad zones throughout the substance of the kidney. This leads to the characteristic "rat-bitten" appearance of the outer surface which is deformed by broad sunken scars. While both kidneys may be involved to a similar extent, pyelonephritis is usually more marked in one kidney than in the other and there may be gross inequality in size. Not infrequently one kidney alone is involved, the other showing compensatory hypertrophy. It is highly probable that local obstructive lesions such as have been discussed under acute pyelitis are responsible for this uneven distribution. Obstruction is also indicated by the presence of some degree of hydronephrosis, although this may be slight. Microscopically there is in many cases little evidence of active pyelitis, but some degree of sub-pelvic fibrosis is usually seen. In the renal substance areas of scarring with dense round-cell infiltration alternate with normal kidney tissue. In the fibrotic zones the tubules are atrophied and, characteristically, groups of surviving tubules are seen in the cortex, distended with hyaline material and presenting an appearance resembling thyroid tissue. The glomeruli in the affected zones show ischæmic atrophy, with hyaline thickening of Bowman's capsule; aggregates of completely hyalinised glomeruli in the shrunken areas of the cortex are typical. Occasionally, glomeruli in the less affected areas show great dilatation and wavy distortion of Bowman's capsule, the capsular space being filled with albuminous material. In severely scarred kidneys

medium and large arteries are often prominent and show obliterative endarteritis. Arteriolar changes are inconspicuous except in those rare cases which are complicated by malignant hypertension.

**Symptoms.**—There may be no symptoms in chronic pyelonephritis until attention is drawn to the condition by the development of uræmia or hypertension. Alternatively there may be recurrent attacks of pyelitis or cystitis. High blood pressure is not a common or prominent feature of chronic pyelonephritis; nevertheless in some cases severe hypertension is observed and may progress to the malignant phase. This complication is occasionally seen in unilateral disease. It is difficult to say why only a minority of patients with pyelonephritis develop hypertension but there is a possibility that some other factor such as a congenital obstructive lesion of the kidney, or even a constitutional tendency to hypertension may be responsible. Albuminuria is usually present throughout the course of pyelonephritis, the urine may also contain pus and bacteria, but in many cases the ascending infection has resolved and pyuria is absent; occasionally the urine may even be free from albumin. A diagnosis of essential hypertension is then likely to be made and the underlying condition is only revealed when intravenous pyelography shows distortion of the renal calyces or evidence of renal contraction. In the absence of hypertension, uræmia may be so protracted in chronic pyelonephritis that osteodystrophy with metastatic calcification occurs. In very rare cases chronic acidosis leads to severe sodium depletion and hypotension (so-called salt-losing nephritis), so that the clinical picture may closely resemble Addison's disease.

**Diagnosis.**—Persistent albuminuria associated with renal impairment, with a past history of attacks of pyelitis, will suggest the diagnosis. Many patients with other forms of Bright's disease develop urinary tract infection, however, so that there will often be an element of doubt. In the late stages the presence of uræmia with little or no hypertension should bring to mind the possibility of chronic pyelonephritis. Intravenous pyelography should not be carried out if there is impaired concentrating power since concentration of the radio-opaque solution is also defective. Retrograde pyelography may show distortion of the renal calyces but this investigation is hardly justified in the presence of renal insufficiency.

**Prognosis.**—This depends on the extent of the lesion, *i.e.* whether it is unilateral or bilateral and on the effectiveness with which active urinary tract infection can be controlled. In established bilateral disease progress is very slow, largely due to the absence of severe hypertension, and the patient may continue in good health for 10 or 20 years before uræmia develops. Even the stage of renal insufficiency tends to be protracted and consequently a long period of ill health must be expected in the later stages of the disease.

**Treatment.**—Active infection of the urinary tract should be treated as described under pyelitis. Nephrectomy should be considered in unilateral pyelonephritis and particularly if hypertension is present. Many cases have been reported where nephrectomy has been a life-saving measure after the hypertension had entered the malignant phase, *i.e.* when papillœdema had developed. When renal failure develops, treatment is that described for the corresponding stage of chronic Type 1 nephritis.

## PERINEPHRITIS AND PERINEPHRIC ABSCESS

Suppurative perinephritis may be due to blood-stream infection when the invading organism is usually *Staphylococcus pyogenes*; or it may arise from direct extension of local suppuration, the invading organism being a member of the coliform group or other bowel pathogen.

**Ætiology and Pathology.**—Blood-stream infection may follow injury, but more

4-hourly in a dose of 0.5 g., namely 3 g. daily for 2 days. With further experience smaller doses may be found effective, and 2 days' treatment may prove sufficient.

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In the uncommon fulminating cases with unilateral suppurative nephritis, nephrectomy may save the patient's life.

## CHRONIC PYELONEPHRITIS

It has already been stated that infection may spread from the renal pelvis into the kidney substance and produce pyelonephritis. The recognition of this extension is difficult in the early stages because renal involvement is focal so that the diagnostic signs of nephritis are absent. In severe cases of pyelitis, however, a slight degree of oedema and hypertension may be observed. A further pointer to the diagnosis is the persistence of albuminuria when the pyelitis has been effectively treated and pus and organisms are no longer found in the urine. In chronic pyelitis, particularly when there are recurrent attacks over a period of years, the presence of chronic pyelonephritis is strongly presumptive. An acute ascending infection, particularly when drainage is defective, as in neurogenic retention of urine, may lead to suppurative pyelonephritis with the formation of multiple small abscesses. Fever and toxæmia are severe, and in such cases pyuria may persist in spite of antibiotic therapy. A particularly intense and often fatal type of suppurative pyelonephritis occurs in diabetes and, especially in elderly patients, extensive medullary necrosis may be produced (see p. 1127).

The particular importance of chronic pyelonephritis lies in the fact that it may persist and progress after the pelvic inflammation has subsided. Gradual destruction of the renal parenchyma continues over a period of many years, usually in the absence of symptoms, and the clinical course resembles very closely that of chronic Type 1 nephritis. The similarity is further enhanced by the observation that a large proportion of patients presenting with this condition in its late stages give no history of acute pyelitis. The incidence of this form of the disease is much higher in women than in men, which suggests that sub-clinical pyelitis may possibly have occurred during pregnancy at some time in the past.

**Pathology.**—Pyelonephritis is an interstitial inflammation of the kidney which leads to focal scarring and destruction of nephrons extending upwards from the medulla to the cortex. Involvement of the kidney may be irregular, so that scarring may be confined to a single area, or may involve broad zones throughout the substance of the kidney. This leads to the characteristic "rat-bitten" appearance of the outer surface which is deformed by broad sunken scars. While both kidneys may be involved to a similar extent, pyelonephritis is usually more marked in one than in the other and there may be gross inequality in size. Not infrequently one kidney alone is involved, the other showing compensatory hypertrophy. It is highly probable that local obstructive lesions such as have been discussed under acute pyelitis are responsible for this uneven distribution. Obstruction is also indicated by the presence of some degree of hydronephrosis, although this may be slight. Moreover, there is in many cases little evidence of active pyelitis, but some degree of fibrosis is usually seen. In the renal substance areas of scarring with dense cell infiltration alternate with normal kidney tissue. In the fibrotic zones the are atrophied and, characteristically, groups of surviving tubules are seen indistended with hyaline material and presenting an appearance resembling the tissue. The glomeruli in the affected zones show ischaemic atrophy, with thickening of Bowman's capsule; aggregates of completely hyalinised and the shrunken areas of the cortex are typical. Occasionally, glomeruli in affected areas show great dilatation and wavy distortion of Bowman's capsular space being filled with albuminous material. In severely scarred



medium and large arteries are often prominent and show obliterative endarteritis. Arteriolar changes are inconspicuous except in those rare cases which are complicated by malignant hypertension.

**Symptoms.**—There may be no symptoms in chronic pyelonephritis until attention is drawn to the condition by the development of uræmia or hypertension. Alternatively there may be recurrent attacks of pyelitis or cystitis. High blood pressure is not a common or prominent feature of chronic pyelonephritis; nevertheless in some cases severe hypertension is observed and may progress to the malignant phase. This complication is occasionally seen in unilateral disease. It is difficult to say why only a minority of patients with pyelonephritis develop hypertension but there is a possibility that some other factor such as a congenital obstructive lesion of the kidney, or even a constitutional tendency to hypertension may be responsible. Albuminuria is usually present throughout the course of pyelonephritis, the urine may also contain pus and bacteria, but in many cases the ascending infection has resolved and pyuria is absent; occasionally the urine may even be free from albumin. A diagnosis of essential hypertension is then likely to be made and the underlying condition is only revealed when intravenous pyelography shows distortion of the renal calyces or evidence of renal contraction. In the absence of hypertension, uræmia may be so protracted in chronic pyelonephritis that osteodystrophy with metastatic calcification occurs. In very rare cases chronic acidosis leads to severe sodium depletion and hypotension (so-called salt-losing nephritis), so that the clinical picture may closely resemble Addison's disease.

**Diagnosis.**—Persistent albuminuria associated with renal impairment, with a past history of attacks of pyelitis, will suggest the diagnosis. Many patients with other forms of Bright's disease develop urinary tract infection, however, so that there will often be an element of doubt. In the late stages the presence of uræmia with little or no hypertension should bring to mind the possibility of chronic pyelonephritis. Intravenous pyelography should not be carried out if there is impaired concentrating power since concentration of the radio-opaque solution is also defective. Retrograde pyelography may show distortion of the renal calyces but this investigation is hardly justified in the presence of renal insufficiency.

**Prognosis.**—This depends on the extent of the lesion, i.e. whether it is unilateral or bilateral and on the effectiveness with which active urinary tract infection can be controlled. In established bilateral disease progress is very slow, largely due to the absence of severe hypertension, and the patient may continue in good health for 10 or 20 years before uræmia develops. Even the stage of renal insufficiency tends to be protracted and consequently a long period of ill health must be expected in the later stages of the disease.

**Treatment.**—Active infection of the urinary tract should be treated as due to under pyelitis. Nephrectomy should be considered in unilateral pyelonephritis and particularly if hypertension is present. Many cases have been reported in which nephrectomy has been a life-saving measure after the hypertension had reached the malignant phase, i.e. when papillœdema had developed. When renal insufficiency develops, treatment is that described for the corresponding stage of chronic T<sub>1</sub> nephritis.

## PERINEPHRITIS AND PERINEPHRIC ABSCESS

Suppurative perinephritis may be due to blood-stream infection when the invading organism is usually *Staphylococcus pyogenes*; or it may arise from direct extension of local suppuration, the invading organism being a member of the coliform group or other bowel pathogen.

**Ætiology and Pathology.**—Blood-stream infection may follow injury, but more

frequently results from boils, carbuncles and tonsillitis, or complicates an acute specific fever. J. Koch has shown experimentally that intravenous injection of staphylococci is followed by their excretion in the urine after an interval of 4 to 6 hours. In the process of excretion, according to Koch, they may give rise to multiple cortical abscesses, cylindrical medullary abscesses, or, passing along the cortical lymphatics, may gain access to the perinephric tissues and there cause abscess formation. In these circumstances perinephric abscess is an example of staphylococcal pyæmia with single metastatic abscess formation. Perinephritis by direct extension may complicate suppuration in the neighbouring organs, such as the kidney, liver, gall-bladder or appendix. It may be secondary to caries of the spine. In other cases the infection may be carried by lymphatics from a focus in or around the bladder, rectum or female pelvic organs.

**Symptoms.**—The onset is generally gradual. It is characterised by fever and malaise as in typhoid fever. There may be no local symptoms for the first 7 to 14 days, and during this period there is increasing toxæmia, general abdominal discomfort or pain, slight fullness and resistance, with deep tenderness, in the affected loin. As the abscess forms, pain and tenderness increase, there is induration and, later, redness of the skin and œdema in the lumbar region. The tumour first tends to spread backwards, obliterating the normal hollow in the loin, and then as pus collects it may spread forwards, forming a tender tumour palpable from the front. In its relations to the colon it resembles a renal tumour, but does not move with respiration. There is resistance or rigidity of the abdominal wall on the affected side. There is an increasing polymorphonuclear leucocytosis up to 20,000 or even 40,000. The urine is "febrile" in character, containing a trace of albumin and perhaps a few white blood corpuscles; it does not contain pus, unless the kidney itself is involved, but hæmaturia may occur. In some cases the disease runs an acute course, and there may be rigors at an early stage.

**Diagnosis.**—Before localising signs appear the disease may be mistaken for typhoid fever, malaria or septic endocarditis. The blood examination is important for the purpose of excluding malarial parasites; leucocytosis is against typhoid fever, and when above 15,000 is in general against infective endocarditis. Absence of agglutination of micro-organisms of the typhoid group is further evidence.

When the tumour exists it has to be distinguished from a renal tumour or pyonephrosis. Renal and adrenal growths may be accompanied by fever, but do not usually give the general symptoms of suppuration; they tend to extend forwards rather than backwards, and induration of the tissues is absent. Pyonephrosis causes symptoms of suppuration and a tender swelling, but the tumour is circumscribed, moves with respiration and does not cause any bulging in the lumbar region. Pyuri

is usually associated with other showing compensatory disease and even of myositis as distinguished from that local obstructive lesions such as have been discussed. It is itself induces responsible for this uneven distribution. Obstruction is also indicated by the presence of some degree of hydronephrosis, although this may be slight. Microscopic examination of the kidney shows that there is in many cases little evidence of active pyelitis, but some degree of sub-epithelial fibrosis is usually seen. In the renal substance areas of scarring with dense round cell infiltration alternate with normal kidney tissue. In the fibrotic zones the tubules are atrophied and, characteristically, groups of surviving tubules are seen in the cortex distended with hyaline material and presenting an appearance resembling thyroid tissue. The glomeruli in the affected zones show ischæmic atrophy, with hyaline thickening of Bowman's capsule; aggregates of completely hyalinised glomeruli in the shrunken areas of the cortex are typical. Occasionally, glomeruli in the less affected areas show great dilatation and wavy distortion of Bowman's capsule, the capsular space being filled with albuminous material. In severely scarred kidneys the

an operation is performed and the pus evacuated, penicillin being instilled into the abscess cavity.

## TUBERCULOSIS OF THE KIDNEY

Small grey tubercles are frequently found scattered through the kidneys in persons who die of acute miliary tuberculosis; the kidney disease, however, scarcely affects the clinical aspect of the case, and this form of renal tuberculosis will not be considered here. Further, in patients who die of pulmonary tuberculosis it is not uncommon to find tuberculous foci in the kidneys post mortem, although there was no indication of their presence during life.

Clinical renal tuberculosis is either the fibro-caseating form of the disease, or it is tuberculous hydronephrosis. In either case, the tuberculous infection is generally primary in the kidney in so far as its clinical expression is concerned.

**Ætiology.**—It is more common in women than men. The maximum age incidence is in the third and fourth decades; the disease is uncommon in the young and rare in the old. At an early stage the disease is unilateral. In the majority of cases the tubercle bacilli are carried to the kidney by the blood-stream from a tuberculous focus, such as a caseating lymph gland. Recent experimental work has shown that bacteria do not ascend in the lumen of the ureter unless it is diseased, when the infection may spread by direct extension in its walls. Infection may also reach the kidney via the lymphatics in a proportion of cases. The path of infection is by way of the ureteric lymphatics, and it is probable that in pelvic tuberculosis, for example, tuberculous prostatitis, may spread to the kidney by this route. There is also reason to think that tubercle bacilli from a diseased kidney may infect the opposite healthy kidney by the same lymphatic path, the bacilli first travelling in the urine and walls of the ureter from the diseased kidney and causing disease of the bladder, and then travelling from the bladder by way of the ureteric lymphatics to the sound kidney. On the other hand, there is a shorter path for infection from one kidney to another by the para-aortic lymphatic system. Since the disease in the other kidney takes the same anatomical form as it originally had in the kidney first affected, it is probable that, if the first is due to a blood-borne infection, so is the second. Vesical tuberculosis is, as a rule, secondary to infection elsewhere in the urino-genital system commonly in the kidneys.

**Pathology.**—The initial lesion is in the cortex, or one of the pyramids, and it consists of one or more tubercles. The morbid process spreads by destruction of kidney tissue; there is caseation in the centre of the lesion, inflammatory reaction, with intense small-cell infiltration, giant-cell formation and more or less fibrosis at the periphery. The lesion also spreads by the deposition of tubercles at a distance; these are scattered through the cortex, singly or in groups. Extension through the capsule is uncommon, but extension to the renal pelvis is frequent. Complete destruction of one or more pyramids may occur, or the disease may spread and involve one or more calyces or the entire pelvis. The resulting infiltration and cicatricial contraction may lead to hydro- or pyonephrosis. The disease tends to extend down the ureter, and the bladder is commonly infected at an early stage. Secondary infections may lead to metastatic abscesses in the kidneys and ultimately to destruction of the whole organ.

**Symptoms.**—Frequency of micturition is often the earliest symptom; it is first noticed by day and later at night. Urgency and painful micturition develop next and are due to tuberculous cystitis. The urine may show no other abnormality than a trace of albumin at an early stage; characteristically it is pale and a little turbid from the presence of pus; it is acid in reaction, it may contain a few renal cells, and it is sterile on culture. By appropriate staining tubercle bacilli may be demonstrated

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The diagnosis from caries of the spine, hip disease and even of myositis as distinct from perinephritis may be difficult. Since perinephritis in itself induces lumbar rigidity and some degree of scoliosis, radiographic examination may be required to exclude caries of the spine. This investigation is also important since a diagnostic radiological sign of perinephric abscess is obliteration of the psoas shadow on the affected side. Hip-joint disease is excluded by absence of local tenderness and by the freedom of flexion and rotation of the thigh.

**Course.**—When the condition is simply associated with chronic nephritis it has no separate significance. When it proceeds to suppuration the abscess may rupture into the peritoneum, colon or pleura, or on to the surface, unless the abscess is opened and drained.

**Treatment.**—The patient is treated at rest in bed and given penicillin—30,000 units 4-hourly. Alternatively, sulphathiazole is prescribed, namely an initial dose of 2 g., followed by 1 g. 4-hourly. Fomentations or a kaolin poultice are applied to the loin. Aspirin is given to relieve pain. If there is evidence of abscess formation,

an operation is performed and the pus evacuated, penicillin being instilled into the abscess cavity.

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in the centrifugal deposit. Hæmaturia may be the first symptom, or the disease may develop insidiously with lumbar pain. On examination, the kidney is sometimes enlarged, and it may be hard and irregular; it is often tender. Tenderness along the course of the ureter or thickening of the ureter, as determined by abdominal or rectal examination, is of great importance. The rest of the urino-genital system requires close examination; this should include cystoscopy and in some cases ureteral catheterisation. Radiographic examination of the abdomen may reveal calcified tuberculosis of the kidneys or lymph glands, and it may be required in the differential diagnosis from renal calculus. Finally, a careful review of the patient's history and present condition for evidence of a chronic bacterial toxæmia or of tuberculous infection elsewhere must be made.

**Diagnosis.**—The presence of tubercle bacilli in the urine, whether determined by microscopic examination of the stained deposit or by guinea-pig inoculation, is not absolute proof of renal tuberculosis, because the bacilli may be excreted by a healthy kidney or they may come from some other part of the urinary tract. Nevertheless, the demonstration of tubercle bacilli in the urine is of the first importance in a doubtful case, and the diagnosis may be established by cystoscopy. The cases which require most careful examination are those with an atypical onset, such as massive hæmaturia, and those in which there is a gross secondary infection when first seen. The possibility of renal tuberculosis must always be borne in mind in hydro- and pyonephrosis. The differential diagnosis from simple albuminuria and the several forms of Bright's disease is made on the presence of pyuria and the absence of signs and symptoms of chronic nephritis.

**Course and Prognosis.**—The onset is insidious and the course progressive. Natural recovery is hardly known, though occasionally an unsuspected caseous kidney may be found at autopsy in patients dying of other diseases. The disease runs an uncertain course, having a duration of a few years up to 10 or 12 years from the date of diagnosis. Death results from tuberculous toxæmia, secondary infection or failure of renal function.

**Treatment.**—When the disease is unilateral the kidney should be removed, but nephrectomy is rarely justified if the other kidney is involved. In any case the patient's health and resistance should be raised to the utmost by rest, fresh air and good food, on the general lines of treatment of tuberculosis of the lungs. Therapeutic trials of the specific remedies against tuberculosis, streptomycin with isoniazid or sodium aminosalicylate, have shown that renal tuberculosis is more resistant to treatment than other forms of the infection and further experience is required before their effectiveness can be assessed.

## RENAL CALCULI (NEPHROLITHIASIS)

Renal calculi may be composed of calcium oxalate or phosphate, uric acid, urates, phosphates, cystine or of a mixture of these.

**Ætiology.**—All these materials are sparingly soluble in water and their solubility in urine is dependent on (i) its pH. If this stands at 5 uric acid is precipitated, while phosphates and carbonates are deposited at pH about 8; the others at some intermediate point. (ii) On the presence of urea, which renders both uric acid and oxalates more soluble. (iii) The protective action of certain non-albuminous colloids. If these become coagulated their protective influence is lost. Any condition which interferes with the free flow of urine and so leads to stagnation, predisposes to and may determine the formation of calculi. Thus, prolonged recumbency, as after fracture of the femur, may determine calculus formation due to stagnation in the dorsal portion of the calyces. Infection of the urinary tract may be secondary to the calculus, but it is also a cause of calculus formation by altering the colloid content of the urine or

by its effect on the pH of the urine. Metabolic disorders may be a factor in some cases as, for instance, in the uric acid stones which may occur in young children. Hyperparathyroidism leads to excessive mobilisation of calcium from the bones and this is followed by "metastatic calcification" in various tissues including the kidneys. Hot climates tend to favour stone formation owing to concentration of the urine due to excessive sweating.

**Pathology.**—The pure oxalate stone is very hard, mulberry-shaped, stained by altered blood, and varies in size from that of a mere granule to that of a walnut. If it is encrusted with uric acid it becomes brown, and in form a coral-shaped mass, representing a cast of the renal pelvis and calices. Phosphatic stones are generally smooth and white. A cystine stone is hard, oval, light amber or greenish in colour, with a glistening surface. Other forms are rare. If the stone remains in the renal pelvis it may (1) by gradually increasing in size lead to the atrophy of the renal tissue (2) by eroding the capsule of the kidney produce a fistula into the perinephric tissues, resulting in a perinephric abscess (3) by obstructing the outflow of urine cause hydronephrosis or, more frequently, pyonephrosis. If it passes into the ureter it may become impacted, in this way again exciting hydronephrosis or pyonephrosis, or if it obstructs the ureter completely, may produce atrophy of the kidney. If it causes ulceration of the ureter, this may be followed by stenosis. If it passes into the bladder it is very likely to excite ammoniacal decomposition, and thus become encrusted with phosphates.

**Symptoms.**—A stone may remain latent in the kidney without causing any symptoms. More usually it causes pain, particularly on any jolting movement. This is occasionally referred to the opposite side, a point to be borne in mind when considering operation. A bout of pain may be accompanied by hæmaturia, and there may be albuminuria for some days afterwards. A small oxalate stone may produce more pain than a large uratic stone, because of its hardness and roughness. A large, branched uratic stone occasionally causes profuse hæmaturia without any pain. The results of renal calculi may be classified as (a) mechanical, (b) septic. Under the first heading come colic, hæmaturia, anuria, hydronephrosis; under the second, pyelitis, perinephric abscess, pyonephrosis.

Renal colic is the most severe and distressing manifestation of calculus. It is particularly likely to be started by riding on a horse or in a jolting vehicle, which causes the calculus to engage in the entrance to the ureter. Violent paroxysms of pain then occur, radiating along the course of the genito-crural nerve down into the groin and testis which becomes retracted in the scrotum. The pain is also felt in the loin, and the muscles overlying the kidney become rigid. Vomiting and sweating are common. The patient is unable to keep still, and rolls about or gets on to his hands and knees, calling out with each paroxysm. He becomes pale and his pulse increases in frequency, and the temperature is apt to rise. During or after the attack there is usually some hæmaturia, and crystals may be found in the urine. The attack may last several hours and then end as abruptly as it began. Anuria is a serious symptom and implies that the ureter is completely blocked, and the other kidney is either diseased or its secretion reflexly inhibited. Occasionally both ureters may be blocked by calculi. Symptoms referred to the bladder, prostate or seminal vesicles do not occur until the stone reaches the bladder or the lower end of the ureter.

**Diagnosis.**—The occurrence of renal colic and hæmaturia suggests stone, but these symptoms may be produced by the passage of a blood clot from renal neoplasm or by acute pyelitis, especially in a movable kidney. Ordinary examination of the abdomen reveals nothing beyond lumbar tenderness in uncomplicated cases. Radiographic examination is of great value. Oxalate stones are the easiest to detect by this method, as even when small they throw a dense shadow. This is fortunate, since oxalate stones are the commonest. Pure uratic stones may not be detected unless they are large. Cystine stones throw a less dense shadow than calcium oxalate stones.

Calcareous abdominal glands and phleboliths may be mistaken for calculi on radiographic examination. In doubtful cases, pyelography, intravenous or instrumental, should be done. A radiograph of the pelvis should never be omitted, since a stone may have passed down to this region. Attacks of pain and hæmaturia with the presence of calcium oxalate crystals in the urine, but with a negative radiographic examination, are probably due to crises of oxaluria. Appendicular colic may simulate renal colic, but the point of maximum tenderness is different.

**Prognosis.**—As long as there is no serious destruction of kidney substance or septic complication the outlook as to life is good, if treatment is adequate. Attacks of renal colic may occur from time to time, with great suffering, and even after stones have been removed by operation they may form again. Occasionally stones may be followed by chronic pyelonephritis with its usual consequences.

**Treatment.**—Indications for treatment are provided by the ætiological factors already discussed. In any case of long recumbency the patient must lie on his face several times in the 24 hours. Any condition of stasis in the urinary tract will be dealt with as far as is possible. The treatment of infected urine is described under pyelitis. If a renal calculus is present, and this is confirmed by radiography, removal by operation is indicated. The following points, however, are generally contraindications for operation: (i) large bilateral stones; (ii) stones which are only the size of a pea or smaller, unless there is severe pain, extensive absorption of renal substance causing toxic symptoms, or obstruction to the outflow of urine. If a small stone is not passed as a result of medical treatment, its removal by operation should be seriously considered; (iii) in some patients small calculi are repeatedly formed and passed. In these cases operation is better postponed because of the likelihood of recurrence. If the diagnosis is uncertain, or operation is refused or postponed or considered inadvisable because of the patient's general condition, the treatment appropriate to the deposit found in the urine should be continued. Violent exercise and jolting movements should be avoided. Small stones can often be got rid of by giving the patient 5 to 10 minims of tincture of belladonna with gr. 10 of potassium citrate every 4 hours for a few days, and directing that 5 pints of water should be taken in the 24 hours. For the symptomatic relief of pain, aspirin in 10-grain doses, hot baths and kaolin poultice (antiphlogistine) may be of service. Morphine should be avoided in the treatment of chronic renal pain, on account of the danger of establishing a habit.

For an attack of renal colic, morphine gr.  $\frac{1}{2}$ – $\frac{1}{4}$  together with atropine sulphate gr.  $\frac{1}{100}$ , should be given hypodermically. The anti-spasmodic effect of the atropine aids the onward passage of the stone, while the morphine relieves the pain. If morphine be given alone, the pain is apt to recur as soon as its anodyne effect passes off. Ten minims of tincture of belladonna should then be given in an ounce of water every 3 or 4 hours, with abundant fluids, as described above, until the pupils are dilated and the face rather flushed. Hot applications to the loins or hot baths may help to relax spasm. After the paroxysm is over, a radiograph should be taken to locate the stone if it has not been passed.

## HYDRONEPHROSIS

**Definition.**—A condition in which the pelvis and calyces of the kidney are distended by the accumulation of non-infected urine due to ureteral or urethral obstruction.

**Ætiology.**—**CONGENITAL.**—The condition may be congenital, due to an abnormality of the ureter or urethra; other congenital defects may be present. The urethral stricture is commonly found at the exit of the ureter from the pelvis of the kidney, or near its entrance into the bladder. Congenital narrowing of the ureter is much



more common than was previously recognised. Other congenital causes are a faulty connection of the ureter to the pelvis of the kidney or an aberrant renal artery. Hydro-nephrosis is sometimes found post mortem in infants and children without evidence of obstruction to the outflow of urine. In these cases the condition is presumed to be due to a neuro-muscular inco-ordination comparable to congenital hypertrophic stenosis of the pylorus.

**ACQUIRED.**—It is more common in females than in males, and the maximum age incidence in 74 cases collected by Herringham was between the third and sixth decade.

(a) *Bilateral* hydronephrosis results from stricture of the urethra, phimosis, enlarged prostate, obstruction within the bladder, or from a pelvic tumour; the last named is the commonest cause.

(b) *Unilateral* hydronephrosis is due to ureteral obstruction from—

1. Obstruction of the lumen by a stone, growth or blood clot.

2. Stricture of the ureter following ureteritis.

3. Pressure from without due to growths.

4. *Torsion of the ureter by displacement of a movable kidney.* It is also thought that chronic prostatitis or cervicitis may cause sufficient inflammation to produce some dilatation of the kidney pelvis and upper ureter which lengthens and thus kinks the latter.

**Pathology.**—Two types of hydronephrosis are recognised, namely, the pelvic type due to upper urinary tract obstruction and the renal type from obstruction to the lower tract. In the former the pelvis of the kidney is dilated and there is less absorption of renal parenchyma in the calyces. In the latter the calyces are more dilated and there is considerable destruction of kidney substance.

It is generally held that hydronephrosis results from intermittent obstruction. It has been produced experimentally, however, by ligature of the ureter causing complete obstruction. But complete obstruction is more usually followed by atrophy of the kidney.

**Symptoms.**—Many cases are latent, and give rise to no symptoms. The tumour may be discovered accidentally, or there may be complaint of pain in the flank or back. The onset is insidious.

The symptoms by which a hydronephrosis is indicated are the presence of a renal tumour and complaint of an aching pain in the flank or back, and sometimes polyuria or hæmaturia. In intermittent hydronephrosis, the tumour suddenly disappears with the passage of a large quantity of watery fluid; after an interval the tumour gradually reappears and finally empties suddenly as before. This sequence may be repeated at intervals. Where true polyuria or hæmaturia occurs it is due to a coincident nephritis or pyelitis. There may be acute exacerbations of the chronic pain, with vomiting and collapse; such attacks may accompany emptying of the hydronephrotic sac.

**Diagnosis.**—The condition, especially when bilateral and unaccompanied by symptoms, is generally overlooked. In its most characteristic form, where the hydronephrosis is intermittent, the diagnosis is readily made. When the condition is apparent simply as a renal tumour the diagnosis from renal neoplasm (or retro-peritoneal glands in a child) is difficult. When the tumour is large it may be mistaken for an ovarian tumour. A urinary infection is often the first sign of hydronephrosis. The diagnosis can be established by intravenous pyelography supplemented, if necessary, by instrumental pyelography. Aspiration of the sac has occasionally been done for diagnostic purposes; but surgical exploration is a safer measure. Fluid from a hydronephrotic kidney is clear or slightly turbid; it contains albumin, and traces of urea and other urinary constituents; in the deposits there are epithelial cells.

**Course.**—When unilateral, hydronephrosis may never cause serious trouble, and intermittent cases may persist for years. In bilateral cases uræmia may supervene.

Infection of the kidney is not uncommon, and may lead to acute pyonephrosis. The sac may discharge spontaneously through the ureter, and the fluid never reaccumulate. The sac may rupture into the peritoneum, or rarely through the diaphragm into the lung. Cases have occurred in which the ureter of the sound kidney has been blocked by a calculus.

**Prognosis.**—This depends on the cause of the hydronephrosis and the condition of the opposite kidney.

**Treatment.**—The first indication is to remove the cause. A narrowing of the ureter, generally congenital, or stenosis at the ureteropelvic junction are especially important causes of hydronephrosis. Whereas in the past slight cases of hydronephrosis were treated on general lines and nephrectomy was performed for large hydronephrotic kidneys, nowadays slight cases of hydronephrosis are examined with the greatest care and surgical treatment is more often undertaken as a preventive measure. An abdominal belt or nephropexy may prevent the development of hydronephrosis in a movable kidney. When a hydronephrotic kidney is infected, the infection should be eradicated, and with modern methods of treatment (see treatment of pyelitis) this can sometimes be achieved.

In unilateral hydronephrosis causing serious symptoms, or of large size, a plastic operation or nephrectomy is advisable. Since the state and function of the opposite kidney can be fairly accurately ascertained by pyelography and examination of a sample of urine obtained by ureteral catheterisation, nephrectomy is a less serious risk than it was before these exact methods of diagnosis were available.

In bilateral hydronephrosis the main indication is to remove the cause when possible, and to adopt every measure that may aid in preventing infection of the urinary tract.

## PYONEPHROSIS

**Definition.**—Distension of the renal pelvis with pus, to an extent sufficient to cause a renal tumour.

**Ætiology.**—The affection is a sequela of pyelitis or hydronephrosis. There are two main types, namely, tuberculous and pyogenic pyonephrosis. The latter, which is the commoner, is most frequently due to an impacted calculus.

**Symptoms.**—The patient is wasted, toxic and febrile. Rigors are common. There is a renal tumour, which is tender on palpation, and moves to some extent with respiration. Pyuria is present, unless the ureter is completely obstructed.

**Diagnosis.**—The differential diagnosis from hydronephrosis is made from the presence of pyuria and of local and general symptoms of bacterial infection. Perinephric abscess gives signs of a more diffuse swelling, usually with œdema and redness of the surrounding skin, and does not move with respiration.

**Treatment.**—In bilateral cases the treatment is palliative. In unilateral cases nephrectomy is indicated, if tests show that the other kidney is adequate.

## TUMOURS OF THE KIDNEY

### BENIGN GROWTHS

These are of relatively slight importance.

**ADENOMATA** are the most common, occurring in the cortex or under the capsule. They may be single or multiple; multiple nodules commonly occur in sclerotic kidneys in old age. They seldom attain any size.

**FIBROMATA** are not uncommon, as nodules, sometimes multiple, in the cortex or medulla. **LIPOMATA** and **ANGIOMATA** are rare.

## MALIGNANT TUMOURS

**DYSEMBRYOMATA.**—These tumours are found most commonly in children under 3 years, and almost always under the age of 11. They are more often bilateral than carcinoma. They consist of cells remaining at the embryonic level and failing to differentiate in any direction ("Round-celled Sarcoma"). There is a stroma of undifferentiated fetal connective tissue which resembles spindle-celled sarcoma. In some tumours some degree of differentiation may take place. Thus these tumours may contain embryonic striped muscle, primitive cartilage or nervous tissue, and primitive poorly formed tubules can usually be found. They are yellow and homogeneous on section.

**ADENOCARCINOMA OF RENAL TUBULES.**—The Grawitz tumour or hypernephroma is now recognised as an adenocarcinoma arising in tubular epithelium. These tumours are single, large, well circumscribed, and often surrounded by a capsule of compressed kidney tissue which is destroyed by pressure rather than by infiltration. These tumours consist of solid anastomosing columns of cells. Their blood supply consists of irregularly shaped, lake-like sinusoids which lie between the tubules of the growth in contradistinction to adenomata, which are composed of well-formed tubules having well-defined lumina and a simple capillary circulation. Both in adenomata and adenocarcinomata, and especially in the latter, the cells are infiltrated with a lipoid-fat-glycogen complex ("lipoid infiltration"), which gives these tumours their peculiar yellow colour. Recent and old hæmorrhage is commonly seen. Cystic degeneration often occurs. On section there is fine and coarse lobulation. These tumours may spread along the renal veins into the inferior vena cava, and to the pelvis of the kidney and perinephric tissues.

**Symptoms.**—1. Hæmaturia is the first symptom in more than 70 per cent. of the cases. It is much less frequent in children. The blood is fluid or clotted, and moulds of the pelvis or ureter may be passed. The hæmaturia is spontaneous, profuse and intermittent; it is little influenced by rest, nor is it provoked by exertion. It may be the only evidence of a neoplasm, and after lasting for a week or 14 days may cease, leaving no further evidence of the growth until at some later date a tumour is felt. The urine frequently contains albumin at intervals.

2. Pain is uncertain. It may be a dragging feeling, or a constant ache. The passage of clots may give rise to renal colic; otherwise the hæmaturia is not accompanied by pain.

3. The presence of a tumour is a most important sign. It is felt on deep palpation bimanually. It is first palpable below the ribs, outside the rectus muscle, as a solid swelling, with rounded borders, that moves with respiration. It may be possible to define its upper border. As the tumour increases, it tends to go forward. It may fill the hollow below the twelfth rib behind, but does not cause a swelling in the back. Large renal tumours cause asymmetry and bulging of the abdominal wall and marked displacement of neighbouring abdominal viscera. On the right side, the ascending colon lies in front, on the left the last part of the transverse colon and the upper part of the descending colon; the tumour is, therefore, resonant on percussion in front. When the tumour is highly vascular, pulsation is felt in it, and a systolic bruit may be heard over it. In later stages it is liable to become fixed by adhesions.

4. Progressive emaciation is generally late. It may be absent although the tumour is large.

5. Metastases are sometimes the first sign of a renal neoplasm, occurring in the lungs, bones or brain. Secondary deposits in the para-aortic lymph glands may cause obstruction to the inferior vena cava, or this may result from pressure of the tumour itself.

**Diagnosis.**—Diagnosis is made on the presence of hæmaturia, with a tumour. When hæmaturia occurs alone, and other causes have been excluded by careful clinical,

bacteriological and radiographic examination, then a more detailed investigation of the urinary tract must be undertaken immediately. This entails cystoscopy, intravenous pyelography and on occasion retrograde pyelography. When a tumour is the only sign an exploratory laparotomy is advised. The tumour requires to be distinguished from splenomegaly, hepatomegaly and Riedel's lobe. A renal tumour has not the definite edge characteristic of splenomegaly and enlargement of the liver. Enlargement of the liver is not often a source of difficulty. A Riedel's lobe is continuous with the liver, does not extend back into the loin and is dull on percussion. Splenic tumours are recognised by the fact that they tend to occupy an oblique position in the abdomen, by the presence of a notch and of a sharp inner margin, free movement with respiration and dullness to percussion.

A differential diagnosis from retroperitoneal tumours, including those of the suprarenal, is not always possible, though the suprarenal growths may sometimes be recognised by certain characteristic features. Thus, there is the medullary sarcoma type described by Hutchison, generally occurring in children, characterised by metastases in the skull, ecchymotic swelling of the eyelids, papilloedema and severe anæmia, and the "infant Hercules" type of tumour of the adrenal cortex (see p. 523).

**Prognosis.**—The disease is almost invariably fatal. Many die within 2 years, and the majority within 4 years, though exceptional cases of survival for 5 to 10 years after operation have been recorded.

**Treatment.**—Surgical treatment alone holds out a prospect of cure. Symptomatic treatment includes the use of drugs for the relief of pain and the control of hæmaturia.

## CYSTS OF THE KIDNEY

### SOLITARY CYSTS

These may occur in an otherwise normal organ. They vary in size from very small cysts to tumours of considerable bulk. They result from dilatation of an obstructed tubule, and they may be congenital.

### MULTIPLE CYSTS

Multiple cysts of small size are commonly met with in sclerotic kidneys. They result from chronic inflammatory changes that lead to obstruction of the tubules with subsequent dilatation. There are also rare cases of multiple cysts, of large size, whose ætiology and course are little known.

## POLYCYSTIC DISEASE OF THE KIDNEYS

**Definition.**—Polycystic kidneys appear as a massive conglomeration of cysts, varying in size from a pin's head to a marble, separated by dense strands of fibrous tissue, in which little or no renal tissue is evident on naked-eye examination.

**Ætiology and Pathology.**—The commonest age incidence is between 40 and 50 years; they are relatively common in the decades preceding and following; they may occur in infancy and childhood, and of these a large proportion are in still-born infants. Those occurring in infants are congenital, and other congenital abnormalities may be present. The disease in adults is probably also congenital in origin. In this case it must be progressive, because the renal damage in the later stages is too severe to have been compatible with many years of active life. In this connection it is noted that the disease is often found in more than one member of a family and in successive generations. Its familial incidence, congenital origin and association with cysts in

other organs, especially the liver, all suggest that this disease belongs to the group of congenital-developmental errors.

The organs are enlarged in size, and weigh 20 to 30 oz. each, or even 3 to 4 lb. They have been compared to a bunch of grapes in appearance. The cysts project from the surface and form the mass of the organ. They are lined by a layer of flattened cells, and are filled with fluid. This fluid is clear or turbid, limpid or viscid, colourless or yellowish; it is sometimes blood-stained, giving it a red, purple or green colour. Urea has been found in the fluid, which may also contain fat globules, cellular debris, cholesterol and triple phosphate crystals. On microscopic examination compressed renal parenchyma is found in the septa between the cysts; the tubules are distorted and exhibit varying degrees of atrophy, degeneration and dilatation, while the glomeruli show changes due to chronic ischaemic or hypertensive damage. The blood vessels of the kidney undergo sclerotic changes; there is increased fibrous connective tissue and small cell infiltration. In some cases cysts are also found in the liver, ovaries, broad ligament, uterus, pancreas and spleen; but they are rare in any other organ than the liver.

**Symptoms.**—The affection is nearly always bilateral. When the tumours develop to large size in the fetus, difficulty in labour may result. In the adult there may be no symptoms, or any of the symptoms of chronic nephritis may develop and may terminate in uræmia, cerebral hæmorrhage or cardiac failure. General arterial disease, with raised blood pressure and cardiac hypertrophy, is commonly present; on the other hand, the condition may reach an advanced stage and fatal termination without appreciable cardiac hypertrophy. In a third group the bilateral renal tumours are the most striking features, associated with general malaise, dull aching pain in the loins and recurrent hæmaturia. The tumours are not tender, and present the ordinary signs of renal tumours (*q.v.*). The urine is of low specific gravity, and commonly contains a trace of albumin; there may be polyuria.

**Diagnosis.**—The finding of albuminuria in association with large, irregular, bilateral renal enlargement should suggest polycystic disease. Hydronephrosis produces a smooth rounded renal swelling. Renal neoplasms other than sarcomata are nearly always unilateral. The absence of fever and pyuria excludes bilateral pyonephrosis. Intravenous pyelography often shows characteristic ring shadows due to distortion of the calyces by the cysts.

**Course.**—This closely resembles that of chronic nephritis.

**Treatment.**—The treatment is that of chronic nephritis. Operation is contra-indicated, since both kidneys are nearly always equally affected.

#### OTHER FORMS OF CYSTIC DISEASE

*Echinococcus* cysts may occur in the kidney, and the discharge of the daughter cysts has produced attacks of renal colic. *Cystic degeneration of renal neoplasms* is described elsewhere.

#### MOVABLE KIDNEY

**Synonym.**—Nephroptosis.

The kidney is normally held in place by the perirenal fat, the renal vessels and the peritoneum stretched over it. But this does not prevent a certain amount of respiratory excursion, as may be seen either by radiographic examination or in the operating theatre. The range of movement varies between 1 and 2 inches, and is more marked on the right than the left side. The term movable kidney should therefore only be applied to cases where there is an excessive respiratory descent, so that the upper as well as the lower pole can be felt, or where the kidney can be moved

about by external manipulation. As the kidney slips downwards, the lower pole gradually passes towards the middle line, while the organ rotates slightly, causing the hilum to look somewhat upwards.

**Ætiology.**—Movable kidney is about seven times more common on the right than on the left side. The ascending colon and the hepatic flexure lie on the inner aspect of the right kidney, thus tending to drag it down when the bowel is loaded or dropped. On the left side, on the other hand, the strong costo-colic fold suspends the splenic flexure much more securely, while the descending colon lies to the outer side of the left kidney.

The condition is much commoner in women than in men. In men the kidney pouches are deep, narrow and rapidly diminish in breadth from above downwards, while in women they are much shallower and broader, and diminish only slightly in breadth from above downwards. This natural difference is accentuated in the spare, long-waisted women with narrow loins, who are recognised as specially liable to floating kidney.

**Pathology.**—Many reasons have been given for the occurrence of movable kidney; but few will stand investigation. Wasting with loss of perirenal fat, or loss of tone in the muscles of the abdominal wall, have been held responsible, but movable kidney is so common apart from such conditions that their importance is doubtful. Glénard emphasised the frequency with which movable kidney is associated with a general visceroptosis; indeed it is rare to find a movable kidney without coloptosis. Movable kidney is the most obvious sign of visceroptosis because the organ is easily palpable.

A serious sequel is the occasional occurrence of hydronephrosis produced by torsion of the ureter during the forward rotation of the organ or by its becoming kinked over the renal vessels. If hydronephrosis occurs, a subsequent infection may convert it into a pyonephrosis.

**Symptoms.**—There may be no symptoms at all and, if the movable kidney is only discovered in the course of routine examination, it is better not to tell the patient of its existence. The commonest symptom is a constant dragging pain owing to traction on the renal plexus. This most frequently first declares itself between 25 and 35 years of age. A zone of hyperæsthesia corresponding to the distribution of the tenth thoracic segment may also be present. More serious symptoms directly due to movable kidney are Dietl's crises; but these are not common. The attacks are characterised by severe pain, radiating down the ureter and through to the back, and may be accompanied by shivering, nausea, vomiting, fever and collapse. The urine is scanty, and may contain blood. Sometimes the pelvis of the kidney may become distended, giving rise to an obvious increase in the size of the organ, thus causing a tumour which is easily palpable, and may be so large as to be obvious on abdominal inspection. This may pass off later, with abundant discharge of urine, showing that the crises are due to kinking and consequent partial obstruction of the ureter. If repeated, they may lead to hydronephrosis. The other symptoms which have been attributed to floating kidney are really due to the associated visceroptosis (*q.v.*). A movable kidney usually feels larger than the normal excised organ. This is because of the surrounding investments through which it is felt.

**Diagnosis.**—Usually this is obvious, as the shape and mobility of the organ are so characteristic. Occasionally, a Riedel's lobe has been taken for movable kidney; but the continuity of the former with the liver should prevent this mistake being made. In the same way, a distended gall-bladder is continuous with the liver, and cannot be separated from it. Moreover, it is not nearly so movable, and curves characteristically towards the umbilicus. Carcinoma of the pylorus has offered difficulties in some cases; examination of the stools for occult blood, a test-meal and radiographic examination will clear up the diagnosis. Scybala near the flexures of the colon may be mistaken for floating kidney; but their indefinite shape and inelasticity

generally help to distinguish them. Their disappearance after a series of enemata will settle the question. In one case a mesenteric cyst appeared closely to resemble a floating kidney.

**Prognosis.**—Apart from the development of hydronephrosis, movable kidney does not tend to shorten life in any way. It is doubtful whether a kidney once prolapsed can ever maintain the normal position unaided.

**Treatment.**—Some cases call for no local treatment, though the associated viscer-optosis and neurasthenia will require attention. If pain is felt, the adoption, for a short time, of the knee-elbow position or simply lying flat on the abdomen will help to replace the kidney and relieve the tension on the renal plexus. If pain is at all frequent, an abdominal support should be worn, namely, a corset especially designed to give support to the lower abdomen and increase the general intra-abdominal pressure. Kidney belts and special pads to support the movable kidney are no good. Breathing exercises to develop the expansion of the lower thorax, with exercises to improve the tone of the abdominal wall, and general measures to improve muscle tone should be prescribed in all cases. Treatment on these lines may make the wearing of a special corset unnecessary. Operation should not be advised except for recurrent Dietl's crises or when there is evidence of hydronephrosis, when nephropexy may be done. But even this may not be successful, and ultimately nephrectomy may be required for the hydronephrosis.

**Treatment of Dietl's crises.**—The patient is put to bed, and is advised to lie on his abdomen or try the effect of the knee-elbow position. Hot fomentations or a kaolin poultice are applied to the affected side. A hypodermic injection of a quarter to one-third of a grain of morphine may be required if the pain is severe. Usually this is sufficient but, should the attack last more than a few hours, an attempt must be made, under an anæsthetic, to rectify the position of the kidney by manipulation. Naturally, conditions are unfavourable for nephropexy during or immediately after a crisis, because of the congested state of the organ.

HORACE EVANS.  
CLIFFORD WILSON.

## SECTION XV

# DISEASES OF THE JOINTS, FIBROUS TISSUES AND MUSCLES

## ARTHRITIS

The diagnosis of "arthritis" should be reserved for cases in which there are intrinsic pathological changes in a joint.

The clinical conception of chronic arthritis is much simplified by modern classification, which divides it into two clear-cut *clinical* types, each of which presents distinctive features. These are the rheumatoid arthritic type and the osteo-arthritic type. The features of the rheumatoid and osteo-arthritic types of arthritis will be found under their respective headings below, and since the criteria of these types are clinical, this terminology can be correctly employed in those cases in which the aetiology remains obscure.

The basic difference between these two types is that rheumatoid arthritis is a general disease in which the most obvious local effects fall upon the locomotor system; while osteo-arthritis is a degenerative type of change, which, without affecting the patient's general health, for various reasons becomes localised in certain joints.

There are, in addition, certain cases which are referred to as "mixed", in which the degenerative lesions of osteo-arthritis become superimposed upon those of an inflammatory arthritis of the rheumatoid type.

### 1. RHEUMATOID ARTHRITIS

**Synonyms.**—Atrophic Arthritis; Polyarthritis.

Rheumatoid arthritis is a general progressive disease affecting principally the joints, which become swollen and painful. If unchecked great destruction and deformity results.

**Ætiology.**—The malady is said to occur at least three times as frequently among females. Women between the ages of 20 and 40 years are most commonly affected and the disease seldom commences after the menopause. Predisposing factors exist in many cases and include infection, malnutrition and emotional shock. Focal infection may be present, but this is not usually the main causative factor.

**Pathology.**—The pathological processes are inflammatory in nature. The soft tissues and the white fibrous structures around the joints are the first to be affected. The inflammation then spreads to the capsule and synovium, and granulation tissue forms in the angle made by the articular cartilage with the synovium. The latter then gradually extends inwards as a ring of "pannus", covering and eventually replacing the articular cartilage. As this happens on both articular surfaces the tendency is for them to adhere, especially if the joint is immobilised for long periods, and so fibrous ankylosis occurs, which in some cases progresses to a bony ankylosis. In some cases there is a marked tendency for the development of ganglia and cysts, which are generally in close association with joints or tendon sheaths.

There are atrophic changes affecting the skin, subcutaneous tissues, muscles, ligaments, joints and bones. This latter condition of generalised osteoporosis shows



as the first *radiographic* evidence of the disease. The peri-articular swelling can also be seen in outline, but actual joint destruction does not occur until considerably later. Some degree of patchy recalcification may be observed when the progress of the disease is checked. Osteophytes are never found in rheumatoid arthritis, but in late cases very considerable disorganisation of the joints takes place, and in these areas the bone sometimes gives the appearance of having been dissolved away.

The chief pathological change in the blood is an increase in the sedimentation rate of the red blood cells. This is an important index of activity, and the response of a patient to treatment over a considerable period can be estimated with some accuracy by means of this together with clinical observation. A secondary anaemia is usually present in the pre-arthritic phase. The glucose tolerance of the patient is generally found to be reduced in the active stages of the disease; the albumin-globulin ratio in the plasma is often reversed.

**Symptoms.**—There is in most cases a prodromal period, during which the patient loses a considerable amount of weight; and fatigue, both mental and physical, is a marked feature in nearly all cases. There may be other symptoms, such as paræsthesia, Raynaud-like phenomena, irregular menstruation, tachycardia, sweating and a secondary anaemia. Certain pioneer symptoms are not uncommon and it is of the utmost importance to recognise these; amongst them is pain and tenderness of the heads of the metacarpal bones, and especially of the second (Morton's disease). Intermittent attacks of synovitis without apparent cause and affecting tendon sheaths and joints may also occur.

The onset of the arthritic phase is often announced by a swelling of the proximal interphalangeal joints of the second and third fingers of both hands. It is usually insidious, but is acute in about 10 per cent. of cases. In the case of the former, it is not uncommon for the disease to be marked by long periods of low and intermittent fever. The thyroid gland is also sometimes enlarged, and fibrositic pains may be complained of.

Wasting of the small muscles of the hands is generally the next event, and the fingers tend to fall into the position of ulnar flexion, in which they may ultimately become fixed. The affection then spreads centripetally towards the trunk, involving in turn the wrists (which often become ankylosed), ankles, elbows, knees, shoulders, hips and jaw. The bilateral and symmetrical way in which the joints tend to be affected is a striking feature of the disease. In some cases the spine itself in due course becomes affected.

Whenever a joint becomes involved it will be noticed that the muscles which control it, particularly the extensors, waste rapidly, giving rise to the varying flexion deformities typical of the later stages. These may be perpetuated by a fibrous ankylosis of the affected joints, and contraction of the joint capsule. Bony ankylosis may follow this stage, and when it does so it generally occurs in the wrists and the bones of the carpus in the first place.

In certain cases enlargement of the lymphatic glands occurs, and even the spleen may become palpable. In those cases in which, in addition, leucopenia is present the condition is known as Felty's syndrome. Sufferers with rheumatoid arthritis generally experience considerable pain which interferes with their sleep, and this adds progressively to the severity of the condition.

*Symptoms often clear up if pregnancy or jaundice occurs during the course of the disease, but in most cases they return with renewed vigour after parturition. Periodical remissions are a well-known occasional feature of the disease; they may last for months or even years.*

**Prognosis.**—Under a properly planned and supervised programme, about 20 per cent. of patients recover. A further 50 per cent. show considerable improvement, and an additional 20 per cent. are improved to some extent; leaving 5 to 10 per cent. of cases which appear to be entirely resistant to treatment of all kinds. With

modern methods of treatment, gross deformity should very seldom occur, even when ankylosis takes place. It should be remembered, however, that in many cases treatment of some sort is required for months or even years, and that relapse may occur even after apparent cure. If the disease is not checked, the end-result is often complete and painful crippling. This sometimes takes place within a very short period, particularly when the patient is young. Cases which occur later in life tend on the whole to be less rapidly progressive in their course.

**Treatment.**—It is by a careful and intelligent selection and combination of methods suited to the individual patient that the most favourable results will be obtained. A period of rest in bed is essential when the disease is progressing rapidly and there is much swelling of weight-bearing and other joints.

**Diet.**—This should be rich in vitamins, especially the B complex and C, and extra calcium in the form of milk and cheese is advisable. It should also be rich in calories, and there is no reason to restrict any particular type of food in this disease.

When the sufferer is much underweight and does not return to normal by dietetic means alone, a small dose of insulin (5 to 10 units) may be administered 15 to 20 minutes before two meals in the day, the allowance of carbohydrates being adjusted accordingly.

**Physical therapy.**—In the acute phase these are of necessity reduced to sedative applications and gentle movements. They may be supplemented by progressively graded ultra-violet rays, which stimulate to some extent the patient's powers of resistance. Later, massage, heat and supervised voluntary movements help to relax the muscle spasm, which is often in itself a cause of pain and tends to increase the ultimate deformity.

Splints may be necessary at all stages, to prevent contracture and maintain movement in the affected joints.

**Drug therapy.**—Anæmia will respond to iron, sometimes only when it is administered intravenously, and on general principles the patient needs laxatives for constipation and analgesics for the relief of pain and sleeplessness. If aspirin or phenacetin is not effective, Dover's powder (gr. 10 to 15) or codeine phosphate (gr.  $\frac{1}{4}$  to  $\frac{1}{2}$ ) may be tried. A time-honoured remedy is guaiacol carbonate, which may be given with aspirin, thus: Guaiacol carb. gr. 8, aspirin gr. 4, in cachet form, three times daily after food.

**Phenylbutazone (Butazolidin).**—This drug has a powerful analgesic action on many patients with rheumatoid arthritis, but in others it appears to be without effect. It may be tried in severe cases before resorting to the use of cortisone. The dosage should not exceed 200 mg. three times a day because of the danger of toxic effects, which include nausea, vomiting, stomatitis, œdema, agranulocytosis, hæmorrhages and skin eruptions.

Gold is believed, by many observers, to be the most valuable drug in the long-term treatment of rheumatoid arthritis. It appears to cause remissions in a high percentage of cases and is most effective when the onset of the disease is recent and the blood sedimentation rate is high. *This method of treatment is contraindicated in the presence of renal or hepatic damage, diabetes mellitus, eczema, severe anæmia, colitis, pregnancy, hæmophilia or purpura.* With regard to other cases, the dangers of reaction, complications and mortality should be taken into consideration. There should be a complete blood count, blood sedimentation test and an examination of the urine for albumin. The main toxic effects are purpura, boils, exfoliative dermatitis, gastroenteritis and colitis, nephritis, aplastic anæmia and stomatitis. There is, however, a negligible mortality attendant upon this form of therapy. The patient should not be exposed to strong sunshine or ultra-violet light during the treatment for fear of pigmentation.

It is well not to administer gold near the period of the menses, as skin eruptions are said to be more liable to occur then. There are several preparations of gold salt.

on the market. It is wise always to employ those which are administered intramuscularly. Whether they are suspended in an oily or in an aqueous solution appears to be immaterial. The initial dose should be 0.01 g., and subsequent doses may be 0.02 and 0.05 g. This latter dose should not be exceeded, nor should the injections generally be given more frequently than once weekly. If no improvement follows the administration of 1.0 g. of gold it should be discontinued, but when the response is good, relapse can usually be prevented by prolonging treatment for an indefinite period. Injections of 0.05 g. are given at 2- to 4-week intervals unless undesirable side-effects occur. The complete blood count, blood sedimentation rate and urine examination for albumin should be repeated at regular intervals during the treatment. If toxic effects are produced the injections should be discontinued immediately and on no account should the patient receive further treatment with gold. Serious complications, such as exfoliative dermatitis will respond to a short course of corticotrophin. Dimercaprol (B.A.L.), which is itself toxic, need no longer be used for this purpose.

Preparations of bismuth and copper have recently been introduced, but it is the experience of British workers that they are not efficient substitutes for gold. Prostigmine (physostigmine) has also been advocated as an antidote to muscular spasm, which is a painful feature of certain cases of rheumatoid arthritis and a cause of increased joint deformities. Current opinion in this country is, however, unfavourable.

*Vaccine therapy.*—This form of treatment is claimed sometimes to reduce the activity of the disease, particularly when focal sepsis is an important factor in its aetiology. The correct dose of the vaccine is probably the lowest which is found to provoke a favourable reaction, and not the highest which can be tolerated.

*Protein shock* may be given in the form of intravenous T.A.B. vaccine injections. This is a non-specific procedure designed to raise the patient's temperature temporarily in the hope of benefiting him subsequently. Such treatment should never be undertaken when the patient is in an active phase of the disease. Once improvement has started, however, it may be justifiable to endeavour to speed its tempo by this means. Three to five injections should be administered, the dose varying according to the age and weight of the patient. At least 24 hours of normal temperature should be allowed between the injections, which should not in any case be given more frequently than twice weekly.

Repeated blood transfusions, apart from correcting the anaemia, are sometimes of value in retarding the progress of the disease. The value of blood from pregnant women for this purpose is being investigated. Thyroid in small doses (gr.  $\frac{1}{4}$  to  $\frac{1}{2}$  twice daily), or iodine, may be useful during the menopause.

*Focal sepsis.*—It is unwise to embark upon operative procedures while the patient is in a condition of debility, or while the disease is running an acute febrile course, with marked joint pain and swelling. In such patients an endeavour should previously be made to build up the general health. If after 4 to 8 weeks no improvement has occurred and the focus is still believed to be of importance, cautious measures for its removal may be initiated. The patient should in such cases be warned that it is unlikely that the removal of such a focus will cure the arthritis, but that his general health, and the powers of active resistance will be stimulated thereby. The foci of infection which are of particular importance and should always be investigated are situated in the tonsils, the nasal sinuses and the teeth; but the colon, appendix, gall-bladder, cervix, Fallopian tubes, prostate and bladder should also be investigated. If more than one focus of infection is found the one most apparently active should be treated first. In cases in which the sinuses and the tonsils both require surgical attention it is important to allow a period of several weeks to elapse between any two operations.

*The steroid hormones.*—Cortisone and corticotrophin (A.C.T.H.) are not as valuable in the long-term treatment of rheumatoid arthritis as first experience seemed to

suggest. Suppression of the disease occurs in the majority of cases at the time of administration, but relapse almost invariably follows the withdrawal of treatment. A lengthy course of treatment is justified in selected cases with rapidly worsening disease, and cortisone, which can be given by mouth, is the hormone of choice. An initial dose of 100 mg. daily, in three divided doses, is gradually reduced to 25 to 75 mg. daily over a period of 2 weeks. The equivalent amounts of long-acting corticotrophin, given intramuscularly once daily, are 30 to 60 mg. initially, reduced to a maintenance dose of 20 mg. Complete prolonged suppression of symptoms cannot always be achieved without the production of side-effects. These include rounding of the face, obesity, œdema, disorders of menstruation, insomnia, tachycardia and hypertension. Hirsuties, acne, diabetes, severe mental changes, hæmorrhages and thromboses are less common.

A short course of treatment can sometimes be given as an adjunct to physical measures aimed towards rehabilitation. Definitive treatment with repeated short courses has proved disappointing. Withdrawal symptoms in the form of weakness, malaise, loss of appetite and depression are common, and in some patients they are more distressing than the disease. When inflammation is limited to a few joints, the standard methods of treatment can be supplemented by the intra-articular injection of small doses of hydrocortisone (compound F). The steroid hormones should not be prescribed when disability is due to irreversible changes and they are contra-indicated by such conditions as peptic ulceration, acute psychosis, tuberculosis and severe acute infections. They should be administered with caution when there is hypertension, diabetes or severe osteoporosis. Patients on steroid hormone treatment must remain under regular observation.

## 2. SPECIFIC INFECTIVE ARTHRITIS

### GONOCOCCAL ARTHRITIS

From 1 to 5 per cent. of those infected with gonorrhœa develop gonococcal arthritis. The disease is also found in babies, whose infection occurs at birth. In view of the fact that infection due to this cause frequently ends in crippling and bony ankylosis of the affected joints, it is important to make the diagnosis at the earliest possible stage. If this is done the prognosis is good.

The clinical appearance and course of gonococcal arthritis is similar to that of rheumatoid arthritis when the onset of this disease is acute. A differential diagnosis may be made from the following points: (1) A recent history of gonococcal infection or urethritis. Unless specifically questioned, patients often omit to mention this. (2) The onset of joint symptoms within 3 weeks of such an infection. (3) There is a predominance of 3:1 in males, unlike true rheumatoid arthritis. As in the latter disease, however, the malady is often a polyarthritis from the onset. (4) The knees, wrists, ankles and frequently the plantar fascia are involved in a virulent attack. A painful teno-synovitis around the wrists and ankles is a common forerunner of arthritis. (5) Conjunctivitis and irido-cyclitis are not uncommonly associated with gonococcal arthritis.

The complement fixation test of the blood is found to be positive in about 80 per cent. of cases after the first month, and gonococci may in many cases be grown by special methods from samples of the joint fluid, affording an immediate confirmation of the diagnosis.

**Treatment.**—Although penicillin will invariably cure the primary infection it is less effective in the treatment of gonococcal arthritis and the most favourable results have been obtained with artificial fever therapy. In the chronic stages it is important to guard against contractures of the affected joints.

## MENINGOCOCCAL ARTHRITIS

This is not uncommon in the second week of cerebrospinal fever, and may be polyarticular or monoarticular. It closely resembles gonococcal arthritis, except that it is generally less severe. There is also a milder sporadic form—chronic meningococcal septicæmia—which occurs in the absence of meningitis and which is probably more common than is generally suspected, passing as influenza or subacute rheumatism. The diagnosis in these cases rests upon the presence of intermittent low fever, a rash, which may be purpuric and sometimes simulates erythema nodosum, and a positive blood culture. Leucopenia is usual in this syndrome. The patients often seem surprisingly well, and complain of little except joint pains. Both these types respond well and rapidly to sulphonamide therapy.

## PNEUMOCOCCAL ARTHRITIS

A polyarthritis of the rheumatoid type is a rare sequel of pneumonia. It affects children more commonly than adults. An arthritis affecting one or more of the larger joints is somewhat commoner. These conditions generally occur subsequent to the stage of pneumonic resolution.

**Pathology.**—The joint fluid is in most cases purulent, and pneumococci can be found in it except in cases which have received chemotherapy.

**Prognosis.**—If the patient survives the pulmonary infection his resistance to the organism is good, and joint function is in most cases preserved provided erosion of the cartilage has not taken place.

**Treatment.**—Joints affected in this way should be aspirated early and they should be immobilised in light plaster splints, which should be removed daily to permit of gentle movement. Specific treatment for the pneumonia must be given.

## ACUTE SUPPURATIVE ARTHRITIS

This is often polyarticular in its distribution, and may be mistaken at first for acute rheumatic fever or rheumatoid arthritis. It occurs more often in children than in adults.

**Ætiology.**—The condition may be a blood-borne infection (metastatic), or may arise as an extension from neighbouring areas of osteomyelitis, or other infection. The former is the more common and may be secondary to a focus of infection in the middle ear, throat, sinuses or prostate. It may also follow the acute specific fevers, particularly scarlet fever and septic tonsillitis. It has also been reported following meningitis, septic endocarditis, infected varicosities and burns, pyelitis and furunculosis. An arthritis following typhoid fever is not generally suppurative, but may become so.

The organisms which are chiefly responsible are the hæmolytic streptococcus, the staphylococcus, the pneumococcus, the gonococcus and, after typhoid, *Salmonella typhi*.

**Symptoms.**—These include an acute onset of chills and sweats, pyrexia, local pain and tenderness in the joints, with redness, swelling and limitation of movement. There is in most cases a high degree of polymorphonuclear leucocytosis.

**Course.**—The joint fluid rapidly becomes purulent and extensive damage to the joints occurs if treatment is not instituted rapidly. Badly damaged joints generally ankylose ultimately. The mortality amongst such cases used to be in the neighbourhood of 20 per cent.

**Treatment.**—Treatment with the antibiotic to which the organism is most sensitive should begin as soon as possible, and in the case of penicillin or streptomycin it can also be given directly into the joint. Pus should be removed by drainage or aspiration. When the infection has been controlled impairment of function due to

muscle wasting will respond to exercises and other methods of rehabilitation, but orthopaedic treatment may be necessary when there are irreversible destructive changes in the joint.

#### TUBERCULOUS ARTHRITIS

Tuberculous arthritis usually occurs in young patients, and is an infection from a primary tuberculous focus elsewhere in the body. The possibility of an arthritis in a young subject being tuberculous should always be borne in mind, and a radiographic examination is of great value in differentiating this type from other varieties. The subject is dealt with fully in surgical books, to which the reader is referred.

Tuberculosis may also be responsible for certain cases of idiopathic polyarthritis.

#### DYSENTERIC ARTHRITIS

A polyarthritis of the rheumatoid type follows bacillary dysentery in about 3 per cent. of cases, at an interval varying from 3 weeks to several months after the cessation of acute symptoms. It may also occur in the course of a chronic ulcerative colitis. In some cases the process only affects one joint, but in either event the process commences as an inflammation of the periarticular tissues and progressively invades the joint surfaces. Suppuration is rare.

Treatment should be directed to the dysenteric condition, and should be palliative so far as the joints are concerned. Severe arthritis due to ulcerative colitis is an indication for colectomy.

#### REITER'S DISEASE

This is an illness of undetermined aetiology which is often self-limiting, and which is characterised by polyarthritis in association with non-venereal urethritis and conjunctivitis. Attention was drawn to this syndrome during the campaigns in the Middle East, where it was not uncommon amongst young soldiers. It was originally held to be related to dysenteric polyarthritis, but the consensus of opinion now tends towards a virus aetiology (see p. 310).

#### UNDULANT FEVER OR BRUCELLOSIS

A mild polyarthritis due to chronic infection with the organism of this disease is probably more frequent than is usually believed and is commonly seen in Mediterranean countries. It is generally associated with myalgia, and sometimes with intermittent hydrarthrosis. The onset may be acute or chronic, and the clinical picture may closely resemble a subacute attack of rheumatoid arthritis. The pain is often very acute.

The general symptoms are indefinite and multiple, and include malaise, long-continued low-grade pyrexia, which "undulates", loss of weight, sweating and depression. The blood may show a secondary anaemia and a leucopenia. The agglutination tests are usually positive if the disease is of some weeks' duration, but a negative result is inconclusive. The only fully satisfactory diagnosis is based on cultivation of the organism which is, however, very difficult.

#### DENGUE

This disease gives rise to a very acute form of peri-arthritis. Intense pain and sometimes swelling occur in the tendons and muscles around the joints. These

usually disappear when the fever subsides, but in the stage of convalescence may recur and last for weeks or months. The condition should be differentiated from rheumatic fever, from which it differs in being epidemic and in not responding to salicylates.

### LEUKAEMIA

Acute leukaemia in children not infrequently presents with swelling, redness and pain of one or more joints. The disease may thus be confused with rheumatic fever or rheumatoid arthritis.

### DISSEMINATED LUPUS ERYTHEMATOSUS (see p. 933)

### 3. OSTEO-ARTHRITIS

**Synonyms.**—Hypertrophic Arthritis; Arthritis Deformans; Morbus Coxæ Senilis (of hip).

Osteo-arthritis is a degenerative condition which affects the articular cartilages and weight-bearing surfaces, in most cases, of the larger joints.

**Ætiology.**—The known factors include trauma, congenital joint deformity, senility, certain disorders of metabolism and nervous diseases, e.g. Charcot's joint. Prolonged toxæmia is occasionally important but there is no evidence that focal sepsis is concerned in the ætiology of this type of arthritis. There may be an hereditary factor, particularly in certain cases of osteo-arthritis of the hips.

The malady tends to occur principally in men over middle life who have led a strenuous life; in women it mainly affects the knees and is often secondary to the proliferative synovitis which is often a distressing feature of the menopause.

**Pathology.**—The changes which occur in the joint affect primarily the articular cartilage, which in the early stages shows grooving and "fibrillation", starting at the points where the pressure of the opposing surfaces is greatest. Later, the cartilage may actually wear through at these points, and the two bony surfaces come into contact. When this happens, the constant rubbing of bone on bone gradually polishes and "eburnates" these areas. At the same time a gradually progressive enlargement of the articular surfaces occurs which culminates in the production of "lipping" and of bony outgrowths from the joint margins called osteophytes. These excrescences may, in well-established cases, be easily palpable at the joint margins, and are the typical lesions of osteo-arthritis. No constant changes, other than degenerative, are found in the synovium.

**Symptoms.**—The onset of the disease is insidious. The first symptom to be complained of is usually stiffness, often accompanied by pain after exertion. The site is generally one or more of the larger joints; or it may be any joint which is subjected to particular stresses as the result of the patient's occupation or recreation. In the course of time considerable wasting of the muscles controlling the affected joints supervenes. The joints therefore tend to become unstable and so liable to further trauma. The coarse grating which can be elicited in joints affected with the disease is due to an accompanying teno-synovitis, and is no measure of the actual damage to the joints themselves. When extrinsic joint changes have occurred, the patient usually experiences considerable pain, particularly on bearing weight. The movements of the joint also become much limited on account of spasm of the surrounding muscles, which may in itself be a cause of pain. There is generally not much effusion present. Occasionally new bone formation may limit the movements of the joint, although this is not very common. Small rounded bony swellings on the terminal phalanges of the fingers and thumbs, termed Heberden's nodes, not

infrequently develop during the course of the disease. These may be the cause of considerable pain in their early stages, but, on the other hand, they may be quite painless.

The examination of a hip joint affected with early osteo-arthritis reveals some limitation and pain on rotation and often also of abduction of the joint some time before the movements of flexion and extension are appreciably interfered with. In addition, it may be found that such a patient when standing, in order to avoid pain, does not support his weight equally on both hips. Some wasting of the gluteus muscle on the affected side is also evident fairly early. In advanced cases actual shortening of the affected limb occurs either as the result of absorption of the femoral head or from its dislocation upwards. Pain complained of in the knee may in reality be referred from a diseased hip; in such cases, if a full examination of the patient is omitted, treatment may be directed to the wrong joint. "Sciatica" is often found to be the result of osteo-arthritis of the hip, or of the lumbar spine, and is sometimes the initial symptom.

Osteo-arthritic changes in the lumbar spine are frequently present without giving rise to symptoms and such changes are often discovered radiologically in the course of an examination for another purpose. The sacro-iliac joints are in the same way frequently reported as being the seat of osteo-arthritis. Many of these patients are symptom free, while others complain of low backache or sciatica.

The osteo-arthritic joint does not ankylose, but may become locked as the result of excessive osteophyte formation. In other cases it becomes unstable, owing to continued use in the presence of insufficient muscular support, due to muscular wasting; in these cases the joint surfaces may ultimately become very disorganised.

When a weight-bearing joint is affected, the patient suffers great pain on standing, and a certain amount of absorption of articular bone may occur, resulting in some shortening of the limb.

In some cases the articular cartilage may become fragmented, or osteophytes may break off into the joint cavity. In both these circumstances they form loose bodies which give rise to all the symptoms usual in that condition, in addition to those of the arthritis.

The general health is not affected, unless as the result of enforced inactivity or of pain.

**Diagnosis.**—Unless the observer be a slave to names it must be allowed that it is not always easy to call a case one of pure rheumatoid arthritis or osteo-arthritis. But, speaking generally, the distinction is a true one and it is important to make it whenever possible. Osteo-arthritis is a degenerative condition affecting one or two joints, usually the larger ones. There is generally a history of trauma in the past, or of continued trauma of a minor nature, such as some occupational or sporting stress or strain; or a postural defect; or in some cases a sudden increase of weight, with resultant strain on the ankles, knees or hips, such as may occur at the menopause. Apart from the menopausal group of cases, the patient is more often a male, and his general health is not directly affected by the disease. Again, the pain is generally relieved by rest.

Rheumatoid arthritis, on the other hand, is a general disease, the joint changes being a conspicuous part of it. These changes are inflammatory in nature, and trauma is not a marked feature. The onset is in the smaller joints, many of which are generally affected, symmetrically and bilaterally. The patient is most often a woman, and there are, as suggested, indications of general ill health and loss of weight, which often precede the joint manifestations.

The *radiographic* appearance of a joint affected with osteo-arthritis is usually typical. The bone density is unaffected, but the joint space is narrowed to a degree which depends upon the amount of erosion occurring in the cartilage. Osteophytes are seen at the joint margins, and there is frequently also a deposition of calcium in



the attached ends of certain tendons, such as those of the patella and ligaments, e.g. the cruciates, which result in an appearance of "spiking". This is sometimes found independently of the existence of osteo-arthritis. In osteo-arthritis of the hip considerable deformity, both of the head of the femur and of the acetabulum, may be seen, and, in addition, small degenerative cystic areas adjacent to the joint are not infrequently noticed. The radiographic findings are often unrelated to the degree of pain in the particular case; this may be severe with very little radiographic deviation from the normal, whereas the grossest radiographic changes are sometimes compatible with little pain.

The blood sedimentation rate, glucose tolerance test and streptococcal agglutination reaction are normal.

**Differential Diagnosis.**—Conditions which are liable to be confused with osteo-arthritis are Paget's disease, *osteo-chondritis dissecans* and occasionally neoplastic growths of the articular ends of bones.

**Prognosis.**—If not treated the course of osteo-arthritis is progressive and generally ends in disablement. Much, however, can be done in the early stage to prevent this, by relieving the affected joint of all possible strain, and by support and correct treatment. The outlook is perhaps best in that form known as "menopausal arthritis", provided full and adequate measures are taken before the malady becomes firmly established.

**Treatment.**—As there is usually an absence of general symptoms, there is no indication for general treatment other than seeing that the patients receive an adequate supply of vitamins and that definite periods of rest are secured. If the patient is obese, a diet low in fats and carbohydrates should be insisted upon if success from other measures is to be achieved. The caloric value should not exceed 1600 calories, and fluids should not be taken at the same time as food. The patients should be reassured that they will not become extensively and hopelessly crippled, as may occur in rheumatoid arthritis.

It is the experience of most observers that little benefit is to be anticipated as the direct result of removing foci of infection. If, however, these are found they should be dealt with on their merits. If varicose veins are present, as is often the case when the malady is situated in the knees, treatment directed towards these may result in some improvement in the joints.

The drugs chiefly valuable in this condition are those of the analgesic group, such as aspirin, phenacetin and codeine. They should not be prescribed as a routine and should only be used when pain is severe. Phenylbutazone is very effective in certain cases, but must be prescribed with caution; 200 to 400 mg. daily may relieve the pain and this dose can be maintained over long periods with reasonable safety. It can often be reduced to 100 mg. daily, with equal effect. Gold salts are not indicated in this type of arthritis. The intra-articular injection of hydrocortisone, 25 to 50 mg., at frequent intervals, gives considerable although temporary relief of symptoms in some cases.

In cases which arise about the time of the menopause small doses of iodine and thyroid are often of value, but should be combined with the other measures outlined, particularly those for reduction in weight and muscular re-education. Central heating in the home is desirable.

Physiotherapy of some sort is essential in the treatment of osteo-arthritis. Heat is required, to stimulate the failing circulation locally and to relieve muscle spasm and consequently pain; massage, to maintain and stimulate the nutrition and drainage of the skin and underlying tissues; and movement, in order to maintain the mobility of the joint, to prevent or repair muscle wasting and discourage the formation of adhesions. When dealing with the extremities, paraffin wax applied at a high temperature is also useful as a means of applying heat.

Movement should, if possible, be active, i.e. special exercises, or if this is not

feasible at the outset, electrical stimulation by means of the surging faradic current, or hydrotherapy, if available, may be substituted. Movement of the affected joint should, however, as far as possible be dissociated from weight-bearing through the affected joint, in order to allow of repair in the cartilage. Where the deep pool or the Guthrie-Smith slings are available for this purpose they are helpful.

The question of posture, or "body mechanics", is an important and neglected aspect in many cases of osteo-arthritis. For instance, pronated feet may cause strain and, later, arthritis, in both knees and lumbar spine, as may a pendulous abdomen. Proper postural exercises should be taught, and the patient should continue with these until the correct posture is maintained reflexly.

When, after a period of rest, the patient begins to put weight on to the affected joint again, the latter should always be adequately supported. For this purpose a crêpe bandage, or Elastoplast, is of great value. In some cases special appliances, such as the Howard Marsh splint for the knees, or a back support when the spine is affected, may be needed for a period in order to protect the joint. For the feet proper arch supports may be necessary, while in cases of severe arthritis of the hip or knee, when weight-bearing continues to give great pain, some form of walking caliper, whereby the weight of the body is "by-passed" from the ischium down to the heel of the shoe by a light metal rod, is indicated.

In very advanced cases operative procedures may prove necessary. Chief amongst these are synovectomy in those cases in which soft tissue proliferation is not responsive to other treatment. When in the hip-joint a small degree of painful movement is all that remains possible of achievement, arthrodesis, either by open operation or by means of the Smith-Petersen pin, is often the best method of treatment. Arthroplasty in experienced hands is a successful operation, but old age is a contraindication, because of the considerable length of time necessary for rehabilitation. Tavernier's operation for section of the obturator nerve, if successful, is pain-relieving.

#### 4. HYPERTROPHIC PULMONARY OSTEO-ARTHIROPATHY (see p. 1171)

#### 5. ARTHRITIS DUE TO GOUT (see p. 444)

#### 6. SPONDYLITIS

Spondylitis is arthritis of the spine. Most cases fall into one of three types: (1) the ankylosing type—spondylitis ankylopoietica; (2) rheumatoid arthritis, in which the spine is involved as part of the general disease and (3) osteo-arthritis of the spine.

##### 1. ANKYLOSING TYPE OF SPONDYLITIS

**Synonyms.**—Ankylosing Spondylitis; Spondylitis Ankylopoietica; Atrophic type of Spondylitis; Spondylose Rhizomélisque; Von Bechterew's Disease; Marie-Strumpell Disease. It is now realised that all these terms apply to the ankylosing type of spondylitis or sub-varieties of this.

**Ætiology.**—The predisposing and exciting factors are probably the same as in rheumatoid arthritis. In America, where it is known as Rheumatoid Spondylitis, it is believed to be a variant of that disease. The age of onset is similar, occurring chiefly in the young, but males are predominantly affected. The disease is sometimes familial.

Non-specific urethritis is considered by some authorities to be a cause of ankylosing spondylitis.

**Pathology.**—The only true joints in the spinal column are those which permit of movement between the intervertebral articular facets and the costo-vertebral joints.

corticotrophin are of considerable value in suppressing the acute exacerbations. The principles of treatment and dosage are the same as in rheumatoid arthritis (p. 1152).

In the active stage rest in bed and mobilisation of the chest by means of breathing exercises are essential. Fracture boards should be placed under the mattress, to prevent sagging, and the patient should be as flat as possible, the pillows being removed several times daily in order to hyperextend the spine. Better still, a plaster cast should be made of the back in which the patient can lie, thereby maintaining the natural curves of the spine. Breathing exercises undertaken in this position should aim at keeping the chest wall mobile by restricting abdominal breathing. Physiotherapy is chiefly of value in the form of radiant heat or infra-red rays to the back, in order to relax spasm and relieve pain. Gentle massage is useful for the same purpose, and, later active movements should be performed under supervision. If there is already some deformity of the spine a plaster shell is essential and the patient should lie in this night and day to relax completely all spasm. It should be altered frequently so as to take advantage of the gradual postural improvement, and when the patient first assumes the upright position he should be fitted with a light spinal brace to relieve the back from all strain. Special mobilising exercises are indicated when the disease is less active.

Radiotherapy to the sacro-iliac joints and the spinal column is an important part of the treatment of these cases. Its effect appears to be more than merely palliative.

Even with the greatest care it is sometimes impossible to avoid ankylosis of the spine. But if this does occur it is almost always possible to ensure that it does so in the optimum position and thus the patient will ultimately be able to lead a reasonably active life in an erect posture.

## 2. RHEUMATOID ARTHRITIS WITH SECONDARY SPONDYLITIS (see p. 1151)

### 3. OSTEO-ARTHRITIC TYPE OF SPONDYLITIS

**Synonyms.**—Osteo-arthritis of Spine; Hypertrophic Spondylitis; Degenerative Spondylitis; Spondylosis.

Some degree of osteo-arthritis of the spine is present in the majority of people over 50 years of age; but it is unusual for these changes to cause symptoms. Its incidence is rather higher in men than women and it seldom occurs before middle life. It often follows trauma.

**Pathology.**—The changes are not inflammatory in nature and are identical with those of osteo-arthritis met with elsewhere in the body. Bony ankylosis does not occur in this type of arthritis, but osteophyte formation is always seen, together with narrowing and degeneration of the intervertebral spaces. The areas most commonly involved are the cervical and lumbar regions, and in the former protrusion of the intervertebral disks may result in spinal cord and nerve-root compression.

**Symptoms.**—When symptoms are present they may include the following: root pains, of which sciatica is the most frequent example; increasing stiffness of the back, which, however, never becomes completely rigid. Headache and pains in the neck, shoulders and arms are common, sometimes in conjunction with areas of paræsthesia or anæsthesia in the skin. Pains are generally aggravated by movement of the spine, as the nerve roots are liable to pressure in or around their exit from the spinal foramina. Cervical spondylosis may cause paraplegia due to ventral compression of the spinal cord, a Brown-Séquard syndrome due to lateral compression of the spinal cord and radicular symptoms when nerve roots are involved.

**Diagnosis.**—This should be confirmed radiologically. The lesion typical of osteo-arthritis is the osteophyte; while marginal exostosis and shrinking of the vertebral margins, with narrowing of the intervertebral spaces, are also seen. The sacro-iliac joints are generally normal. In all cases the possibility of malignant growths

or Paget's disease in the spine should be borne in mind, as the symptomatology may be the same. Myelography may be required to establish the diagnosis in doubtful cases.

**Treatment.**—This is similar to that of osteo-arthritis elsewhere in the body and includes the correction of body posture and flat feet. The frequent application of heat in some form, followed by rest and muscular relaxation, is important. Massage and faradism at a later stage helps the muscular support of the back. Sometimes it is necessary to supplement the support of the back mechanically by a plaster cast or a brace. Radiotherapy sometimes relieves intractable pain which proves resistant to analgesic drugs, such as aspirin, phenacetin, codeine or phenylbutazone. Conservative treatment of cervical spondylosis with neurological complications consists of bed rest, physiotherapy and the immobilisation of the head and neck by means of a collar-support. Surgical treatment is confined to laminectomy, because the offending osteophytic ridge is anterior to the cervical cord and is therefore inaccessible.

### 7. STILL'S DISEASE

This disease is believed by most observers to be the juvenile form of rheumatoid arthritis. But although the articular changes are of an inflammatory nature their effects are more often confined to the periarticular tissues. Again, even in cases of long standing, it is not unusual to find little or no radiological evidence of destruction at the actual joint surfaces.

**Ætiology.**—The sexes are affected in about equal proportion, while the age incidence resembles that of rheumatic fever. Thus the malady is seldom met with before the age of 3 years and the average age at onset is between 6 and 7 years. The cause remains unknown, although the factors held to be responsible for rheumatoid arthritis are usually invoked to account also for Still's disease. These are focal infection, metabolic or endocrine disorder, or, in some cases, unsuspected and attenuated infection with the tubercle bacillus. In the majority of cases it is very difficult to assign any one cause. It is certain, however, that once the disease has commenced a cold damp environment exacerbates it considerably.

**Symptoms.**—If a careful enquiry of the history of the patient's illness be made it is often found that a considerable period of prodromal ill health preceded the onset of the joint symptoms.

The onset of the joint condition is not infrequently rapid, with pyrexia and pain and swelling of several joints. This often leads to an initial diagnosis of rheumatic fever, but it is soon found that sodium salicylate has no beneficial effect and that the joint swellings, far from being transient, increase in number and intensity. When the onset is gradual there is little pyrexia but a slowly progressive degree of swelling and limitation in movement of the knees, wrists, elbows, fingers and ankles—usually in that order. Later, the cervical spine and also the hips may become affected and the patient becomes completely crippled. The foregoing joints are usually attacked symmetrically, and their appearance is characteristic in that the periarticular swelling renders the joint fusiform in shape. The skin over this swelling is rather stretched and often slightly bluish. The muscles adjacent to the affected joints waste, which further exaggerates the fusiform appearance. In the case of the wrists, ankles and elbows the bony contours are often completely obscured. The affected joints are generally tender on pressure, but usually are not painful except on movement. This leads to further voluntary limitation of movement and so intensifies the muscle wasting already present.

In many cases of this disease the joint swelling and muscular wasting are accompanied by a lymphatic reaction which shows as enlargement of the glands, especially those around the elbows and in the axillæ. In abo

seen there is also enlargement of the spleen. These changes were present in the cases originally described by Still in 1897. The enlarged glands are not tender, and are generally discrete and "rubbery". Subcutaneous nodules are sometimes found in addition.

There is generally a secondary anaemia, and quite often patches of light-brown pigmentation on the skin. When the disease is established, the extremities are cold and clammy, and there is an increase in the temperature before other joints are affected. In long-standing cases normal growth is considerably interfered with.

In the late stages the type of deformity seen in adult rheumatoid arthritis develops. There is flexion of the fingers and ulnar deviation of the hands, and also flexion of the knees and elbows.

The radiographic picture is chiefly remarkable for the advanced degree of the osteoporosis which occurs. There are often little or no actual joint changes, and osteophytes are never found.

The end result, so far as the joints are concerned, is a fibrous ankylosis, or a fibrosis of the joint capsule, which is sufficiently complete to resist all attempts at movement of the joint.

It is stated that at post-mortem examination diffuse pericardial adhesions and adhesive mediastinitis are often discovered, although unsuspected during life, and evidence of valvular disease of the heart has occasionally been reported.

**Prognosis.**—Until recently there was considerable doubt as to what was the ultimate fate of these patients. Some authorities held that they recovered, while others explained the rarity of the affection in adult out-patient departments by assuming that the patients either died or became rapidly bedridden after leaving the children's departments. In one series the mortality in those under 5 years of age was about 25 per cent. (due to intercurrent infections); complete recovery occurred in a small proportion; while in the majority, the disease remained apparently arrested, often for several years at a time, only to resume its ravages at increasing intervals until the patients were entirely crippled and bedridden.

**Treatment.**—When the presence of an infective focus is established, this should be dealt with at an early stage of the disease. In all cases the child's resistance should be built up by all available means. A nourishing diet, an open-air life and a dry, sunny climate are indicated. In addition, cod-liver oil and malt, syrup of iodide of iron, and courses of an arsenic-containing tonic are important. Salicylates have little or no beneficial effect. Non-specific protein therapy is often recommended, but is too drastic and temporary a measure to employ except in the later stages. Good results have occasionally been reported from small doses of gold salts administered intramuscularly in short courses. But in some cases these salts provoke unfavourable reactions, and so should be used very cautiously. No case should receive a larger dose than 0.05 g. and a total course of 0.5 g. should rarely be exceeded. The injections should be given at fortnightly intervals, and the onset of toxic nephritis, stomatitis, diarrhoea and dermatitis should be especially looked for. The response to cortisone and corticotrophin is the same as in adult rheumatoid arthritis. The initial response is generally excellent, but as treatment may have to be protracted the likelihood of toxic effects is thereby increased.

All swollen joints should be bandaged and lightly splinted, or put into thin plaster of Paris casts, to avoid the contraction deformities which otherwise inevitably occur. The child should always sleep in these, and soon becomes accustomed to them. They should be removed daily, however, for a short period, during which the joint must be given active assisted movement, to prevent fixation. Dry heat from a radiant heat or infra-red ray lamp is comfortable and renders the performance of these daily active movements easier. These movements are also essential to remedy the muscular atrophy present. Massage is generally unnecessary in these cases.

In the very late stages, when the patient is bedridden owing to extensive contrac-

tion deformity, minor surgical procedures, such as tenotomy, are justifiable to remedy the deformity.

## PSEUDO-ARTHRITIS (SYNOVITIS)

Effusion of fluid into the joints may be associated with various conditions and is often of a temporary or intermittent nature.

Apart from the various forms of true arthritis already described, the following may give rise to joint effusion :

(i) *The specific fevers*, especially scarlet fever, meningococcal fever, puerperal fever, syphilis, typhoid or paratyphoid fever, yaws and malaria. In the United States a form of pseudo-arthritis associated with lymphogranuloma venereum is not uncommon.

(ii) *Abnormal blood conditions*, such as purpura simplex or purpura rheumatica (Schönlein's disease), scurvy and hæmophilia give rise to swelling of the joints due to an effusion of blood. The knees are most frequently affected.

(iii) *Growths affecting the bones*, in near proximity to a joint.

(iv) *Injection of animal sera*, i.e. apart from "serum sickness" arising on the seventh to tenth day after the use of "foreign" serum in treatment.

(v) *Trauma* may cause synovitis or hæmarthrosis of the affected joint. It should be noted that the strain imposed on certain joints due to faulty body posture occasionally results in a chronic form of hydrarthrosis.

(vi) *Intermittent hydrarthrosis* ; a periodic recurrence of joint effusion of unknown ætiology which persists for several days and usually affects the knees. Attacks tend to recur at regular intervals ; they show no local evidence of inflammation ; and they are refractory to most forms of treatment. This condition is probably the result of an allergic sensitisation, and treatment should be directed along these lines. It may represent an atypical form of onset of rheumatoid arthritis.

(vii) *Palindromic rheumatism*.—This is a form of recurrent painful swelling of the joints which shows intense inflammatory synovial reaction. It has been exhaustively investigated by Hench, but the cause remains unknown.

## NON-ARTICULAR RHEUMATISM; FIBROSITIS

Non-articular rheumatism and fibrositis are the terms employed to designate pain which is situated in the soft tissues of the limbs or trunk and of which the causation is obscure. It is accompanied by muscle tenderness and spasm, but there is no deterioration in the general health of the sufferer. A feature of the "classical" type is that the pain can often be shown to originate in nodules, which are acutely tender to pressure and from which the general pain is referred.

In view of the obscurity which at present shrouds its true nature it can perhaps be best classified according to the part of the body which it affects, e.g. fibrositis of the head and neck, brachialgia, intercostal fibrositis, fibrositis of the back (lumbago), etc. It may also be subdivided broadly according to the nature of the structures which appear principally to be affected, e.g. : *Panniculitis*—inflammation (or increased tension from some cause) of the deep subcutaneous fat. *Peri-arthritis*—inflammation of the structures surrounding joints (including bursæ). *Peri-neuritis*—inflammation of the nerve sheath and fibrous tissue between the nerve fibres. Considerable doubt has, however, been cast in recent years upon the occurrence of the latter as the result of rheumatism.

*Ætiology*.—Fibrositis can sometimes be attributed to focal sepsis, particularly of the teeth, tonsils, nasal sinuses and prostate.

A further group of cases would appear to be of metabolic origin, *i.e.* allied to gout or to a special sensitivity to certain types of food. It may sometimes be the outward manifestation of mental anxiety or tension and in America the term "psychogenic rheumatism" is much employed.

Finally, a certain proportion of cases of fibrositis can be traced to chronic strain, often secondary to faulty posture. A common example of this will be found in those cases in which the fascia lata is tender and painful in conjunction with a flattened plantar arch. Such patients are usually cured when the distribution of the body weight is readjusted by raising the inner edges of the shoes. Some cases of low back-ache seem also to be attributable to the same cause.

**Morbid Anatomy.**—This was investigated originally by Stockman, who believed that the results of injury to fibrous tissue, whether bacterial or traumatic, had the effect of producing in the acute stage an exudate and inflammatory cedema. As the condition becomes chronic there is said to be a production of dense connective tissue in nodules or strands, which differ from normal fibrous tissue in having more fibroblasts. In 1944 Copeman and Ackerman produced evidence, based upon biopsy, that certain cases of fibrositis are caused by a non-inflammatory cedema of fat lobules which are invested with a non-distensible fibrous fascia. This increase in tension appears to be the cause of the pain. In later stages the lobule may actually herniate through a weak spot in its fascial covering, producing a tense palpable nodule.

F. A. Elliott has suggested that in some myalgias, and also in some cases of "fibrositis", local areas of tenderness or "nodules" may be the result of muscle spasm, centrally induced through irritated nerve roots.

**Symptoms.**—The pain complained of in fibrositis is not always at the real seat of the lesion but may be referred from other areas and therefore careful location of the actual seat of the inflammation is essential. Again, the symptoms vary according to the area of the body affected. As examples, the predominant effect of involvement of the muscles of the neck is often headache; of those of the limbs, numbness and tingling; and of the fibrous tissue surrounding joints, stiffness and pain on moving these, often wrongly attributed to true arthritis.

cause of severe bilateral brachial neuritis is a cervical intervertebral disk lesion; unilateral brachial neuritis is frequently due to supraspinatus tendinitis, which is often the cause of inflammation of the subacromial bursa through which this tendon passes. Another group of causes of brachial "neuralgia" are the cervico-brachial syndromes which include the compression of vessels or nerves at the thoracic outlet by a cervical rib or an abnormally placed clavicle, or a spastic scalene muscle (acroparæsthesia). These are all dependent upon a mechanical factor of some sort (see pp. 1577, 1579). "Tennis elbow" is the term applied to the painful fibrositis affecting the origin of the extensor tendons of the forearm from the external condyle of the humerus.

*Bursitis* may occur in any of the large bursæ. The most commonly affected is the subacromial bursa, referred to above. The chief clinical manifestations of "deltoid bursitis" are great pain on actively abducting the affected arm to an angle of 90° with the body. Above this point abduction can generally be completed without pain; the pain returning, however, at the same point when the arm is again lowered. Passive movement through this range is not painful. Pain of this type encourages the sufferer to immobilise the affected arm, and this allows the inflammation to spread to the joint capsule, which contracts and ultimately limits, or even entirely prevents, movement in the joint. This "frozen shoulder" syndrome is not an infrequent late complication of cardiac infarction. The patient is often unaware of the full degree of limitation of the movement which has occurred in such cases, as a considerable degree of movement is possible by virtue of the mobility of the scapula. This condition is the severest type of peri-arthritis, and the apparent ankylosis of the joint must be differentiated from a true arthritis by means of radiography, as peri-arthritis of this type may be cured by the employment of diathermy with active assisted movements and remedial exercises, or, if the diagnosis is clear and these means fail, by manipulation under anæsthesia. The bursæ next most commonly affected are those over the olecranon process, around the knee joint, over the ischium and over the great trochanter. Inflammation of any of these should be differentiated from a true arthritis of the neighbouring joint. Another form of peri-arthritis depends on inflammation of the tendon sheaths of muscles surrounding joints. This may occur as part of a chronic rheumatic process unassociated with trauma or gout. Its association with gonorrhœal and dysenteric infections has been mentioned. The flexor tendons of the wrists and knees are the most commonly attacked. Pain, swelling or crepitus results and sometimes synovial effusion. Occasionally the extensor tendon of the thumb alone becomes painful and thickened, resulting in a loss of abduction and great tenderness and thickening. This is referred to as stenosing tendovaginitis (De Quervain's disease), and is brilliantly amenable to operative treatment.

The palmar fascia is sometimes the site of a chronic fibrositic process, and the resulting thickening and contracture is known as *Dupuytren's contracture*. This is seldom painful, but can give rise to considerable disablement of a somewhat intractable nature. The condition, which is much commoner in males than in females, is often found to be familial. A somewhat similar condition, which, however, does not cause so much contracture, is known as "painful heel". In some cases a small spur of bone is found radiographically at the insertion of the plantar fascia into the os calcis, though spurs may also be found in subjects who are free from the condition. But in the majority of cases, no cause for the pain can be found.

The subjects of fibrositis are usually found to have some degree of defective skin circulation, as evidenced by abnormal sensitivity to cold weather or to local draughts, spontaneous bruising, or the fact that they perspire in the hottest weather only with difficulty. Attacks of fibrositis occur in many people without apparent detriment to their general health.

The group of cases which appear to be allied to gout or to a special sensitivity to certain types of food may be suspected by the excellent general health, even during



attacks, the periodic or seasonal nature of the attacks, a history of familial gout or of being "unable to digest" certain foods or drinks, and finally by the fact that the fibrositis tends to affect the lower limbs and other lower parts of the body. Such patients, in addition, often exhibit the symptom-complex described by the French as "hépatisme". This is shown principally by morning headache, furred tongue and a tendency to incomplete bowel emptying, with light-coloured and offensive stools; often, too, there is slight tenderness on palpation of the liver.

**Prognosis.**—Provided sufficient care be taken and the value of external as well as internal remedies is remembered, the outlook is good. An exception, however, is in the case of old patients, for the senile form of fibrositis is sometimes intractable to all the usual remedies.

**Treatment.**—When symptoms do not call for urgent treatment, the first indication is to investigate the aetiology. In the majority of cases in which the malady is believed to be allied to gout or due to a special sensitivity to certain types of food, appropriate treatment should be adopted.

At the outset, a mercurial purgative, such as calomel (gr.  $\frac{1}{2}$  to 2), followed next morning by a saline, should be prescribed. In the acute stage rest in bed is desirable. The internal administration of analgesic drugs is indicated. Aspirin and calcium acetylsalicylate (gr. 5 to 15) are in the majority of cases the most efficient for this purpose. If necessary, potassium iodide (gr. 2 to 5) may be added, as may phenacetin (gr. 5 to 10) or caffeine (gr. 5) at 4-hourly intervals. A useful addition to aspirin and phenacetin is codeine phosphate (gr.  $\frac{1}{2}$ ) or Dover's powder (gr. 5 to 15). Phenylbutazone (200 to 600 mg. daily) is sometimes effective. An ointment designed to act either as a rubefacient or as a counter-irritant should also be prescribed. In acute cases a hot linseed or kaolin poultice will often give considerable relief if applied every few hours, as may a hot cloth wrung out of a solution of ordinary mustard in water. Massage is undesirable in the acute stage. In certain cases benefit will result from a short course of colonic lavage twice a week for 2 to 3 weeks.

When it is desired to immobilise the muscles of the back during the acute stage of lumbago, the most effective method is by means of a perforated belladonna plaster, which should be made to cross the mid-line behind and come round to the front. Ordinary wide strapping is a good substitute. When the condition is less acute and the patient is able to get up, the application of both heat and massage to the affected regions is indicated. The former may be applied in a dry or a moist form, the one often succeeding when the other has failed. Dry heat may be given by means of a portable lamp, an electric heating pad, exposure to a gas-fire (which gives out infra-red rays), the application of a hot iron through brown paper applied to the skin, a hot-water bottle or a bag of salt or sand which has been heated thoroughly in the oven. When the condition is deep-seated, diathermy is the best form in which to apply heat.

Moist heat may be applied in the form of bread or linseed poultices, kaolin poultice (Antiphlogistine), mud packs or applications of hot paraffin wax of a special melting-point (which is sold for this purpose), or, if the patient is in a condition to have it, a Turkish bath. Perhaps the simplest method of applying moist heat is in an ordinary bath, to which 4 lb. of Epsom salts (or common salt) have been added. It should be taken as hot as possible, and, contrary to the general belief, the patient should not "soak in it" but should get out after only 10 minutes' immersion and be briskly rubbed down, after which some analgesic ointment should be rubbed rapidly into the affected areas, and he should be wrapped in a blanket and put to bed for several hours. After this, deep massage should be ordered for the affected areas, although this may be painful at first.

**Hydrotherapy and counter-irritation.**—When the patient is near a spa or an institution equipped for hydrotherapy, spray douche-massage, followed by "contrast douching" (alternate hot and cold water directed on to the painful areas under pressure

from a hose-pipe), is probably the best follow-up treatment; it stimulates the skin and muscles to resume their normal functions.

In certain cases, particularly when the complaint is that of lumbago, counter-irritation by means of a cautery may be of great value. A small blister should result from each application, and the whole area may then be covered over with a gauze dressing. Another method is to produce blisters by means of "blistering fluid", or cantharidin plasters, but these are not of such value as the actual cautery. Dry-cupping is a somewhat obsolete method of treatment, but is occasionally effective; as is full exposure to a Kromayer mercury vapour lamp.

In the chronic stage massage is essential if an attack is to be terminated in the minimum time and also if recurrence is to be avoided. To be effective, the indurated areas (nodules) should be carefully sought for in the muscles, and at these points the massage should be deep. It will be found that following deep kneading with the finger-tips or thumbs, after an initial period during which the nodules may be increasingly painful, they will gradually become insensible to palpation and ultimately disappear. This process will be considerably facilitated if it be preceded on each occasion by 20 to 30 minutes' application of heat in one of the forms mentioned above. In certain cases a "nodule" will prove to be too painful for deep massage treatment, which will then induce protective spasm in the surrounding muscles, and so render further "kneading" impossible. In such cases a dose of aspirin or some other analgesic may usefully be administered before beginning the treatment. When one or more discrete trigger-points or nodules can be localised and when the pain is referred from these sites, the effect of injecting a few millilitres of a local anæsthetic, such as procaine hydrochloride ( $\frac{1}{2}$  per cent. in saline) or "A.B.A." compound, with saline, under pressure is sometimes dramatic. When there is diffused pain and tenderness, this method of treatment is not of much use, and unless the injection is made with great accuracy into the nodule the trouble may even be exacerbated. There is no doubt, however, that to achieve a quick result, even if it does not prove to be permanent, this is the method of choice.

*Diet and after-care.*—If obesity be present, this should be treated (see p. 450). In cases in which a gouty origin is suspected, this should be corrected (see p. 448).

After an attack of fibrositis, it is important that the patient should be taught to contract the affected muscles daily by means of appropriate exercises. He should also make a point of obtaining some regular exercise in the open air, even at the cost of rising somewhat earlier in order to walk part of the way to the office. The obese subject must not be allowed to regain his lost weight once the attack recedes, and occupations or hobbies known to precipitate the attacks must be avoided.

## MYOSITIS OR INFLAMMATION OF THE VOLUNTARY MUSCLES

Three forms occur—(1) the suppurative type; (2) the non-suppurative type and (3) myositis ossificans progressiva.

1. **SUPPURATIVE MYOSITIS.**—In this condition there is a primary inflammation of the affected muscles associated with the local signs of inflammation and the general symptoms of a septic infection. Abscesses form in the affected muscles, which may require incision, and in the pus obtained pyogenic organisms, such as staphylococci, or less commonly streptococci, are usually found.

2. **NON-SUPPURATIVE MYOSITIS.**—It must be remembered that the voluntary muscles are affected in the course of several diseases. Thus, degeneration of the striped muscle, known as Zenker's degeneration, may occur in any acute infection of long duration; it was first observed in typhoid fever. In scurvy, intra-muscular

hæmorrhages are common, and these may be followed by a chronic inflammation, which usually resolves; but in a few such cases suppuration occurs. *Trichiniasis* is accompanied by myositis, set up by the encapsulated larvæ of the *Trichinella spiralis* deposited in the voluntary muscles.

*Dermatomyositis*, see p. 936.

3. *MYOSITIS OSSIFICANS PROGRESSIVA*.—This is a progressive inflammatory affection of the locomotor system of unknown origin, characterised by the deposition of bony substance in the fasciæ, muscles, aponeuroses, tendons, ligaments and bones, with resulting ankylosis of the affected articulations. The disease is rare. It usually commences in early life, and is commoner in males. Three stages occur in the muscle changes. In the first stage, swelling and infiltration of the affected muscle with embryonic connective tissue occurs. In the second stage, the embryonic connective tissue becomes organised and forms ordinary connective tissue, which retracts to a hard fibrous mass. In the third stage, calcification of the fibrous mass occurs and this becomes replaced by bone.

The muscles of the back and neck are usually the first to be involved. The vertebral ligaments become ossified and the irregular bony swelling produced causes deformity and fixation of the spine. The upper and lower limb are later involved, the muscles contracting and causing fixation of the joints. Finally, the muscles of mastication are affected and this prevents movement of the lower jaw. The patient becomes helpless and bedridden, and usually dies from some intercurrent infection, such as pneumonia, or pyæmia resulting from bed-sores. The disease is always progressive, but is usually of long duration, and there may be a cessation in its progress for several years. No specific treatment is known.

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## SECTION XVI

### DISEASES OF THE SKELETON

DISEASES of the skeleton will be considered under three headings, according to whether bone, cartilage or bone marrow is primarily affected.

### DISEASES OF BONE

#### HYPERTROPHIC OSTEO-ARTHROPATHY

**Synonyms.**—Hypertrophic Pulmonary Osteo-arthritis; Secondary Hypertrophic Osteo-arthritis; Marie's Disease; Bamberger-Marie's Disease; Acropachy. Simple clubbing is sometimes referred to as Hippocratic Fingers.

**Definition.**—A symmetrical enlargement of the bones of the hands and feet, and of the distal ends of the long bones, accompanied by clubbing of the fingers and toes, and sometimes by joint swellings, occurring in association with certain chronic diseases, especially of the chest and abdomen. Clearly, simple clubbing of the fingers, which is a common phenomenon, exists in countless patients without advancing further to produce hypertrophic osteo-arthritis, which is rare.

**Ætiology.**—The disease is eight times more common in males than females. It may occur at all ages, including childhood. The most striking examples are seen from 30 to 50. The primary diseases in the course of which hypertrophic osteo-arthritis may develop are:

1. Diseases of the lungs, such as abscess of the lung, empyema, bronchiectasis, carcinoma of the lung and mediastinum, or endothelioma of the pleura. The condition is rarely seen in cases of pulmonary tuberculosis, or non-tuberculous fibroid lung.

2. Congenital heart disease, and infective endocarditis. Here there is clubbing of the fingers but the bones are not affected.

3. Diseases such as dysentery, idiopathic steatorrhœa, subphrenic abscess, pyelonephritis, polycythæmia rubra vera and hypertrophic cirrhosis of the liver.

4. In 10 to 15 per cent. of cases the most minute search may fail to reveal a primary cause for the disease. Such cases may be familial.

5. Pressure on the brachial plexus by a subclavian aneurysm has been known to cause the disease, which is then unilateral and confined to the upper limb concerned.

**Pathology.**—The bones most frequently affected are the metacarpal bones and the first two rows of phalanges. There are no bony changes in the terminal phalanges, the soft tissues and nails alone being involved. The radius and ulna may be affected, and more rarely the lower ends of the humerus and femur, the scapula, patella, iliac crests, nose and malar eminences. Radiographic examination shows a thin layer of newly formed bone beneath the periosteum which is raised unevenly, so that its outline appears serrated and the deposits beneath it are unevenly calcified giving a lace-work effect.

**Symptoms.**—The onset is usually gradual, with little pain, though stiffness and clumsiness of movements occur. Sometimes marked clubbing of the fingers develops in a few weeks; but usually several months or more elapse before the condition is characteristic. There is a remarkable symmetry in the pathological changes. The ends of the fingers and toes may be cyanosed. The nails are large, broad and curved

both longitudinally and transversely—the so-called parrot-beak or drumstick. They show longitudinal striation and are brittle and easily split. The root of the nail is raised above its bed, and if pressure is applied at the root a distinct space between them can be made out. The hands and feet become greatly enlarged, owing to the bony changes and thickening of the soft parts. The forearms and legs are thickened. The pelvis, sternum, ribs and clavicles may be thickened, and the vertebrae may show changes resulting in kyphosis. Swelling of the joints occurs in about a third of all the reported cases and in practically every one of those in which the process is of long standing. The joints involved are those in the neighbourhood of the bones affected, particularly the knees, ankles and wrists. The lesions are not confined to the synovial membranes and periarticular tissues but may progress to erosion of the articular surfaces. Acute painful swelling of the joints occurs especially in cases of endothelioma of the pleura.

**Diagnosis.**—The disease is recognised by the presence of the characteristic changes in the extremities, and by the presence of signs of one of the primary diseases already mentioned.

*Acromegaly* is to be distinguished by the spade-like hand, the spatulate fingers, enlarged knuckles and the characteristic facial appearance. The kyphosis is more often cervico-dorsal, whereas in hypertrophic pulmonary osteo-arthritis it is more often dorso-lumbar.

*Osteitis deformans* shows irregular enlargement of the bones but there is a good deal of bowing, the hands are normal and the radiographic appearances are pathognomonic.

*Rheumatoid arthritis* is distinguished by the involvement of the joints of the fingers, the absence of clubbing and the changes shown by radiographic examination.

**Prognosis.**—Where successful treatment of the primary disease is possible, simple clubbing of the fingers may disappear entirely. This commonly occurs in empyema and subphrenic abscess. In a similar way regressions can occur both in the soft tissues and in the periosteal changes in hypertrophic osteo-arthritis. In some cases, however, cure or arrest of the primary lesion may have no effect on the osteo-arthritis. Many cases progress unchecked until they show extreme changes in the skin, nails, soft tissues, bones and joints. A considerable degree of ankylosis of the knees sometimes occurs.

**Treatment.**—This should be directed towards the cure or improvement of the primary disease. Other treatment is symptomatic. Care should be taken to avoid ankylosis of the knees at an awkward angle.

## OSTEITIS DEFORMANS

**Synonym.**—Paget's Disease of Bone.

**Definition.**—A chronic and somewhat rare disorder causing enlargement and deformity of many bones. It is not a generalised disease of the skeleton. The bones are affected in the following order of frequency: pelvis, spine, femur, tibia, skull, fibula, clavicle, humerus, radius and rib. In a few cases the disease is confined to one bone or to part of one bone: tibia, femur, clavicle, a vertebra, the ilium or half the pelvis.

**Ætiology.**—This is unknown. The disease is sometimes familial. It rarely begins before the age of 40, and the commonest age of onset is 55. The sexes are affected in the proportion of 3 men to 2 women. Osteitis deformans is not inflammatory in origin. It seems likely that it is a disorder of mineral metabolism. Syphilis is not an ætiological factor. No alteration in the parathyroid glands nor in any other endocrine gland has been demonstrated. Both histological and chemical investigations

proved beyond doubt that generalised osteitis fibrosa (hyperparathyroidism) is related to osteitis deformans.

**Pathology.**—There is a great alteration in the architecture of the bones affected. They become enlarged, irregularly thickened and sometimes bowed. The skull is very thick, the sutures and foramina being narrowed in consequence. The cortex of the long bones ceases to be pure ivory bone but looks coarse and spongy with red streaks and dots. Histologically there is continuous excessive resorption of bone associated with an increased new bone formation that more than compensates for the bone lost. The excessive erosion disturbs the skeletal architecture, the compact bone being replaced by irregular angular trabeculae, which also form the cancellous bone. There is still an attempt at structural adaptation to stresses, but this is very imperfectly achieved because the material is not used to the best mechanical advantage.

**Biochemistry.**—The serum calcium and plasma phosphorus are normal. The plasma phosphatase is constantly high, as in many other diseases of bone. In more than 80 per cent. of cases the calcium output in the urine is increased and sometimes reaches four or five times the normal figure. There seems to be a complete absence of correlation between the length of history, the density of bone shadows in radiographs and the calcium output. A case showing increased density of bone trabeculae throughout pelvis, lumbar spine and femora is just as likely to reveal a high output of calcium in the urine as a low output.

**Symptoms.**—The disease may remain symptomless for 10 years or more. It is very slow in progress and rarely influences the general health, giving rise in most cases to few symptoms other than those which are due to changes in the shape of the bones. In 80 per cent. of cases there is pain, and the patient usually recognises its origin in the bones. It varies widely in severity from a dull ache to a severe shooting stabbing like a knife. The back and lower limbs are the parts usually affected. Headache is fairly common. When the skull is involved the patient may have to wear a larger size in hats. The enlargement in the circumference of the head leads to the forehead being prominent and the face small in proportion. In the later stages the head is held forward and the back is so bent that the arms appear too long and an ape-like attitude results. There may be considerable reduction in total height. The lower limbs especially are bowed, the knees being widely separated and slightly flexed. The bones are enlarged, and bowing usually takes place in such a manner as to accentuate the normal curve of the bone. The enlargement is particularly noticeable in the case of the tibia. The changes in the vertebrae may cause encroachment on the spinal canal, resulting in compression paraplegia. Bony compression of the optic nerve may lead to optic atrophy, and of the oculo-motor nerves to diplopia. Otosclerotic deafness is common in advanced cases. Spontaneous fracture is rare, but when it takes place there is no delay in union. Osteogenic sarcoma may occur, but is much less common than Paget thought and is not seen until the changes in the bones have been present for 10 years or more. Osteo-arthritis of the hip, knee, ankle or spine is an occasional complication. Arterial degeneration, sometimes with hypertension, is found in most cases over the age of 50. It is possible that an excess of phosphoric esterase in the blood accelerates and intensifies the deposition of calcium salts in degenerate vessels. Retinal arteriosclerosis is a frequent finding, and it may be associated both with retinal hæmorrhages and extensive choroidal changes.

**Radiographic appearances.**—The altered bone appears in radiographs in two forms, which may be called the spongy and the amorphous, the former being the more common. The two types are often found in the same patient. The spongy form consists of coarse irregular striæ, arranged either as parallel trabeculae or running in the direction of normal lamellae of cancellous bone. The amorphous form is a generalised deposit, producing an opaque finely granular appearance. The diameter of the bone is increased, sometimes to a marked degree, and in the medullary cavity the trabeculae

are accentuated and too widely separated, giving a streaky appearance. The corticalis is partly or entirely replaced by bone similar to that seen in the medullary cavity, and in an extreme case the impression is that the whole bone consists of cancellous tissue highly magnified. Irregular cyst-like areas are sometimes observed. Widening and bowing of bones are important points in the radiological diagnosis. The vault of the skull is thickened, and the differentiation between the inner and outer tables is lost. Small islands of dense bone are evident alongside pale cyst-like areas. A large clean-cut area, *osteoporosis circumscripta*, may sometimes be noted. In those cases in which part of one bone is affected there is a definite line of demarcation where the abnormal ends and the normal begins. Thus there may be definite changes in the upper two-thirds of the tibia, while the lower third is normal. The average rate of progress of such a lesion is about 1 cm. in 2 years. Radiographs reveal the shadows of arterial calcification in more than 40 per cent. of cases. Such calcified arteries are best seen in the lower limbs. There is no evidence of a higher incidence of renal or vesical calculus in osteitis deformans than in the normal.

**Diagnosis.**—When advanced, the condition is unmistakable. In the early stages muscular rheumatism or osteo-arthritis may be wrongly diagnosed. Pulmonary osteo-arthropathy is distinguished by the clubbed fingers. In radiographs the amorphous type of osteitis deformans is sometimes mistaken for secondary carcinomatosis of the osteoplastic type. The difference is distinct and important, namely, that in carcinomatosis the bones are neither enlarged nor bowed. Syphilis of bones is now very rare, but when only one or two bones are involved in a supposed case of Paget's disease the Wassermann reaction should be performed.

**Prognosis.**—Because the disease is uncommon there is a tendency to regard its effects as dreadful. To announce the diagnosis as though it were a profound mystery may alarm both patient and relatives unnecessarily. Paget's disease is slowly progressive but does not usually shorten life. Thus, one patient, though much deformed, continued to drive a crane in a dockyard 15 years after the onset of the disease. Another was quite happy to have somebody hold him on a rock while he fished a stream, long after he was unable to walk unaided. Death usually results from the effects of arteriosclerosis or intercurrent infection, and only rarely from compression paraplegia or sarcoma of bone.

**Treatment.**—No known treatment alters the course of osteitis deformans in the slightest degree. Since the bones at one stage are sufficiently decalcified to bend, methods have been used which aim at increasing the calcium intake. The patient is given a high calcium diet, that is a diet containing 3 pints of milk or milk products daily, together with butter, cheese and eggs. If milk is not tolerated in these quantities, calcium caseinate or calcium lactate (10 g. a day) may be prescribed. Vitamin D may be conveniently given in the form of tab. calciferol (3000 units) one or two daily. The claim that prolonged exposure to general ultra-violet irradiation has resulted in increased density of the shadows of bones in radiographs has not been confirmed. Such treatment can be carried out, starting with short exposures to the mercury vapour or carbon arc lamp. Paget treated his patients with potassium iodide, but was not enthusiastic over the results. When there is pain in the bones Lugol's solution (of iodine in potassium iodide) may be given in milk, beginning with a dose of 3 minims three times a day, and increasing to ten times this amount. If iodine fails to relieve the pain, aspirin or tabs. codeine co. B.P. should be tried. Exploration of the neck for a parathyroid tumour is never justified. Osteotomy is rarely necessary, but it is interesting that when portions of bone have been removed for histological section relief of pain has sometimes occurred. Occasionally, and especially in those cases with secondary osteo-arthritis of the hip joint or knee joint, an ambulatory splint supporting the weight of the body on the tuber ischii is of value. A cork sole is often necessary, and when kyphosis causes pain a spinal jacket is useful.

## LEONTIASIS OSSEA

**Synonyms.**—General Hyperostosis of the Skull; Cranio-sclerosis; Megalophaly; Fibromatosis Osteoplastica Osseum.

**Definition.**—The term leontiasis ossea is now used in two senses, specifically a progressive sclerosing hyperostosis of the skull, and symptomatically when citis deformans and the various types of osteitis fibrosa happen to involve the nes of the calvaria and face.

**Ætiology.**—This is unknown. The fact that the disease commonly arises in the ion of the nasal sinuses has led to an erroneous view that it is infective in origin.

**Pathology.**—When Virchow suggested the use of the term "leontiasis ossea" cases of hyperostosis of the skull he had in mind fibroma molluscum in which sses of new connective tissue develop in the skin. He believed that the overgrowth bone in hyperostosis corresponded exactly to elephantiasis of the soft parts, and he ided to call these cases leontiasis ossea, not because the bone disease produced a nine appearance, but because he considered it to be analogous to the disease of : soft parts which did. The disease is very rare. It occurs in either sex, arising ally in early adult life. In most instances it begins in the nasal fossæ and sinuses, ough in some cases the origin is near the orbit or in the base of the skull. Dense ry bone appears and spreads slowly under the periosteum, being held up sometimes the region of the suture lines but ultimately breaking through and spreading in ny directions across the skull. The serum calcium and plasma phosphorus are rmal.

**Symptoms.**—The early clinical features include nasal obstruction, blocking of : lacrimal ducts and alteration in the shape of the face and jaws. Ultimately ge masses of bone, increasing in various directions, give rise to terrible disfigure- nt. The cavities of the mouth, nose and orbit may be greatly lessened. The eye- ls may protrude even beyond the lids, and blindness may occur from optic atrophy. ere may be loss of the sense of smell, and interference with the mobility of the ver jaw. Except in the later stages pain is unusual.

**Diagnosis.**—Paget's disease usually begins at 55, and the pelvis, spine and lower bs are nearly always affected. Generalised osteitis fibrosa leads to decalcification the whole skeleton, with a high blood calcium and low blood phosphorus. Focal itis fibrosa often shows multiple lesions scattered throughout the skeleton.

**Treatment.**—No treatment has any permanent effect though it may be possible remove some of the more disfiguring masses of bone.

## HYPERPARATHYROIDISM (GENERALISED OSTEITIS FIBROSA CYSTICA (see p. 501)

## FOCAL OSTEITIS FIBROSA

**Synonyms.**—Osteitis Fibrosa Circumscripta (Schmidt); Local Fibrocystic Dis- se; Benign Giant-celled Tumour; Osteoclastoma; Osteogenetic Myeloma; yeloid Sarcoma.

**Definition.**—A focal or multifocal disease of bone unassociated with constitutional mptoms or with any known endocrine disturbance.

**Ætiology.**—This is unknown. The disease occurs chiefly in adolescence, and is uch more common than is generalised osteitis fibrosa (hyperparathyroidism).

**Pathology.**—The lesions are benign, firm, grey or brown tumours. Histologically



they show osteogenetic fibrous tissue and giant cells which, of course, are osteoclasts. This explains the numerous synonyms which are used. The tumours sometimes expand the corticalis and may give rise to cysts lined by osteoclasts. Even when the lesions are multiple the rest of the skeleton consists of normal bone. The figures for serum calcium and plasma phosphorus are invariably normal, a finding in striking contrast to that of the generalised disease. The calcium balance is usually normal, and, taken in conjunction with the normal blood chemistry, this finding is strong evidence against hyperparathyroidism.

**Symptoms.**—The malady affects one or more bones, is usually not disabling, is of slow progress, and shows a tendency to become arrested. Pain is unusual and the disease is often symptomless until spontaneous fracture occurs. Severe cases of the multifocal type may show considerable deformity, especially of the pelvis, femora and skull.

**Radiographic appearances.**—In radiographs the principal changes are found in the ends of the long bones. Usually more than one-third of the shaft is affected by a fusiform enlargement composed of a pale cyst-like area divided by a few coarse trabecular strands. The cortex is thin and may be expanded. The periosteum and adjacent bone are normal. Radiographs taken with controls show that the whole skeleton apart from the lesions is normally calcified. The floor of the skull and the lower jaw may be affected.

**Diagnosis.**—The normal blood chemistry serves to distinguish the focal from the generalised disease. In adult cases it is sometimes difficult to differentiate between focal osteitis fibrosa and osteitis deformans, and it may then be necessary to follow the progress of the condition over a period of time before a definite conclusion is reached.

**Treatment.**—Fractures are treated in the usual way. If spontaneous fracture occurs in a long bone through one of the lesions, union is usually strong, and radiographs subsequently show that the pale cyst-like area of osteitis fibrosa becomes filled with bone. Exploration of the neck for a parathyroid tumour is quite unjustified.

## THYROTOXIC OSTEOPOROSIS (see Hyperthyroidism, p. 493)

## OSTEOMALACIA

**Synonyms.**—Mollities Ossium; Adult Rickets.

**Definition.**—A generalised disease of the skeleton in which there is defective calcification of osteoid tissue accompanied by an insufficiency of phosphates or calcium salts in the blood. The condition may arise in several ways, of which three will be described. In dietetic osteomalacia it is due to inadequate intake of vitamin D and calcium salts and in idiopathic steatorrhœa to impairment of absorption. In the Fanconi syndrome defective tubular reabsorption of phosphates leads to their excessive loss in the urine.

**Ætiology.**—Osteomalacia is rare in England. It is endemic over wide areas in Northern India, Japan and Northern China, and occurs sporadically in the Rhine Valley, Danube Valley, Vienna and certain parts of Italy, Switzerland, Flanders and the Balkans. Heredity plays no part. The disease pre-eminently affects women, and is likely to recur earlier and with greater severity with each successive pregnancy. It is a mistake however to suppose that pregnancy is essential in the ætiology. The malady is sometimes seen at puberty and is quite well known to occur, though rarely, in boys and men. In the majority of cases the symptoms begin between the twentieth and thirtieth year.

**Pathology.**—Rickets and osteomalacia are essentially identical. What difference

exists is merely that of age incidence. Osteomalacia is adult rickets. Morbid anatomists agree that in rickets and osteomalacia the essential abnormality is a deficient calcification of osteoid tissue. This deficiency is generalised throughout the skeleton. The broad osteoid seams in both diseases are due to deficiency of the calcifying mechanism, which should convert osteoid tissue into true bone. In osteomalacia the bones throughout the skeleton are so soft that they readily bend and cut with a knife like rotten wood. Spontaneous fractures are common. The blood chemistry is comparable in experimental rickets of rats, in children with rickets and in women with osteomalacia. The plasma phosphorus and sometimes also the serum calcium are diminished, and the serum alkaline phosphatase is raised. The occurrence of *fœtal* rickets has been proved in babies born of osteomalacic mothers.

**Symptoms.**—Pain is a prominent symptom. It occurs especially in the back and thighs, is aching in character and is worse in the winter months. The pelvis, thorax or long bones exhibit deformity in a haphazard way; one woman suffers in the pelvis, another in the ribs and a third in both. Besides the changes in the pelvis, marked deformities occur in the chest and spine. Severe kypho-scoliosis may reduce the height by several inches and cause the head and neck to sink downwards and forwards on to the chest. Deformities of the sternum and ribs give rise to marked prominences and depressions in the chest wall. *Coxa vara* and irregularly curved long bones are less common. The bones are soft and flexible, rather than fragile, so that bending is much more common than is spontaneous fracture, though both are well recognised. The patient develops a characteristic waddling gait, and muscular weakness may add to her incapacity. In many cases the pelvic deformities interfere with marital relations or with labour, Cæsarean section frequently being necessary. Tetany is common. The teeth are normal. The course of the disease may be fairly rapid, lasting several months, but untreated cases extend over many years. The patient then becomes bedridden, spontaneous fractures, anæmia, cachexia and bed-sores adding to her discomfort and to the difficulties of nursing.

**Radiographic appearances.**—The degree of lack of calcification in radiographs will vary with the severity of the disease, and it is therefore important to take radiographs with controls. In the slight cases the bones of the patient will be slightly more translucent than those of the control. The cortex will be less dense than normal, but the bone pattern, especially the trabeculation, will be accentuated by contrast. In the severe examples there will be little or no difference between the density of the bone and surrounding soft tissues, and the cortex will appear as a mere pencilled outline. The bone pattern will have disappeared, the long bones will bend and occasionally show fracture. All deformities, apart from fracture, are the result of weight stress or muscular action. The pelvis is tri-lobate, owing to the thrusts of the heads of the femora and sacrum. Lordosis is marked and kyphosis may be present. In severe cases the chest and ribs are usually deformed. The vertebræ are biconcave, having the appearance of fish vertebræ. In severe cases the vault of the skull may show numerous areas of uneven translucence, varying in size and shape but all fairly clean-cut. The spontaneous fractures are usually subperiosteal, and radiographs sometimes show pseudo-fractures. These appear as areas of complete translucence, running across the bone, the edges being quite clean cut and separated from each other by 1 or 2 mm.

**Diagnosis.**—The occurrence of pregnancy and the examination consequent upon this lead commonly to the recognition of the pelvic deformity and of the disease which has given rise to it. Differential diagnosis from other generalised diseases of the skeleton usually produces no difficulty. In hyperparathyroidism there is a high serum calcium, a low plasma phosphorus and an increased calcium excretion in the urine. In senile osteoporosis the patient suffers from kyphosis and a tendency to fractures particularly of the neck of the femur, and the blood chemistry is normal. In thyrotoxic osteoporosis, the usual signs of hyperthyroidism are present, and the

blood chemistry is normal. In multiple myeloma the Bence Jones protein is found in the urine in 75 per cent. of cases, the serum globulin is usually increased, and the albumin : globulin ratio diminished. The serum calcium is usually normal, but sometimes raised. The plasma phosphorus is normal, but it rises in cases showing renal insufficiency. In radiographs the condition may closely resemble osteomalacia.

**Treatment.**—Pure vitamin D is called calciferol because of its power to induce calcification in tissues, especially in osteoid tissue. It is 300,000 times as potent as cod-liver oil, weight for weight. The good effects not only of calciferol but also of cod-liver oil and ultra-violet irradiation have been noted both clinically and chemically, since they are capable of raising the serum calcium to normal. In cases where tetany is present, calcium salts should be administered in addition. The diet of a woman suffering from osteomalacia should contain 3 pints of milk a day, with plenty of milk puddings, eggs, butter, cheese, green vegetables and even nuts and raisins. The dose of cod-liver oil should be large, up to 2 or 4 oz. daily. This treatment relieves the pain in 3 to 4 weeks. Some cases are refractory, and it is then necessary to add 0.5 mg. of calciferol to the cod-liver oil daily. Tetany is rapidly removed by treatment with cod-liver oil and calcium lactate. A powder containing at least 10 gm. of the latter should be used daily, and is best administered fasting with a glass of milk. The patient should be exposed to sunlight when this is possible; otherwise treatment by ultra-violet irradiation may be used, starting with a short exposure to a carbon arc lamp and increasing gradually up to 30 minutes. There is no evidence that phosphorus is of any value in the treatment of osteomalacia. Where the disease exists in great endemic areas, questions of diet and social and religious customs are proving very difficult. In large areas of China and India the diet is often deficient in quantity, and inadequate in calcium and vitamin D. In the high mountain valleys of these countries and in areas of India where purdah is practised, darkness adds to the danger by causing further deprivation of vitamin D. With regard to China, Maxwell states: "We want flocks and herds, milk and meat, with security of life and property". The suggestion has been made that it might be practicable in India and China to dispense calciferol freely at a low price just as quinine is dispensed in malarial districts. The relation of ovarian function to calcium metabolism has not yet been settled. Osteomalacia gets worse during lactation, no doubt because of the great drain of calcium from the body. Improvement has been observed after ovariectomy. This operation may act merely by preventing pregnancy, and it is presumably just as reasonable to ligate the Fallopian tubes. The pelvic deformity may necessitate Cæsarean section.

#### OSTEOMALACIA IN IDIOPATHIC STEATORRHOEA

When osteomalacia occurs in the course of idiopathic steatorrhœa (Gee's disease), the following features may be present: fatty stools, dilatation of the colon, tetany, anaemia, skin lesions and infantilism (see p. 620). The disease occurs in both sexes and the history nearly always goes back to early childhood. The symptoms develop in spite of an adequate diet. We must, therefore, suppose that there is some disturbance of gastro-intestinal function resulting in deficient production, absorption or utilisation of one or more essential factors. The serum calcium is low and the plasma phosphorus is low or normal. The total fat in the stools may reach 40 per cent. or more, and the bulk of this is unsplit fat. The clinical and radiological features are exactly the same as in dietetic osteomalacia. An opaque enema will reveal dilatation of the colon. In treatment the fat in the diet must be cut down to a minimum, and the calcium salts and vitamins kept high. Vitamin D must be given in a solid and not in an oily medium. The prognosis of this type of osteomalacia is good, especially in young people. Splinting or even osteotomy may be necessary to correct deformities such as genu valgum. The pelvic deformity may necessitate Cæsarean section.

## THE FANCONI SYNDROME

**Synonyms.**—The de Toni-Fanconi Syndrome; Hypophosphatæmic Rickets with Renal Glycosuria; Osteomalacia with Renal Glycosuria.

**Definition.**—A rare form of osteomalacia readily identified by the presence of renal glycosuria and persistent amino-aciduria. The bone changes are due to excessive renal excretion of phosphates.

**Ætiology and Pathology.**—There is impaired tubular reabsorption of glucose, amino-acids, bicarbonate and phosphate, probably due to an inborn error of enzyme metabolism. It was first described in children by Fanconi in 1931 and was identified in adults and found to be hereditary in 1935. In some cases storage of cystine in the reticulo-endothelial system has been found at necropsy. Although the association of inhibition of growth and rickets with cystinosis has been known since the work of Lignac in 1924 the relationship between disturbances of cystine metabolism and the Fanconi syndrome is still imperfectly understood. The following amino-acids have been identified in the urine in abnormally large amounts: aspartic acid, glutamic acid, glycine, serine, alanine, threonine, valine, cystine, leucine, tyrosine, arginine, hydroxyproline and phenylalanine. The excessive drain of phosphates through the kidneys leads to a constant low level of inorganic phosphate in the blood, which may reach a figure of less than 1.0 mg. per 100 ml. As a result of this the ossification of osteoid tissue in the skeleton is always imperfect.

**Symptoms.**—The disorder is usually discovered in infancy even in babies of 2 months. Sometimes it does not make itself evident until adult life. In children the skeletal changes of rickets appear and there may be dwarfism and infantilism. Loss of appetite, polydipsia and polyuria are commonly present. The urine shows marked increase of ammonia, glucose from time to time, and albumin rarely; a variety of amino-acids can be identified by chromatographic methods (see above).

**Radiographic appearances.**—Radiographs of the bones cannot be distinguished from those of ordinary rickets. The changes include absence of calcification of the metaphyses with saucer-like splaying of the growing ends of the bones, extreme poverty of calcification of the cortex and spongiosa, deformities, fractures and poorly calcified callus. Where infantilism is present the state of development of the bones of the carpus is correspondingly delayed. In adults the spine shows well-marked osteoporosis, individual vertebral bodies being bi-concave. In radiographs the pelvis, the long bones and especially the bones of the hands and feet are very poorly calcified. The ivory corticalis is either reduced to a mere shell, or it retains its normal thickness and is greatly reduced in density. The spongiosa is deficient owing to disappearance of the smaller spicules, and in some places only the coarser trabeculae are left. Fractures and deformities are constant. Bowing of the humerus, radius and ulna is common, and bowing and twisting of the femur is found in many cases. Subperiosteal fractures unsuspected by the patient are seen in radiographs in every case. The pelvis is usually trifoliate owing to the thrust of the femora, and in advanced cases the deformity is grotesque. The extreme poverty of calcification sometimes progresses to such a degree that it is difficult in radiographs to distinguish between bone and soft tissue. Nevertheless, the skull is often little affected and usually shows only a fine mottled appearance.

**Prognosis.**—Fractures of bones recur and may be multiple. Extreme deformity of the thoracic cage usually ends in death from broncho-pneumonia. Though damage to the liver is not an invariable feature of the Fanconi syndrome focal necrosis, fibrosis and even primary carcinoma of the liver do sometimes occur even in children. Rarely the renal lesion progresses in such a way as to cause nitrogen retention and consequent death.

**Treatment.**—The osteomalacia responds imperfectly to vitamin D in large doses. A moulded steel spinal support or other orthopaedic apparatus may be needed. When there is acidosis due to loss of bicarbonate in the urine, sodium bicarbonate or citrate should be administered by mouth. Portal obstruction and hepatic or renal insufficiency will need symptomatic treatment.

## OSTEOGENESIS IMPERFECTA

**Synonyms.**—Fragilitas Ossium Congenita; Osteoporosis Congenita; Congenital Osteopsathyrosis; Osteopsathyrosis Idiopathica.

**Definition.**—A generalised disease of the skeleton in which the bones are so fragile that repeated fractures occur. Multiple fractures may occur *in utero* (pre-natal type of Vrolik, 1849), or fractures may not occur until after birth (post-natal type of Lobstein, 1833). The disease is congenital and in some 25 per cent. of cases hereditary. Both sexes are affected equally.

**Ætiology.**—This is unknown.

**Pathology.**—In both types the basic defect appears to be defective osteoblastic activity. The cortex of the bones may be scarcely thicker than paper, and the trabeculae of spongy bone are extremely thin. In the pre-natal type many fractures are seen; in some cases practically every bone in the body has been fractured. The older fractures exhibit good callus formation. In extreme cases, especially in the pre-natal type, the cranial ossification is so disorganised that the vault of the skull consists of a mosaic of small Wormian bones. Congenital hypoplasia occurs in other mesenchymal tissues, notably the ligaments and the sclerotics. There is no evidence whatever of vitamin deficiency. No abnormality in the serum calcium, plasma phosphorus or calcium output has been demonstrated. The plasma phosphatase tends to show a raised value but this is not constant.

**Symptoms.**—The general health of the patient is good but fractures occur from the most trivial violence or even normal muscle action. In the course of time, 20, 30 or even 100 spontaneous fractures may occur. They are often subperiosteal and cause little pain. The patient tends to be short in stature and slender in build. As a result of anomalous cranial ossification, the shape of the head is often striking. A bitemporal protuberance so marked as to turn the ears outwards is frequently observed, but protuberances in the occipital and frontal regions are also seen. Every bone in the body may be deformed. The limbs are often bowed and of unequal length. Kypho-scoliosis, distortion of the ribs and sternum and asymmetry of the pelvis all occur. Three other defects are commonly found in association with the fragile bones, namely, leaden blue sclerotics, a tendency to dislocation of joints, and after the age of 20 years otosclerotic deafness. Amongst the adult population affected with blue sclerotics approximately 60 per cent. have an associated liability to fracture, approximately 60 per cent. an associated otosclerosis and 44 per cent. suffer from all three defects. Osteogenesis imperfecta sometimes occurs in an hereditary form without blue sclerotics.

**Diagnosis.**—Severe cases and all those with blue sclerotics are unmistakable. In the new-born great shortening of the limbs may suggest achondroplasia, but the skull is quite different. Cases of spontaneous fracture in the adult occurring in hyperparathyroidism, hyperthyroidism, myelomatosis, osteoclastic carcinomatosis and neuropathic atrophy of bones really cause no difficulty.

**Prognosis.**—Severe cases of the pre-natal type are either stillborn or live only for a short time. In post-natal cases the condition proves more severe the earlier the first fracture appears. Multiple fractures in the first few years of life may lead to such deformities that the patient can never walk and may die before puberty. In those who survive, the liability to fractures tends to become less before puberty.

In general the longer the patient lives the greater will be the improvement, and in many of the adult cases the disability is slight only.

**Treatment.**—The utmost care must be taken to avoid the occurrence of fractures. Treatment consists in gentle handling and careful splinting. Union usually occurs without delay and is firm. Dislocations are reduced without difficulty. Vitamin D, calcium salts and a high calcium diet have no effect on the course of the illness.

## OXYCEPHALY

**Synonyms.**—Tower Skull; Steeple Head; Sugar Loaf Head; Acrocephaly; Craniostenosis.

**Definition.**—A congenital deformity of the skull due to premature synostosis of the cranial sutures. The skull is short from front to back and its vertical diameter is increased. Allied forms of craniostenosis are scaphocephaly, the boat-shaped head, and plagiocephaly, the obliquely flattened head.

**Ætiology.**—This is unknown. The disease is more common in males than females. It is sometimes hereditary and familial. It is usually present at birth but it may develop subsequently up to the age of 6.

**Symptoms.**—In its slightest form it attracts attention, while in its grosser forms there is no passer-by but is shocked by the disfigurement and repelled by its hideousness. The forehead is much increased in height, sloping gradually upwards to the vertex with feebly marked superciliary arches. The vertex of the skull appears pointed instead of flattened or rounded, and a thin bony prominence is sometimes felt in the region of the bregma. The hairy scalp may be raised above the normal level and present the appearance of being perched on the top of a cone. Viewed laterally, the ears appear placed on a lower level than normal. Proptosis is present in most cases, and it may be so considerable that the eyeballs become dislocated in front of the lids. Failure of closure of the eyes, especially during sleep, may lead to lachrimation and conjunctivitis. Divergent squint is common and nystagmus is present in some cases. *Symptoms arise from insufficient room within the skull for the developing brain.* There is increased intracranial pressure with headache and sometimes vertigo. The condition is compatible with normal intelligence, but not infrequently optic atrophy supervenes. This is secondary to papilloedema in some 85 per cent. of cases. In the remainder it is brought about by narrowing of the optic foramen and is of the primary type. The sense of smell is often completely lost, but taste is affected very rarely. Hearing is unaffected. The following associated congenital malformations have been described in a few cases: webbing of the fingers and toes; malformation of ears, elbow and shoulder joints and fingers.

**Radiographic appearances.**—Radiographs show an increased vertical diameter of the skull with its highest point either at the bregma or somewhere between it and the lambda. The anterior fontanelle closes late, and its site is marked by a slight protuberance over which the bone is thinned. The sutures of the vault are partly or entirely absent, but the basal suture between the sphenoid and the occipital bone may be widely open. The air sinuses are rudimentary, and the middle fossa bulges forward. The most characteristic feature is the presence of numerous deep convolutional markings.

**Prognosis.**—The optic atrophy, whether primary or secondary, may advance to complete blindness. There is nothing to show that oxycephaly shortens life.

**Treatment.**—Anodynes should be used in the relief of headache. If the symptoms of increased intracranial pressure become marked, and the changes in the optic discs progress, decompression may be necessary.

## DISEASES OF ENDOCHONDRAL OSSIFICATION

## ACHONDROPLASIA

**Synonyms.**—Chondrodystrophia fœtalis (Kaufmann); Micromelia fœtalis.

**Definition.**—A disease of fœtal life in which defective endochondral ossification makes the bones preformed in cartilage short, but stout and strong.

**Ætiology.**—This is unknown. Both sexes are affected equally. It is hereditary and has been recorded in six generations. Several members of the same family may be affected. The condition is unrelated to rickets, cretinism, syphilis or tuberculosis.

**Pathology.**—The essential abnormality is found in the cartilaginous epiphyses. The cartilage does not prepare itself for ossification, which is in consequence so slow that the long bones are too short. Since, however, the periosteum goes on laying down bone normally, the bones are stout and strong. The membrane bones of the skull are unaffected, so that the calvaria is of normal size. Premature synostosis of the cartilaginous bones at the base of the skull leads to shortening, and consequent depression of the bridge of the nose. The clavicles are not affected. The pelvis is distorted and contracted, the sacrum being tilted forwards. Extreme lordosis may be present. The costo-chondral junctions are enlarged to form a rosary. The scapula is so small that the glenoid fossa scarcely holds the head of the humerus.

**Symptoms.**—The patient is dwarfed but of normal intelligence. The usual height of the adult is about 4 ft. The vault of the head is large and the frontal and parietal eminences prominent. The face is small and the nose has a depressed and flattened bridge. The nostrils are large, the lips thick and the lower jaw and chin well developed. The teeth are normal. The trunk is of normal size but the extremities are much shortened, and with the arms at the sides the fingers reach no farther than the great trochanter of the femur. The humerus and femur are relatively more shortened than the other bones of the extremities, so that the proximal segments of the limbs show the most marked shortening. The arms are muscular and are held a little abducted from the trunk. The hands are short, thick and trident-shaped, the fingers being almost equal in length. The lower limbs are thick and often show deep transverse furrows as if there were redundancy of the soft parts. This appearance is due to the packing of well-developed muscles into the restricted long axis of the limb. This muscular development enables the achondroplastic to perform feats which are surprising in one so small. He rises from the lying-down position by a characteristic springing movement from the legs without any assistance from the arms. The curving and enlargement of the ends of certain bones gives rise to bow legs and beading of the ribs. The lumbar curve is increased owing to tilting forward of the sacrum and excessive development of the buttocks. In consequence the gait has a peculiar duck-like waddling character. The genital organs are normal. The fact that the female may become pregnant makes the pelvic deformity of great importance. The conjugate diameter is greatly narrowed, and it is almost impossible for an achondroplastic woman to give birth to a living child except by Cæsarean section. That the disease has existed for something like 5000 years is known from models found in mummies of two achondroplastic gods of ancient Egypt, namely Ptah-Sokar and Bes. In the Middle Ages the attractive antics of achondroplasias made them much sought after as court jesters or dwarfs. To-day not infrequently they play the parts of clowns at fairs, circuses and music-halls, and sometimes break chains on the stage.

**Diagnosis.**—In the new-born the great shortening of the limbs may suggest osteogenesis imperfecta, but the skull is quite different. In childhood the malady is readily distinguished from rickets and congenital syphilis by careful attention to the physical signs. Achondroplasia differs from cretinism in that the patient is of

average intelligence, and has normal skin, hair and voice. The pituitary dwarf presents no difficulty because the limbs and trunk are in perfect proportion.

**Prognosis.**—The majority of infants suffering from achondroplasia are either still-born or die shortly after birth. If the child does survive, the expectation of life is normal. The female achondroplastic faces greater risks in parturition than a normal woman.

**Treatment.**—No treatment is of any avail. Orthopædic treatment for bow legs is unnecessary. The pelvic deformity may necessitate Cæsarean section.

## DYSCHONDROPLASIA

Three clinical conditions are included under this heading. In all of them islands of ectopic cartilage are found giving rise to multiple *ecchondromata* or *enchondromata*. The three conditions are grouped together because of one feature they have in common, namely, arrest or perversion of the normal process of endochondral ossification in certain bones. This change differs from that seen in achondroplasia only because it is neither symmetrical nor universal. Different manifestations of dyschondroplasia may occur in various members of the same family.

(i) *Hereditary multiple ossifying ecchondromata (hereditary deforming chondrodysplasia, diaphysal aclasis or multiple exostoses)*. This is a fairly common disease in which multiple bony tumours are found in association with certain other skeletal deformities. It is hereditary and may affect several individuals of the same family. It is more common in males than in females in the proportion of 3 to 1. It is usually discovered in childhood. Palpable bony tumours up to 2 cm. or more across are found more or less symmetrically placed near the knee, shoulder, hip, ankle and wrist. The scapula, ribs and pelvic bones may sometimes be affected. The stature is shortened and the limbs may be unequal in length. In the majority of cases the ulna and fibula are disproportionately short in relation to the radius and tibia. Bowing of the radius, ulnar deviation of the hand, irregular length of the fingers and valgus deformity of the foot all may occur. Sarcoma supervenes in 5 per cent. of cases. Local exacerbation of symptoms in a patient over 30 years of age may be the first indication of its onset. Rarely, pressure of an exostosis upon the spinal cord may cause paraplegia, or upon a nerve trunk pain or local paralysis. Aneurysm has been recorded from pressure upon an artery. The radiological appearances are characteristic. The metaphysis of the bone affected is broadened and distorted, and ossifying *ecchondromata* with broad bases and pointed tips project from it. The cartilaginous cap of the tumour is not seen unless it is calcified. The earlier the *ecchondroma* occurs the nearer to the centre of the shaft will it be. Where *ecchondromata* protrude between adjacent bones such as the tibia and fibula, local fusion may occur. The ulna is likely to be short and to end in a point, articulating with the radius on its mesial aspect but not partaking in the carpal articulation. Usually no treatment is required but should it be necessary to remove any particular swelling this is easily carried out.

(ii) *Multiple chondromata (Enchondromatosis)*. This is a rare disease affecting the bones of the hands and feet. Cartilaginous swellings in the fingers and toes begin in childhood and increase in size up to the age of 30 years. The swellings are firm, elastic, rounded and slightly translucent. The skin over the larger ones may be tightly stretched and shiny and show prominent veins. The hands and feet may become hideously deformed. Sometimes a rib near the costal cartilage, the sternum, the pelvis and the scapula are affected. In certain cases the ulna and fibula are disproportionately short as in diaphysal aclasis. Spontaneous fractures may occur, and sarcoma may supervene after years. Radiologically *chondromata* are seen as rounded, eccentric, translucent areas expanding the corticalis, interrupting its outline and projecting into the soft tissues. Sometimes the swellings are trabeculated and they may



contain dense, punctate, calcified areas. Where operation is undertaken to excise some of the chondromata care must be exercised to avoid spontaneous fracture of the phalanges or metacarpals.

(ii) *Unilateral chondrodysplasia (Ollier's disease)*. This is a very rare type of chondrodysplasia occurring in children and sometimes familial. It usually has a completely unilateral distribution, but some cases have only one bone or one limb affected, and others are bilateral. Some abnormality is often first noticed between the first and second years of life, when, as a rule, one limb is found to be shorter than its fellow. The difference in length becomes progressively greater as growth proceeds. Deformity may occur either because weight bearing causes bending of the bone, or because of the different rate of growth where only one of the paired bones is affected. Most patients seem to reach adult life, when their symptoms are mainly those of their deformities and sometimes of a secondary arthritis. In a small proportion of cases sarcoma supervenes. The diagnosis largely depends upon examination of radiographs. The ends of the long bones show translucent longitudinal striæ, interrupted by small pale mottled areas and dark punctate spots. In the areas affected there is extensive alteration in the pattern of the corticalis and spongiosa, but the centre of the shaft remains normal. As the child grows older the typical striped appearance disappears and is replaced by dense punctate speckling due to areas of calcification. The disease has occasionally been mistaken for osteitis fibrosa, but the radiological appearances are pathognomonic. Treatment is concerned with the prevention and relief of deformities, and proceeds along the usual orthopædic lines. Osteotomy is sometimes necessary. Fractures are of fairly common occurrence, and like the osteotomies appear to unite well.

## DISEASES OF THE BONE MARROW

### MULTIPLE MYELOMA

**Synonyms.**—Myelomatosis; Kahler's Disease; Plasmacytoma; Hæmatogenous Myeloma.

**Definition.**—A fatal disease characterised by the development of multiple tumours in the skeleton, which arise from cells of the bone marrow. It is very rare. The bones are affected in the following order of frequency: spine, ribs, sternum, skull, scapula, pelvis, clavicle, humerus and femur.

**Ætiology.**—Multiple myeloma is of unknown origin. It is a malignant neoplasm of the hæmatogenous marrow occurring in multiple foci. The disease is related to leukaemia, but differs from it in the sharper localisation of the neoplasia, the absence of enlargement of the spleen or lymph-glands, the much smaller tendency for the abnormal cells to enter the blood stream and the frequent appearance of Bence Jones protein in the urine. Intermediate forms occur with features of both diseases. It is associated with interesting alterations of protein metabolism. The disease is sometimes familial. It begins typically at the age of 55, and only 10 per cent. of cases occur before 40. The sexes are affected in the proportion of 3 men to 2 women.

**Pathology.**—Multiple deep red or reddish-grey sharply defined tumours are found distributed throughout the red bone marrow. They are usually a few millimetres in diameter and very numerous. Occasionally a tumour may reach a diameter as great as 5 cm. They are composed of blood-forming cells, which resemble plasma cells. They erode bone, sometimes expand the cortex, and cause deformities and spontaneous fractures. Rarely a diffuse hyperplasia of the marrow is associated with foci of tumour formation. Tumours may also be found outside the skeleton in the tonsils, liver, spleen, kidneys or sex-glands, and these lesions may even precede those

in the bones. The marrow tumours give rise in the urine to the Bence Jones protein which appears as a cloud when the urine is heated to 55° C., redissolves at 85° but reappears on cooling. It is found in 75 per cent. of cases, from a trace to a large amount. In some cases it appears early in the disease, in others late. Its occurrence may be continuous or periodic. Sometimes a substance allied to amyloid material is deposited in the muscles and in nodules connected with the periosteum, bursæ, tendon sheaths and joints. It is possible that both the Bence Jones protein and the amyloid substance are produced from the breakdown of myelomata. The serum globulin is usually increased even as much as to 8 per cent. (normal 2 per cent.). The albumin-globulin ratio may drop from the normal 2.2 to a figure as low as 0.5. The formol-gel reaction is positive (see p. 267), and there is a very rapid rate of sedimentation of the blood. Metastatic calcification while by no means constant has been frequently observed in the kidney, lung, stomach, myocardium and uterine mucosa. The serum calcium is usually normal, but, taking into account the bone destruction which occurs as the result of erosion by the marrow tumours and also the metastatic calcification, it is not surprising that high serum calcium values have sometimes been recorded. Figures from 13 to 16 mg. per 100 ml. have been found. Those cases with a normal serum calcium have a normal calcium output, while those with a high serum calcium have an output up to double the normal. Where renal insufficiency complicates multiple myeloma the plasma phosphorus is found to be high and may rise as the kidney condition becomes worse. The parathyroids are not enlarged in multiple myeloma.

**Symptoms.**—The initial symptom is pain, often bilateral, in the thoracic, abdominal and lumbar regions, and sometimes in the neighbourhood of the joints. Progressive kyphosis or angular curvature of the spine with loss of total height follows. The spine, sternum and ribs may be tender on percussion. It is unusual for any of the myelomata to be palpable. In 60 per cent. of all cases spontaneous fracture occurs in the ribs, sternum or later in the long bones. In no other type of bone tumour does pathological fracture occur so frequently. In some cases amyloid masses may be palpable as firm, rounded, slightly tender, subcutaneous nodules more than a centimetre in diameter. They are felt especially in the scalp, along the spine, near the joints and in the musculature, particularly that of the pelvic and shoulder girdles. There is usually a hypochromic anaemia, which becomes aggravated in the terminal stages. In a few instances cells of the type which constitutes the tumour enter the blood-stream in larger or smaller numbers, and it is probable that they can be found in the majority of cases if a sufficiently careful search is made. In rare instances the anaemia is of the leuco-erythroblastic type. Nephritis without hypertension is fairly common. The temperature is usually normal, but recurring fever has been observed. The patient ultimately becomes bedridden and cachectic. It seems justifiable on clinical grounds to consider separately what may be called the vertebral form of the disease. Here the growth is confined for some time to the vertebral and extradural tissues. Moreover, death may occur before the growths become widespread, and sometimes without the Bence Jones protein having appeared in the urine. In this variety the patient rapidly develops signs of a transverse spinal lesion with blockage of the spinal canal. The thoracic cord is usually the site of compression and there is focal spinal tenderness. Radiographs show destruction of the corresponding vertebral body.

**Radiographic appearances.**—In radiographs the marrow tumours are found mainly in the spine, ribs, sternum and skull. They are seen as clean-cut elliptical or circular areas of complete translucence, set closely together and varying from 1 mm. to 5 cm. in diameter. The large tumours may expand the cortex of the bone affected. There is a good deal of generalised osteoporosis throughout the affected bones. The spine shows collapse of the bodies of one or more vertebrae. The skull is not thickened. Spontaneous fractures, especially in the ribs, are very common.

**Diagnosis.**—Once the lesions have appeared in many bones the diagnosis is easily made. The age of the patient, multiple involvement of the bones of the thoracic cage, spontaneous fracture of a rib, Bence Jones protein in the urine, progressive anaemia, cachexia and characteristic radiographs make an unmistakable clinical picture. Biopsy of a portion of bone or examination of a bone-marrow smear from a sternal puncture may reveal the characteristic myeloma cells. Secondary carcinomatosis of bones may cause difficulty, especially in cases in which the primary growth is symptomless. It is essential to differentiate the disease from generalised osteitis fibrosa (hyperparathyroidism). There is some resemblance in the clinical picture as it affects the skeleton, but the presence of the Bence Jones protein and the blood chemistry are characteristic. In multiple myeloma the serum calcium is usually normal. If it is high it is associated with a high plasma phosphorus, whereas the characteristic effect produced by parathyroid hyperfunction is a high serum calcium with a low plasma phosphorus. In osteomalacia the patient is usually a woman in the child-bearing period of life, and a good deal of bending occurs in the bones. The blood chemistry is characteristic. Sometimes in the early stages of multiple myeloma widespread pain in the thoracic, abdominal and lumbar regions may lead to a mistaken diagnosis of fibrositis. In tuberculous caries of the spine neither the ribs nor the sternum are involved. The fact that the Bence Jones protein is found in the urine in an occasional case of leukaemia need cause no mistake. In those cases in which nephritis complicates multiple myeloma the albuminuria may cause difficulty. The Bence Jones protein may be detected in the presence of albumin by making the urine slightly acid with acetic acid, boiling it and filtering while hot, using a funnel with a hot-water jacket. If Bence Jones protein is present the filtrate will become cloudy as it cools.

**Prognosis.**—The prognosis is hopeless. Death often occurs within 6 months of the onset of symptoms, but occasionally a patient survives for 2 years or more. Broncho-pneumonia, cachexia or compression paraplegia with ascending pyelonephritis are the usual terminal events.

**Treatment.**—The patient should be treated by rest in bed, anodynes and suitable splinting when necessary. Occasionally deep X-irradiation can be used with good effect. It alleviates pain and reduces the size of the tumours, but it does not retard the progress of the disease. It is clearly unjustifiable to explore the neck in search of a parathyroid tumour. When the symptoms and signs point to compression of the spinal cord surgical intervention may be worth while. Laminectomy reveals a grey or reddish-grey extradural mass either pushing the cord backward or encircling it. Removal of the mass decompresses the cord and is followed by improvement. Deep X-irradiation and the wearing of a spinal brace are advised after laminectomy.

## GAUCHER'S DISEASE

In 1922 Pick discovered a gross osseous form of Gaucher's disease. It is exceedingly rare. The symptoms are pain in the bones, spontaneous fractures and sometimes angular deformity of the spine. Limitation of movement of the hip joint is sometimes found. In radiographs the bones show patchy osteoporosis. A characteristic feature is that the lower ends of the femora are widened evenly. Both skull and pelvis may be involved. Sometimes scattered through the bones there are focal, pale, rounded areas which expand the cortex. These areas are deposits of kersin, a galactolipin. The usual characteristics of Gaucher's disease are, of course, present (see p. 784).

## HAND-SCHÜLLER-CHRISTIAN'S DISEASE

The . . . of . . . Schüller-Christian's syndrome (lipoid granulomatosis or not confined to the calvaria, the orbit or the sella turcica

(see p. 783). Erosions of the maxilla and mandible have been described, resulting in loosening or falling out of the teeth. Erosion of the petrous bones may lead to a syndrome simulating otitis media, and bilateral deafness has been observed. Large areas of rarefaction have been described in the long bones of the extremities, and in the spine, pelvis, ribs and clavicles. Pain may occur in the bones affected, especially the head, pelvis and thigh. Spontaneous fracture is not uncommon. When the pelvis is involved there may be deformity, including shortening of one lower limb. In some cases the skull escapes entirely, diabetes insipidus and exophthalmos being absent. Radiologically the deposits of cholesterol-ester are seen as irregular clean-cut translucent areas sometimes with a few coarse trabeculae. In order to distinguish the condition from multifocal osteitis fibrosa it may be necessary to excise a portion of bone for histological section. The lesions tend to yield temporarily to treatment by X-irradiation.

DONALD HUNTER.

## SECTION XVII

# DISEASES OF THE SKIN

## INTRODUCTION

SKIN diseases are essentially similar in their pathology to diseases of other organs or tissues. Congenital anomalies, acquired inflammatory, degenerative and neoplastic processes affect the skin; but the skin is peculiar in that it is exposed to changes of environmental conditions, to physical and chemical traumata, and to invasion by many different organisms. Skin diseases are under the patient's direct observation to a greater extent than occurs with any other organ; the lesions are often scratched and rubbed, with the result that secondary changes of infection and thickening may be superimposed. Self-treatment and over-treatment with topical applications often have unfortunate results and may mask the original pathological process. Many so-called skin diseases are, in fact, physiological reactions which have become fixed or which are excessive and too easily induced; others are pathological modes of reaction of the skin to different stresses.

It is assumed that the reader is conversant with the anatomy, histology and physiology of the skin, and with the descriptive terms used in dermatology. A few remarks about the functions of the skin are, however, relevant to the subsequent discussion of cutaneous pathology.

The skin protects the organism as a whole from any harmful environment. The epidermis acts as a tough outer covering, protecting the layers beneath from excessive insolation, minor traumata and infection: the sebum lubricates the horny layer and has bactericidal properties by virtue of its fatty acid content; the sweat helps to keep the body temperature steady and emulsifies the sebum and helps to spread it over the body surface. If the epidermal barrier against infection is breached, the mesenchymal defensive mechanisms come into play, with dermal and hypodermal vascular dilatation, and the passage of leucocytes and tissue cells into the infected area. The cutaneous blood vessels conserve body heat by contracting and dissipate it by relaxing, so acting as a thermostat: they also help to keep the blood pressure steady. The dermal collagenous and elastic fibres give the skin its tough yet elastic character and enable it, at least in youth, to conform to the underlying tissues.

The sensory end-organs in the skin provide for accurate localisation of touch and a delicate perception of slight variations in temperature: these set into play a chain of involuntary reflexes and voluntary actions.

The skin is an organ of antibody formation, a fact made use of in the Mantoux, Dick, Schick and other tests: it is also the organ of vitamin D synthesis from solar irradiation of sterols in the upper layers of the dermis. Its functions of excretion and of respiration are minimal and need not be considered, but its power of absorption is most important: some drugs and other chemicals can have serious or even lethal effects by this route.

Two other functions of the skin are important to the practising physician. In all communities, primitive or civilised, the skin is the chief organ of display: some cosmetics, particularly those of a synthetic nature used in civilised communities, may cause inflammatory reactions in a few individuals. The skin is also the chief organ of emotional expression, various feelings being portrayed by alterations in tone of the cutaneous blood vessels, in the amount of sweating, hair erection, etc., with secondary effects on the sebum, epidermis and dermis.

**THE DIAGNOSTIC APPROACH.**—Bearing the above facts in mind, it will be appreciated that the approach to dermatological problems has to be somewhat different from that of "internal" medicine. The ætiology of many skin diseases and reactions remains obscure; often several ætiological factors operate together or in sequence. Variations of individual reaction to a particular agent, for example a drug, are marked; on the other hand, various physical, chemical, emotional, malnutritional and infective noxæ may in the one individual produce eruptions closely similar to each other.

In the sections that follow, skin diseases have been grouped according to their causes when these are known; when the cause is vague or unknown, they have been grouped according to the presenting symptom or sign, this being the most practical way of considering the differential diagnosis, just as it was in the days of Robert Willan.

It is essential first to obtain certain historical data in every case. Only the patient knows the duration, site of onset, original appearance and the manner of spread of the malady: whether there have been previous attacks, and what the past treatments have been with their effects. It is legitimate to ask the patient what he believes to be the cause when an irritant contact is suspected. The patient is now examined in routine, head to foot fashion, unless the condition is obviously local, and further questioning depends to some extent on the nature and distribution of the lesions. Suitable subheadings to the history include family history, past history, general health, personal history, domestic and occupational history: special attention is directed to racial characteristics and to the presence or absence of evidence of emotional instability.

On inspecting the skin, it is necessary to decide the nature of the eruption: erythematous, macular, squamous, papular, vesicular, bullous or some combination of these; granulomatous, nodular or ulcerative; hyperpigmented or depigmented, and so on. This should enable the diagnosis to be narrowed down to a few possibilities. The final diagnosis is then attempted from a consideration of the colour, morphology and anatomical situation in the skin of any elementary lesion that may be found, and from the grouping and distribution of the eruption as a whole, and the presence of secondary changes, if any. Most dermatoses can be diagnosed on clinical evidence alone without the necessity for any pathological tests or biopsies. These tests should only be used as ancillary aids in diagnosis, prognosis and treatment.

## SENSORY DISORDERS

*Excessive sensibility* (hyperæsthesia) without obvious skin changes occurs in some disorders of the nervous system (*q.v.*). It also occurs in certain skin tumours, especially glomus hæmangioma and leiomyoma, and in certain inflammatory conditions, for example, periarteritis nodosa.

*Lack of sensibility* (anæsthesia) is found with certain diseases affecting the nervous system, particularly syringomyelia, leprosy, tabes dorsalis, peripheral neuritis and hysteria.

In syringomyelia there may be anæsthesia with trophic changes in the skin of the fingers (Morvan's disease). The shiny, anidrotic skin is liable to become infected leading to destructive changes. The discrimination between heat and cold is lost, and the sensation of touch diminished or lost. Burns may easily occur.

In leprosy depigmented or lupoid, anidrotic, anæsthetic or paræsthetic areas of skin may be found, loss of touch, heat and cold being the earliest sensory changes.

In tabes dorsalis perforating ulcers of the foot are the commonest manifestations of the sensory disturbance.

In diabetes and other forms of peripheral neuritis, glossy skin and perforating ulcers may occur, sometimes complicated by arteriosclerotic ischæmic effects.

In hysteria, glove and stocking anæsthesia is a common symptom, and the presence of Charcot's triad of palatal anæsthesia, conjunctival anæsthesia and suggestion anæsthesia is strong circumstantial evidence suggesting that a dermatosis is being hysterically produced or maintained.

*Abnormal sensibility* (paræsthesia) occurs in a large number of skin diseases, as itching (pruritus).

## PRURITUS

This term is used to describe general or local itching of the skin in which there is either no obvious local cause or physical sign or in which such physical signs as exist are secondary and due to rubbing (lichen simplex), scratching, excoriation, infection or over-treatment.

### GENERAL PRURITUS

**Ætiology and Pathology.**—Generalised itching more commonly occurs in the elderly and is thought to be due to arteriosclerotic changes in the central nervous system. There may be some atrophy of the skin, but this is often seen without pruritus and it probably has no connection with the symptom.

Histologically no changes are observed in the skin except possibly some degree of coincidental atrophy and the effects of physical damage.

**Clinical Picture.**—The patient complains of itching and tingling of the skin, particularly when getting dressed or undressed or a few minutes after getting into bed. Hot baths or proximity to a fire aggravate the condition. Loss of sleep increases the sense of irritability and helps to establish a vicious circle. There may be no physical signs even when the patient complains bitterly of the distress and loss of sleep: or there may be scratch marks, excoriations and areas of lichenification, eczematization and even some degree of infection.

**Course and Prognosis.**—In the idiopathic senile variety the prognosis as regards cure is poor, though longevity is not affected. In all other varieties the prognosis depends on the cause.

**Diagnosis.**—General pruritus may be a symptom of diabetes, jaundice, uræmia or gout; of intoxication by cocaine or opiates including codeine; of leukaemia or Hodgkin's disease; of cutaneous reticulosis; or carcinomatosis. Pediculosis and scabies must be excluded; itching around the shoulders may be due to pediculosis capitis or corporis; the underclothes should always be inspected for lice and nits, particularly at the seams: louse infestation is more often secondarily infected than is "idiopathic" pruritus. The patient must be questioned as to the occurrence of whealing; there may be none at the time of examination, or dermatographism may be demonstrable. General pruritus may be of emotional origin, especially when there is frustration or deprivation of affection. If there are excoriated papules, the diagnosis of dermatitis herpetiformis must be considered.

**Treatment.**—The patient, if retired, should be kept fully occupied so as to distract attention from the skin as much as possible. Sudden changes of temperature must be avoided. Baths should be pleasantly warm, not hot, and 4 oz. of bicarbonate of soda may be added to a 25-gallon bath to relieve itching. Woollen underclothing should not be worn in direct contact with the skin. Condiments, strong hot tea and coffee, and over-indulgence in alcohol must also be proscribed. Sedatives such as phenobarbitone, promethazine hydrochloride or butobarbitone are useful, and in milder cases a bromide and valerian mixture. Opiates should not be given.

For local treatment if the skin is dry, hydrous ointment is useful, or equal parts of glycerine of starch and lanolin. In other patients a lead and calamine lotion or a

lead and glycerin lotion can be used, but tar, phenol, menthol, antihistamines and benzocaine derivatives are best avoided.

### LOCALISED PRURITUS

This may occur without physical signs or friction may produce the condition known as lichen simplex (q.v.). This is of variable appearance according to its situation. The commonest sites are the scalp, the back and sides of the neck, the eyelids, brows or perioral region, behind and above the ears, the elbows, wrists or palms, the external genitalia, the medial aspects of the thighs, the lower parts of the calves and the feet.

### ANOGENITAL PRURITUS

This may occur as pruritus ani in either sex, as scrotal and perineal pruritus in the male, or as vulvar pruritus or combined anal and vulvar pruritus in the female.

### PRURITUS ANI

Pruritus ani is often present without physical signs; if any signs are present they may be either the cause or the effect of the symptom.

**Etiology.**—Often the itching starts from some transitory cause but continues after this has been removed, in part owing to a vicious circle of scratching and further itching, and in part owing to the relief of emotional tension that seems to be provided in some individuals from this practice. Anal irritation may be due to rectal, anal or cutaneous conditions, to diabetes or to drug intolerance. Proctitis with irritating discharge is an occasional cause. Threadworms in the rectum pass into the anal canal for oviposition and cause intense itching. Piles and anal fissures are other common causes but cutaneous tags resulting from fibrosed piles should not be removed in an attempt to give relief. On the skin, lack of cleanliness, monilial and fungous infections, and *Phthirus pubis* infestation, may be responsible, or the condition may have arisen from sensitisation to local applications, from drugs such as phenolphthalein taken internally, from the disturbance of intestinal flora, and the encouragement of monilia by the use of antibiotics such as chlortetracycline or chloramphenicol, or, rarely, from skin diseases such as lichen planus. Patients with pruritus ani often suffer from localised hyperidrosis which aggravates the condition by the discomfort it causes and by its encouragement of fungous and other infections. In resistant cases without physical signs or with lichenification, an emotional factor may be the most important; this may take the form of inadequately expressed rage and aggression, or it may be symptomatic of a passive homosexual tendency.

**Clinical Picture.**—The skin may look normal or there may be scratch marks and deep furrowing and ridging from lichenification. There may be a sodden condition of the anal "funnel" or there may be a patch of lichen simplex 2 or 3 in. on one side of the anus. The psychogenic form may be accompanied by a tendency to exhibitionism, shown by the wearing of effeminate clothing as well as by an exceptional enthusiasm for being repeatedly examined by the doctor.

**Treatment.**—If no obvious cause can be removed the treatment is symptomatic by bland local applications, sedatives and, in the most resistant cases, X-irradiation, in exposures of 50 r or 75 r on up to four occasions at weekly intervals. When lichenification is present thorium-X applications may prove as effective as X-rays and they carry no serious hazard of post-irradiation skin changes. The constant application of first one and then another remedy to the itchy anus must be discouraged, as only increasing introspection. A good standard of cleanliness is important but medicated soaps or antiseptics should not be used. The skin should be dried carefully without friction from a towel, and a dusting powder of talc and boric acid applied.



The best local applications are hydrous ointment or a thin zinc cream to which 1.0 per cent. of phenol may be added; or if any infective element is present magenta paint may give good results. Antihistaminic creams and benzocaine derivatives are best avoided. Good results are being claimed from the use of hydrocortisone ointment.

Aperients, particularly phenolphthalein and aloes, may aggravate the condition, and the patient should avoid them or use only liquid paraffin. Strong coffee and condiments are best avoided.

Psychoanalytical procedures are rarely of value in pruritus ani, nor are nerve undercutting operations or anæsthetic injections a logical or effective procedure.

### SCROTAL AND PERINEAL PRURITUS

Here a fungous cause may be apparent. There may be hyperidrosis. Friction from clothing may aggravate the condition and sensitisation to dyed material may start it. Pruritic scrotal dermatitis may also arise with diets deficient in protein, iron and vitamin B complex; but in the majority, no local cause can be determined. In psoriasis and lichen planus scrotal lesions may be present but they are rarely more than the local manifestations of the general disorder. Lichen simplex is often observed with or without eczematization and infective changes.

Dietetic adjustments and antifungous measures may be indicated, and disorders such as seborrhœic dermatitis, lichen planus and psoriasis are treated on general principles. For lichen simplex in the perineum or on the scrotum bland local applications such as oily calamine lotion or hydrous ointment are preferable to antihistaminic creams which have a tendency to sensitise the skin. Local anæsthetic (benzocaine) applications have strong sensitising properties and may cause a severe eczematous dermatitis which adds to the patient's distress. Thorium-X in spirit in a concentration of 1500 c.s.u. per ml., applied at fortnightly intervals on up to six occasions, may help. X-rays may be used in fractional doses but are best avoided on the scrotum. If they are used here, it is wise to use very small (33 r) individual exposures up to a total of 100 r only.

In addition to these local measures an attempt should be made to relieve sexual maladjustments if present. This is more likely to succeed with scrotal than with perineal or anal pruritus.

### PRURITUS VULVÆ

This term is sometimes applied to dermatoses of the genitocrural region and medial aspects of the thighs, as well as, more correctly, to strictly vulvar conditions.

**Ætiology and Pathology.**—The causes include vaginal discharges due to trichomonas or monilial infections, nutritional deficiencies, drug intoxications, particularly from oral chloramphenicol or chlortetracycline, threadworms (in children), glycosuria, psychosexual difficulties, contact sensitisation to contraceptive jellies, vaginal douche solutions, or to the rubber of contraceptive appliances, to lack of cleanliness or to the excessive use of antiseptics, to *Phthirus pubis* infestation. Localised dermatoses that may be responsible include psoriasis, seborrhœic dermatitis, lichen planus, atrophic senile vulvo-vaginitis, Bowen's precancerous dermatosis; but in all these conditions as well as in lichen simplex there is a possibility of the dermatosis being the result of friction rather than the cause of the pruritus. A most intractable form is that due to lichen sclerosis et atrophicus; this is an atrophic, sometimes bullous condition of the vulva, perineum and perianal skin, often with similar lesions elsewhere.

**Clinical Picture.**—There may be no abnormal physical signs or there may be lichenification, excoriation, boils or impetiginous lesions, or a superimposed mixed contact and infective dermatitis resulting from faulty treatment.

**Treatment.**—This depends on the cause and may consist of the control of diabetes or of a trichomonas infection, the relief of an emotional conflict, the removal

of an offending drug, the avoidance of a contact irritant or the provision of an adequate diet. A drug such as phenolphthalein may cause a fixed erythema at the vulva, with pruritus; or drugs such as chloramphenicol or chlortetracycline may by removing competitors encourage multiplication of monilia, the pruritus in these circumstances being caused by a monilial vulvo-vaginitis, or by vitamin deficiency from the destruction of intestinal organisms having the property of synthesising vitamin B.

Ample sedation with barbiturates is necessary to prevent the establishment of a vicious circle of friction, lichenification and infection, and more friction. It must be remembered, however, that barbiturates can, though rarely, themselves cause pruritus vulvæ.

Local treatment depends on the type of reaction observed. If there is any infection, magenta paint or Vioform cream are usually effective in the less severe forms due to monilia and *Staphylococcus saprophyticus*, and a wide spectrum antibiotic such as chlortetracycline, oxytetracycline or chloramphenicol in frankly pustular, furuncular or impetiginous forms. A 1·0 per cent. solution of cetrimide is useful as a cleansing agent. For vulvar boils the application of a 75 per cent. industrial spirit with 1 per cent. brilliant green and 0·1 per cent. mercuric chloride is useful. For lichen simplex, hydrous ointment, zinc cream or ether-soluble tar paste (Martindale) may be used. Antihistaminic creams are probably no more effective than the base in which they are incorporated and their use carries with it some risk of the development of cutaneous sensitisation. Benzocaine anæsthetic applications are contraindicated because of their powerful sensitising properties. The use of œstrogen creams is restricted to cases of senile vulvo-vaginitis with atrophy. For pruritus vulvæ with lichenification thorium-X in a strength of 1500 e.s.u. per ml. of spirit, applied fortnightly, is sometimes effective, as is X-irradiation given in exposures of 75 r weekly on up to four occasions. For Bowen's disease, excision is preferable to radiotherapy owing to the relative radio-insensitivity of this dermatosis.

Psychogenic forms may respond to the relief of conflicts over sexuality, these usually being due to a guilty liaison or to fear of pregnancy, venereal disease or cancer.

## PRURIGO

Prurigo is a term used for a group of intensely itchy conditions in which the predominant physical signs are lichenification and excoriated papules. Lichenification is produced by friction and presents as terracotta thickened skin with accentuation of the contrast between the normal diamond-shaped elevations and intervening furrows. Prurigo papules are ill-defined obtuse elevations with excoriated tops, caused by trauma from the finger nails. In some forms a contributory factor may be erection of the hair follicles (horripilation) in response to various stimuli.

**Ætiology and Pathology.**—The ætiology of these various disorders will be dealt with individually.

Histologically there is hyperkeratosis, thickening of the granular layer and acanthosis, with elongated rete ridges. In the dermis there is an inflammatory infiltrate. Areas in which the epidermis has been removed in part or in its full depth may be seen, covered by blood scabs or by infected scabs.

## LICHEN SIMPLEX CHRONICUS

(PRURITUS WITH LICHENIFICATION: NEURODERMATITIS CIRCUMSCRIPTA; NEURODERMITE)

**Ætiology and Pathology.**—The sense of itching in this condition is usually central in origin and brought about by frustrated anger or libido; or a trivial local irritant may operate in the first place and the vicious circle of itching, rubbing, lichenification, itching be brought about. This primary form has to be differentiated from lichenification developing on contact dermatitis, a phenomenon not unusual where

compensation claims await settlement or where there is some other significant emotional factor in addition to a contact cause for a dermatosis. In both primary and secondary forms hysterical traits are often apparent.

Histologically there is slight hyperkeratosis and marked acanthosis, with a non-specific infiltrate in the dermis.

**Clinical Picture.**—A patch of lichen simplex is usually oval and, if on a limb, lies in its long axis. The colour is red or reddish-brown and the edge fades off gradually into the normal skin without outlying "satellites". The surface shows an accentuation of the normal skin pattern, creases being increased in both depth and width, and the interposing lozenge- or diamond-shaped areas more obviously elevated above the creases than in the normal skin. These areas are often shiny and resemble grouped papules of lichen planus. There may be a fine scaling or warty thickening. If scratching is carried out as well as rubbing, excoriations and blood scabs may be visible. There is usually marked pigmentation but occasionally depigmentation occurs. Lichenified skin is thickened and inelastic, tending to become fissured and secondarily infected with erysipelas, impetigo or boils. The sites most characteristically affected by lichen simplex are the nucha, the sides of the neck and the supra-clavicular regions, the ulnar aspects of the elbows, the hands, the external genitalia, the anal and perianal regions, the inner and outer thighs, and the antero-lateral aspects of the calves; but other sites may be affected.

Lichen simplex is modified in appearance in certain situations. On the scalp scabbed excoriations are often seen or diffuse redness and profuse, coarse scaling, even with collarettes of coarse asbestos-like scaling for a few millimetres up the hair shafts—the so-called "*fausse teigne amiantacée*". At the nape of the neck an oval area is usually superficially excoriated, with grey scales and light crusting. A mild infection may be superimposed. On the brows the hairs are broken off short. On the palms, dyskeratosis dominates the picture and accentuation of the skin pattern is inconspicuous. In the flexures, the hyperkeratotic skin becomes fissured, sodden and whitened, resembling leucoplakia. The sufferer from lichen simplex may become agitated and start to rub the lesions during the interview when enquiry is made into relevant personal matters.

**Course and Prognosis.**—The malady may persist indefinitely or disappear without treatment: its relief depends on abatement of the emotional tension. Sometimes this is not possible; sometimes if the patient and the source of the tension can be separated the condition may clear without other treatment.

**Diagnosis.**—The diagnosis from lichenified dermatitis of external origin is often difficult. Usually with lichenified dermatitis there is a history of a more widespread eruption which has finally become localised, perhaps in the antecubital regions.

Lichen planus may simulate lichen simplex but there are usually some discrete lesions to be found which clarify the diagnosis. Lichenoid plaques on the legs, however, may be due to lichen simplex, lichen planus or (rarely) lichen amyloidosis: their differentiation may only be possible by biopsy.

At the nucha, lichen simplex may resemble seborrhœic dermatitis and psoriasis, but the circumscribed pattern is not typical of the former and the absence of silvery scaling or of psoriasis elsewhere renders the latter diagnosis improbable. The presence of pediculosis or of hair-dye dermatitis must be excluded. On the palms, psoriasis and dyskeratotic contact dermatitis have to be excluded on the evidence of the history and the presence or absence of psoriasis elsewhere. At the flexures, leucoplakia can be excluded because it only occurs on mucous surfaces; but lichen simplex of the mucosal aspects of the labia majora and of the labia minora may be accompanied by leucoplakia.

**Treatment.**—The treatment of lichen simplex is, essentially, the relief of the related tension state. If, as often happens, this is not possible, an attempt has to be made to break the vicious circle with general sedatives and local applications.

Barbiturates are most useful for this purpose, for example, phenobarbitone gr.  $\frac{1}{2}$  to 1 twice a day, and butobarbitone gr. 3 to 4 $\frac{1}{2}$  in the evening; or a bromide and valerian mixture may prove useful, and promethazine hydrochloride 25 mg. in the evening for its antipruritic action. Occasionally the draught of paraldehyde 1 $\frac{1}{2}$  fl. oz. is indicated as a quick-acting sedative for use in the middle of the night. Amphetamine sulphate 5 mg. after breakfast is useful when there is depression, and helps the patient to obtain relief by deeds or words in place of harmful and useless emotions.

Locally, tar is of great value in the form of the solution of coal tar 2 to 6 per cent. in zinc paste, or the more elegant ether-soluble tar paste (Martindale) may be used. At the nucha it is better to incorporate the tar in the ointment of wool alcohols and when the skin is markedly thickened the solution of coal tar can be applied neat once a day, with considerable relief. At flexures and the anogenital region, tar cannot be used with safety and magenta paint makes a valuable substitute, partly no doubt from its phenol content and partly from its powers of controlling secondary fungous infections. Occlusive dressings are not so effective as might be expected because they may give the patient a feeling of guilt and frustration from the loss of the emotional relief (*onanisme pruritique*) that rubbing these lesions provides.

X-rays in a course of three or four exposures of 75 to 100 r each time are often invaluable; thorium-X, too, 1500 e.s.u. per ml., is often helpful, particularly at hairy sites or if the patch is of a shape and size not easily covered by an X-ray applicator. Thorium-X is applied in spirit or as a varnish and the affected area should not be washed for the next 72 hours. The patient should be warned that considerable pigmentation may develop at the treated site and persist for some months.

The patient should avoid hot baths and proximity to fires and try to avoid emotional heat from the life situation as a whole. Adjustments so as to avoid difficult personal contacts may be necessary, and prove highly effective.

### PRURIGO OF BESNIER

(FLEXURAL PRURIGO; ATOPIC DERMATITIS; ASTHMA-HAY FEVER-PRURIGO SYNDROME; PRURIGINOUS FACIAL ECZEMA, ETC.)

Prurigo of Besnier is an itching condition affecting in particular the flexures and the face; it usually begins in infancy and may alternate with, or more rarely be accompanied by asthma or hay fever.

**Ætiology and Pathology.**—The fundamental abnormality is spasm of plain muscle from many relatively trivial stimuli which would have little or no effect on the majority. The spasm may affect the bronchioles, causing asthma; the vessels of the nose, causing vasomotor rhinorrhœa; and the skin, causing gooseflesh and vasoconstriction. Sweating is often excessive.

Inheritance and the early environment both seem to be of importance in the ætiology but the latter seems more significant than the former. Those affected are of average intelligence but are excitable and prone to feelings of insecurity and are often maladjusted to their parents, particularly the mother (the so-called "maternal rejection factor"). Threats to security or to loss of affection are the most significant and obvious of the many factors that bring about exacerbations. Breakdowns may occur with changes of school or occupation or at times of engagement, marriage or bereavements. Other factors include changes of temperature or of humidity, airborne, injected or ingested allergens, rough clothing, drugs and infections. The pruriginous individual reacts to everyday stimuli with a mechanism designed for emergencies. Thus, pollens, danders and household dusts may cause bronchial spasm or vasomotor rhinorrhœa. Stroking the affected skin causes a white line to develop in 15 seconds; the usual red line does not follow; at unaffected sites the normal reaction of white line followed by red may be observed. Cutaneous infections in these individuals tend to become generalised, in part because of the scratching that

helps dissemination. Thus, pruriginous individuals may get generalised staphylo-derma, generalised herpes or widespread vaccinia.

**Clinical Picture.**—Besnier's prurigo presents as one of the forms of infantile eczema (*q.v.*). It may begin as early as the second month as a papulo-vesicular and erythematous-squamous condition involving parts easily reached by the infant—the face, neck, antecubital regions, wrists, hands, popliteal spaces, calves, ankles and feet. The trunk may escape entirely or it may show a patchy, ill-defined, faintly pink papular and scaly eruption. The lesions may be exudative, infected or lichenified.

The infant periodically indulges in orgies of rubbing, particularly in the evening when bored, frustrated or tired, and with determination overcomes any attempt to restrict this practice. The face may be rubbed by rotation to and fro on the pillow even if the arms are tied. The condition usually becomes milder when the child starts to walk and to do things for itself. It may disappear for several years but there is usually a recurrence at puberty and the prurigo is then more strictly localised to the bends of the elbows and of the knees, the hands and wrists, the face and neck, and sometimes to the genitocrural region and to the feet. The affected areas show lichenification and excoriations. The condition may persist well into adult life, (though it usually gets less severe after 20 years of age) with exacerbations from exposure to heat, anxieties and an ever-varying pattern of contact sensitisers or air-borne allergens (if the results of patch and scratch tests can be accepted as valid in these individuals). Sometimes the first occurrence is in adult life, and engagement, marriage or a bereavement usually precedes the dermatosis.

Xeroderma is often coexistent with Besnier's prurigo and modifies the picture. Cataracts are a serious complication in some cases which persist into adult life. They are believed to be congenital but friction applied to the eyelids may well play a part in their maturation.

**Course and Prognosis.**—This depends upon the possibilities of dealing with the causal factors. If they cannot be eliminated the malady may persist indefinitely.

**Diagnosis.**—The malady has to be differentiated from contact eczematous dermatitis, especially when complicated by lichenification. In prurigo the essential lesion is not a papulo-vesicle but is a prurigo papule, an obtuse elevation of a brown or dusky hue, often with an excoriated top; or if these elementary lesions are not discernible, lichenification dominates the picture.

Besnier's prurigo involving the face (pruriginous facial eczema) has to be differentiated from actinic dermatitis and from eczematous dermatitis of the face caused by air-borne or hand-transferred agents. The former affects the forehead, nose and malar ridges and other parts exposed to light. The latter affects particularly the eyelids and perhaps the skin of the sides of the neck.

**Treatment.**—The treatment of Besnier's prurigo is very much that of the whole patient with his characteristic personality and his personal problems, rather than the management of his skin condition by itself. A change of attitude and co-operation on the part of the parents is equally important. If a steadier level of affection in a calmer home atmosphere can be made to prevail, all well and good. If not, a temporary removal from the unfavourable and often tense atmosphere is the second best choice. This may entail a period in hospital or in a convalescent home, and for some cases special residential schooling facilities are ideal.

Apart from these procedures, treatment is mostly symptomatic, by bland local applications such as calamine liniment and general sedatives in ample dosage, bearing in mind that sufferers from prurigo usually tolerate barbiturates well and need doses larger than the average to bring about quiet and sleep and freedom from scratching. Antihistaminic drugs with antipruritic properties, for example promethazine hydrochloride, are also valuable. Chlorpromazine 25 mg. t.d.s. or methylpentynol (Oblivon) 250 mg. t.d.s. is sometimes helpful. The pruriginous patient needs to be kept fully

occupied, either with suitable manipulative toys in childhood or by manual work in adult life.

For the worst cases in-patient treatment is invaluable; sedation can then be used in larger doses and nonspecific measures tried, such as fever therapy with T.A.B. intravenously in doses of 25 million, 50 million and 100 million organisms at 5-day intervals (for an adult). For localised patches thorium-X or X-irradiation is sometimes indicated. Intravenous injections of corticotrophin 50 mg. 8-hourly will bring about a partial remission, but this treatment is advisable only in exceptional circumstances.

Hydrocortisone ointment has recently been reported to be highly effective in relieving the local manifestations of this malady.

### DISSEMINATED NEURODERMATITIS

This term is used for extensive and severe examples of Besnier's prurigo and other widespread lichenified and pruriginous eruptions in which no contact, toxic or reticulotic cause can be discovered but in which the malady appears to indicate a maladjustment to the environment, particularly in circumstances of deprivation of occupational activities, bereavement, sexual frustration and unwantedness. It affects adults of all ages.

### PRURIGO OF HEBRA (PRURIGO FEROX)

A chronic itchy disease starting as urticaria and persisting indefinitely. Two forms are recognised, prurigo ferox and prurigo mitis.

**Ætiology and Pathology.**—Inheritance is an important factor, but whether this consists of the inheritance of an abnormality of the skin or a low level of intelligence is not clear; probably the second is the more important.

**Clinical Picture.**—The condition usually begins in the first or second years with a polymorphic eruption of scratch marks, erosions, lichenification and papular urticaria. The malady gradually becomes localised to the limbs, particularly to their extensor surfaces. Later, prurigo nodules develop and the urticarial component fades.

As years pass, the picture is of extensive excoriations, lichenification and pigmentation with scarring and thickening of the skin, and freedom of the flexor aspects of the joints. The lymph nodes in the axillæ and groins are enlarged. The trunk, neck and face may be affected. The malady is rare in the British Isles.

**Diagnosis** is from xeroderma and from other itchy diseases of the skin, including crusted scabies.

**Course and Prognosis.**—Prurigo mitis may improve at puberty, but in prurigo ferox the prognosis is unfavourable, the malady persisting in spite of treatment. Infection may occur.

**Treatment** is symptomatic, by bicarbonate of soda or tar baths, antipruritic applications such as 2 to 4 per cent. of solution of coal tar in zinc cream or paste, and adequate sedation by bromides, barbiturates or antihistaminic drugs. A period of removal from the home surroundings to hospital, convalescent home or residential school is often useful.

### PRURIGO NODULARIS

This is a rare malady and may in fact be a variant of lichen planus (*lichen obtusus cornuus*), differing from *lichen planus hypertrophicus* by reason of the large obtuse, dome-shaped nodules affecting the extensor surfaces of the forearms and legs, whereas *lichen planus hypertrophicus* is more plaquelike and usually localised to the calves and ankles.

## SECRETORY DISORDERS

Sweat secretion may be excessive, diminished or suppressed (hyperidrosis, hypoidrosis and anidrosis).

Sebum secretion may be excessive (seborrhœa) or diminished (xeroderma, ichthyosis). Sebum secretion is qualitatively altered in "seborrhœic" dermatitis without there necessarily being any quantitative changes. "Seborrhœic" dermatitis may occur with an average sebum flow or with seborrhœa or even with xeroderma. It is better designated "infective dermatitis".

### HYPERIDROSIS

Generalised sweating normally occurs from heat, exertion, fear, febrile and toxic states. Certain central nervous system lesions, hyperthyroidism and acromegaly, and some drugs (acetylcholine, pilocarpine) can also cause sweating. Adolescents and young adults are affected more often than children or older people by excessive sweating from anxiety; the obese suffer most from heat and exertion.

In localised hyperidrosis, the sites most commonly affected are the palms and soles, the axillæ, the anogenital region or the centre of the face. On the palms and soles there is often also a tendency to perniosi. Involvement of the hands may interfere with working capacity, owing to soiling of paper and other materials handled. Sweaty feet provide damp, dark, poorly aerated conditions which are ideal for the growth of saprophytic organisms. Sweat, acid when secreted, becomes alkaline as it decomposes and this further encourages the growth of pathogens and facultative pathogens, both bacterial and fungous. The decomposing sweat often has an offensive odour (bromidrosis) and may become coloured from the proliferation of chromogenic bacteria (chromidrosis).

Excessive sweating predisposes to contact dermatitis from water-soluble irritants. Dermatitis in the rubber industry is more common in sweaty individuals, the sweat leaching out potentially irritant antioxidants and other preservatives from the rubber. Similarly, dermatitis of the axillary folds occurs from dyed clothing or from dress protectors.

Perianal sweating often becomes complicated by maceration and monilial or other fungous infections.

Axillary hyperidrosis is a serious inconvenience to many women because it may cause discolouration and rotting of fabrics, bromidrosis and other social embarrassments. Offensive axillary odour (bromidrosis) is entirely due to bacterial decomposition of the sweat, the axillary apocrine sweat being without odour when first secreted.

Sweating of the centre of the face may be caused in some individuals by eating hot or spicy foods.

Excessive sweating in fever may cause the eruption of raindrop-like vesicles (*miliaria crystallina*, *sudamina*) situated in the horny layer.

**Treatment.**—The uncovering and removal of any emotional cause that may be present is essential for cure; otherwise treatment is largely symptomatic. A bromide mixture with belladonna to the limit of tolerance may be used to give temporary relief but is not a practical method for prolonged use. Phenobarbitone may be more effective. In severe cases a trial of ganglion-blocking agents, such as pentolinium tartrate is justifiable. The fluid intake should be as small as possible consistent with the relief of thirst. Frequent tepid baths should be taken, and the whole body or the affected parts liberally dusted with a boric acid and talc or salicylic acid powder, the latter being especially useful on the feet. To prevent or combat infection and to minimise bromidrosis, foot soaks in a 1 in 6000 solution of potassium permanganate

are useful. Coarse woollen socks and rubber-soled or tennis shoes should not be worn. The socks should be of a cotton material and should be changed at least once a day. For the axillæ a 1 in 80 solution of aluminium acetate (Burow's solution diluted 1 in 10 with water) is the most effective remedy. The axillary hair should be kept closely shaven to make washing easier. Sympathectomy is not advisable for a malady often emotionally produced and X-ray treatment, if it is to be effective, necessitates a dosage which exposes the patient to the risk of later irradiation effects on the skin.

## HYPOIDROSIS

Diminished sweating occurs in myxœdema, congenital ectodermal defects, extensive scarring, diabetes, renal disease and some cachectic states; also in some skin diseases, particularly xeroderma, scleroderma and in the senile skin; or in the atrophic skin following the administration of liquor arsenicalis, or the excessive use of X-rays, or too much exposure to the sun. In other skin diseases with pathological scaling, partial obstruction of the sweat ducts may cause hypoidrosis.

## ANIDROSIS

Cessation of sweating occurs in the anæsthetic skin areas of leprosy, after sympathectomy, and sometimes in poliomyelitis. Sweat suppression may occur in hot, humid climates as prickly heat (*miliaria rubra*) and as tropical anidrosis (*miliaria profunda*). In temperate climates a similar condition may be caused by hot, humid working conditions and by exposure to moderate heat after having suffered and perhaps partially recovered from some forms of contact dermatitis, for example that due to cement dust.

Prickly heat is peculiar to the white races. Its causes are believed to be the wearing of clothes and the use of spirit, powders and too much soap on the skin in humid, hot climates; also the "seborrhæic" type of skin with follicular vulnerability to infection. The qualitative sebaceous deficiency leads to the formation of "keratin rings" at the ostia of the sweat ducts. These rings act as plugs and the dammed-up sweat bursts out from the ducts causing disruption of the adjoining epidermal cells; rupture of the duct lower down may cause an inflammatory reaction in the dermis. Clinically there are itchy red papules of prickly heat (*miliaria rubra*) and follicular pustules (*ostio-folliculitis*, Bockhart's impetigo) due to infection of the contents of obstructed ducts. Recurrent attacks of prickly heat may lead to destruction of the intra-epidermal portions of the sweat ducts; further exposure to heat and humidity may then lead to *miliaria profunda*, with vesicles resembling sago grains in the dermis, causing non-itchy tropical anidrosis, which may go on to heat-stroke.

Adhesive plaster skin reactions are more often due to sweat-duct obstruction and infection than to eczematous hypersensitivity. It usually starts 48 hours or more after the application of the plaster. It is likely that other forms of dermatitis, for example those due to dress protectors, rubber, cement, etc., are in part due to sweat-duct irritation and obstruction.

**Prevention and Treatment.**—An attempt should be made to maintain an oily film on the surface of the skin in order to replace any sebaceous deficiency. For this purpose anhydrous lanolin or the ointment of wool alcohols may be used. The patient should be advised against the use of degreasing and dehydrating substances on the surface of the skin and should wear loose-mesh cotton underwear.



## SEBORRHŒA

Excessive oiliness of the skin may occur from puberty onwards, and is due to hormonal (androgenic) influences; it usually diminishes with advancing age. It is more common in the coloured races and may show a familial incidence amongst white people. It affects the regions with most sebaceous glands, the scalp, the face, the nasolabial folds, the chest and the back. The skin is greasy, thickened, muddy-coloured and with patulous follicles, from which semi-solid sebaceous material is extruded. There is often a tendency to premature baldness of masculine type, while other areas, such as the beard and chest, grow tough, coarse hair. *Acne vulgaris* is a common complication of seborrhœa. Keratinous plugs at the pilosebaceous follicles cause retention of sebum and inflammatory changes of acne papules and pustules. Infection of the seborrhœic skin with facultative pathogens may cause infective ("seborrhœic") dermatitis, or infection with more virulent organisms may cause impetiginised seborrhœa or furunculosis. The seborrhœic skin is unduly susceptible to fat-soluble irritants; hence the application of ointments containing antiseptics may cause a chemical folliculitis and dermatitis. Seborrhœic individuals have a tendency to develop rosacea.

**Treatment.**—The diet should contain ample protein, vitamins and minerals, and should not contain an excess of fats and carbohydrates. Frequent washing with soap and water is essential. Sulphur compound lotion may help to diminish seborrhœa and to control any associated acne or infection.

## XERODERMA

In xeroderma and its more severe form, ichthyosis, the skin is abnormally dry with a diminished secretion of sebum and, to a lesser extent, of sweat. There is also a thickening of the horny layer, sometimes with preference for the pilosebaceous follicular orifices (*keratosis suprafollicularis*).

**Ætiology and Pathology.**—The disease is inherited, apparently as a dominant factor, affecting both sexes and often several members of one family. It is usually noticed soon after birth and may be present at birth. Histologically there is hyperkeratosis especially at the pilosebaceous ostia and an absence of the granular layer. The prickle cell layer is thin. The sebaceous glands are few and small, but the sweat glands are not obviously diminished.

**Clinical Picture.**—In the milder cases the skin on the extensor surfaces of the limbs and body is dry and rough, with a slight branny scaling. The flexures appear normal. On the extensor surfaces of the limbs the hair follicles are prominent with small horny spines projecting. The hair is dry and lustreless and breaks easily. It may be sparse. In severer cases fish-like, adherent, grey scales cover the whole body. The skin is rough and even the face is affected to some extent. *Ichthyosis hystrix* is a form of hard nœvus occurring in lines or bands, and has no relation to ichthyosis. Xeroderma often accompanies Besnier's prurigo.

**Course and Prognosis.**—The dry, unoiled skin cracks easily and from its deficiency of sebum is susceptible to bacterial infection. Xerodermatous individuals have to be prevented from taking up unsuitable occupations. Excessive contact with soaps, detergents and fat solvents are all likely to be harmful; exposure to cold weather aggravates the condition, the glandular activity then being minimal; on the other hand, extreme heat may lead to heat-stroke owing to the inability of those suffering from severe xeroderma to lose heat adequately by sweating. Xerodermatous individuals should be in clean, dry work in an equable temperature. Xeroderma tends to improve to some extent at puberty, only to get worse again with advancing age. The worst cases remain severe in adult life.

**Diagnosis.**—This is usually easy. Differentiation has sometimes to be made from acquired atrophy with scaling of the legs, or from phrynoderma (*keratosis follicularis*) caused by vitamin A and C deficiency. The history and the distribution of the dry but not inflamed skin usually enables the correct diagnosis to be made.

**Treatment.**—Warm baths may be taken daily, followed by the rubbing in of a suitable ointment. Individual preferences vary. Some like to rub in soft paraffin ointment, while the skin is still moist; others prefer the ointment of wool alcohols or glycerin of starch, with either hydrous lanolin or salicylic acid ointment in equal proportions. A superfatted soap should be used, but not to excess. The administration of thyroid extract or of vitamin A is without effect.

## PIGMENTARY ANOMALIES

The colour of the skin depends on the amount of skin pigment (melanin) it contains, on the thickness of the epidermis and on the amount and oxygen content of the blood flowing through the more superficial vessels of the dermis. The muddy colour of acne is related to the relatively opaque, thickened horny layer and increased sebum flow; the patchy redness of rosacea to the static dilatation of the cutaneous vessels; and the peachlike skin of the maiden to her naturally thin and smooth, relatively translucent feminine horny layer overlying blood vessels neither statically dilated nor contracted but responding normally to changes of temperature and of mood. The colour of the skin is a poor index of the haemoglobin content of the blood. If the blood vessels of the skin are dilated, anaemia may be masked, and if they are contracted there may be considerable pallor without anaemia.

Pigmentary changes in the skin may be due to an excess or insufficiency of melanin or to the presence of extraneous substances including blood pigments, bile pigments, carotene, mepacrine, gold, silver, lead, bismuth and various substances introduced in tattooing, either by accident or intention.

### PHYSIOLOGY OF MELANIN FORMATION

Melanin, a complex iron-free substance, is formed in the melanoblasts by the action of a ferment, dopa-oxidase on a colourless precursor, dihydroxyphenyl-alanine (dopa); dopa is formed from tyrosine by tyrosinase but only in the presence of copper. Melanin-synthesising cells (melanoblasts) can be differentiated from melanin-containing cells (melanophores) by the dopa reaction; fresh tissue is immersed in a solution of *laevo*-rotatory 3:4 dopa when the melanoblasts are stained brown. Reducing substances, for example ascorbic acid, inhibit melanin formation and oxidising agents stimulate it. Dimercaprol (B.A.L.) and thiouracil may inhibit pigment formation, as may the monobenzyl ether of hydroquinone when applied locally.

Melanoblasts are dendritic cells scattered amongst the germinal epidermal cells of the basal layer. The melanin is carried by their dendritic processes to the cells of the basal and prickle layers and deposited as granules within them. Pigment-containing cells (melanophores) are also seen in the dermis; they take up any melanin that passes from the epidermis to the dermis. Increased melanotic pigmentation of the skin may occur with or without previous inflammation of the skin, and may be general or local.

### INCREASED PIGMENTATION

*Racial pigmentation* affects the buccal mucosae as well as the skin. Without prior knowledge of the inheritance it is sometimes difficult to decide if pigmentation is racial, but a consideration of the colour of the eyes and the colour and texture of the

hair, together with other racial anatomical traits of facies, etc., usually prevents error.

**Physiological pigmentation.**—In pregnancy there is patchy facial pigmentation (*chloasma uterinum*), linea nigra in the midline of the abdomen and darkening of the nipples and genitalia, often as an early diagnostic feature.

**Congenital forms** include pigmented, fleshy hairy moles, lentigines and ephelides or freckles. The mongolian spot is a blue-black discolouration of the skin, often in the sacral region, and is a deeply situated mole. In neurofibromatosis (von Recklinghausen's disease) there are pigmented patches on the skin which may precede the development of tumours by many years.

**Ephelides (Freckles).**—These are pale-brownish macules which become darker after exposure to sunlight. They are seen particularly in sandy or red-headed persons and those with ancestors of these colourings.

Histologically the only change is an increase of pigmentation in the basal layer.

Treatment is preventive by the wearing of broad-brimmed hats and the use of sun-screening creams. Attempts at removal of freckles by peeling agents are hazardous and may result in dermatitis.

**Lentigines (Non-hairy Moles).**—A lentigo is a dark brown macule which does not change colour after exposure to sunlight.

Histologically there is excessive pigmentation of the basal layer and an increase of clear cells. The rete ridges are elongated and club-shaped. The basal cells may appear somewhat disorganised but the epidermo-dermal junction is well defined. Nævus cells are not present in the dermis.

**Course and Prognosis.**—Lentigines are seen in children but they become much more numerous after puberty and in pregnancy. It is not uncommon for hundreds to be present on one person. Lentigines are potential melanomata, but malignant change occurs only in a very small proportion of them. The stimulating factors appear to be the endocrine changes of puberty and pregnancy and physical traumata. At certain sites malignant proliferation is much more common than at others. These danger sites include the paronychia and subungual regions, the soles, the lower limbs more than the upper limbs and their distal parts more than their proximal parts, clothing friction sites on the body, and the face. For this reason, it is sometimes advisable prophylactically to excise lentigines on the soles or at friction sites before puberty or early in pregnancy. For the rest, treatment is not necessary but if, for cosmetic reasons, it is desired to remove a lentigo from the face, it should be properly excised in full depth and not subjected to destructive cauterising or freezing procedures, which may lead to activation of any cells that remain.

**Fleshy hairy moles.**—These are dealt with elsewhere (see Tumours).

**Increased pigmentation from physical causes.**—The skin responds to light, X-irradiation, heat and friction by increased pigment formation. This may be seen as sun-tanning and the effects of ultra-violet baths; pigmented macules are often present in the periphery of scars of lupus treated with the Finsen-Lomholt lamp, and prolonged solar irradiation leads to the condition of poikiloderma in which there are telangiectasia, atrophy and macular pigmentation and depigmentation, an identical condition to that occurring after excessive X-irradiation. A similar appearance also occurs in the rare congenital malady, xeroderma pigmentosum, in which there is an inborn susceptibility of the skin to light.

Long-continued exposure to tar or creosote causes pigmentation of the parts exposed to light, the tar apparently being a light-sensitiser. Bergamot oil, too, in creams or perfumery may cause pigmentation. There may be mottled pigmentation of the face with some telangiectasia when creams are responsible, or a necklace-like line of pigmentation from beneath the ears around the neck when Eau de Cologne, placed behind the ears, has trickled down or been carried down in the sweat (berloque dermatitis). A similar pigmentation may occur after thorium-X is applied to the skin.

Certain plant juices have a photosensitising action (phytophoto-dermatitis), par-

ticularly wild parsnips, figs, the common rue and limes; also convolvulus and agri-mony, and even the buttercup and bindweed. A severe inflammatory reaction precedes the pigmentation.

Heat may cause the condition known as erythema ab igne, a network of pigmentation involving areas of skin corresponding to vascular anastomoses.

Friction may cause pigmentation at truss, hathand and other sites of clothing contact; also in rubbed areas of itchy skin, for example in pediculosis (vagabonds' disease), prurigo, lichen simplex, etc.

Certain dermatoses, particularly lichen planus, lichen simplex, dermatitis herpetiformis and exfoliative dermatitis (erythroderma) are often accompanied or followed by much pigmentation. In urticaria pigmentosa the pigmented macules urticate on friction. Incontinentia pigmenti is a peculiar reticular and mottled pigmentation of infants and is thought to be the end stage of an inflammatory process of unknown cause. In pityriasis (tinea) versicolor, the brown lesions are slightly scaly.

Toxic pigmentation occurs from certain drugs, for example arsenic, which causes a raindrop effect of white spots in a dark background, with skin-coloured, pinhead palmar and plantar keratoses and dirty grey keratoses more widespread on the trunk, often leading to skin cancers. Organic arsenic does not have this effect but may cause exfoliative dermatitis and secondary melanosis.

Endocrine, metabolic and nutritional disorders.—In Addison's disease there is a diffuse pigmentation of the skin with involvement of the buccal mucosæ. Pigmentation also develops very often during treatment with corticotrophin. Diffuse pigmentation may occur in liver disease, abdominal tuberculosis, malignancy, malaria, diabetes and thyroid disorders. In Gaucher's disease (kerasin lipoidosis) there is brownish discolouration of the skin. In pellagra, the skin is deeply pigmented on the parts exposed to sunlight, particularly the backs of the hands, probably from the absence of reducing substances which normally check excessive pigmentation on exposure to light. There is also diarrhoea and dementia and often other evidence of malnutrition.

Acanthosis nigricans (q.v.) presents as velvety skin piling up in folds, particularly in the flexures.

## DIMINISHED PIGMENTATION

Racial differences in degree of pigmentation depend on varying physiological activities of the melanoblasts which are present in all races in approximately the same concentration.

Albinism.—In this condition there is a genetic lack of the enzyme tyrosinase, a copper protein complex in which the copper plays an essential catalytic rôle.

Vitiligo.—Vitiligo is the commonest form of depigmentation. There is a macular, discoid and figurate depigmentation of the hands, face, genitalia, or other regions. On the scalp the hair may be white in the affected areas (leucotrichia).

Ætiology and Pathology.—The ætiology is obscure. Histologically melanoblasts are as numerous in the pale areas as in the darker surrounds but the melanoblasts in the pale areas are inactive (dopa-negative) and they and the melanophores are deficient in pigment, whereas those in the adjoining darker areas contain an excess.

Diagnosis has to be made of this primary leucoderma from secondary leucodermas due to eczema, psoriasis, lupus erythematosus, syphilis, leprosy, scleroderma or pityriasis versicolor.

In eczematous or psoriatic leucoderma there is a history of a past inflammatory stage, in vitiligo only of pale areas which redden but do not tan in sunlight. In syphilitic leucoderma colli there are other manifestations of syphilis, the lesions are uniformly small and confined to the neck, and there may be some cutaneous atrophy which is absent in vitiligo.

In leprosy the colour contrasts may not be so marked as in vitiligo; the pale areas are anæsthetic to light touch and differences of temperature; and thickened nerves can be felt serving the area or some other situation, for example, the neck, the ulnar side of the elbow, or the popliteal space. When these nerves are rolled under the fingers the patient may experience paræsthesia but no pain in the area they supply. The pale areas may be anidrotic.

In scleroderma or its localised form, morphœa, there is increase of substance and marked hardening in the pale areas but no loss of sensation. In scars and scarring diseases of the skin there is often depigmentation, whether the scars are hypertrophic, normal or atrophic.

In tinea versicolor the brown areas are "islands", the white areas the "sea" around. In vitiligo the opposite applies, the white areas being "islands" in a "sea" of browner skin. But the diagnostician has to be wary of certain exceptions to this rule. Vitiligo may become so extensive that there is more pale skin than dark and in these circumstances brown areas may seem to represent "islands"; but if they do, their "coastlines" will be a series of bays or concavities, indicative of the condition spreading from pale to darker zones. In the form of vitiligo known as leucoderma centrifugum acquisitum (Sutton's disease) there is an intensely pigmented macule surrounded by a pale area beyond which is skin rather more brown than normal, and beyond this, normal skin.

When skin affected with tinea versicolor is exposed to the sun, the affected areas do not pigment as well as the normal skin around, so that a photographic negative of the original malady is produced (*achromia parasitica*). In coloured people, too, the affected skin of tinea versicolor is paler than the normal skin nearby. The diagnosis is established in all doubtful cases by the more characteristic distribution of tinea versicolor on the trunk and by the discovery of spores and mycelial threads on scraping the lesions and direct microscopic examination of the material in potassium hydroxide.

Leucoderma can arise from contact with rubber, the responsible chemical being the monobenzyloether of hydroquinone used as an antioxidant. Clinically this type may be indistinguishable from the idiopathic form.

**Treatment.**—Meladine is said to bring about repigmentation. It is the refined products of the plant *ammi majus* linn. It is taken internally and applied on the surface, the skin also being exposed to ultra-violet rays. Repigmentation begins around the hair follicles and it is probably only successful in those cases of vitiligo with pigmented hairs growing from the white skin: such cases have melanoblasts in their hair papillæ which are still capable of responding to stimuli.

### NONMELANOTIC PIGMENTATIONS

Hæmochromatosis is a bronzed pigmentation, which may involve the mouth: there is diabetes and enlargement of the liver.

Hæmosiderosis results from blood pigments which may be deposited in eczema and dermatitis involving the lower limbs, in the capillaroses (Schamberg's progressive pigmentary dermatosis, Majocchi's purpura annularis telangiectodes, lichenified and disciform pigmentary dermatosis of Gougerot and Blum, angioma serpiginosum of Hutchinson).

The lemon-yellow to brown pigmentation of jaundice is due to bile pigments in various concentrations. Jaundice can be differentiated from racial pigmentation and other forms due to melanin by the involvement of the conjunctivæ; the conjunctivæ are not tinted in mepacrine pigmentation when this drug is taken in therapeutic doses.

Mepacrine pigmentation slowly develops with the daily ingestion of 0.1 to 0.3 g. of the drug and the discolouration may take a month or two to fade after the drug is withdrawn. The pigmentation of lichenoid mepacrine dermatitis is melanin.

Carotinæmia due to the excessive ingestion of carrots produces an orange tint most marked on the palms. The conjunctivæ remain white.

*Metallic intoxications.*—Lead causes a blue-black line on the gums opposite areas of marginal gingivitis or caries, owing to the deposition of lead sulphide. Silver may, if ingested or applied to the eyes or mucous surfaces, be absorbed and cause localised or general argyria which gives a slaty blue colour to the skin, due to local deposition of the metal. A secondary melanoderma, due to the irritating effects of the silver on the melanoblasts, also may occur. Gold may become deposited in the skin (auriasis), giving it a brownish colour, or may, if it causes a lichenoid or exfoliative dermatitis, result in much increase of melanin formation. Bismuth may cause a black line on the gums but does not affect the skin except secondarily, either generally by the rare occurrence of exfoliative dermatitis or locally when the injection is accidentally given too superficially and a white foreign body reaction occurs with ulceration through the skin, which may persist for months and end in ugly scarring.

### TATTOOING

Tattooing may be accidental or intentional. In the accidental form, explosive materials, coal dust or road surface materials are usually responsible. In the intentional form, when tattooing has been used for identification purposes, only one colour has been used, but various pigments may be used when the purpose is display. The blue-black colour owes its bluish tint to the effects of the overlying dermis, the pigment being some form of carbon, iron oxide or logwood. The colour red is due to cinnabar (mercuric sulphide) and is important because it may be the cause of allergic reactions and may also modify the development of a syphilitic dermatosis owing to the spirochæticidal effect of the mercury. A green colour may be produced by chrome oxide, hydrated sesquioxide, or phthalocyanide dyes; a yellow by ochre or by cadmium yellow, but this has a bad reputation for causing blistering on subsequent exposure to light.

Tattooing has been responsible for inoculating syphilis, tuberculosis, vaccinia and virus hepatitis; psoriasis and lichen planus may be set off in tattooed areas.

Tattoos may be removed by excision with or without grafting or by various methods destructive to the dermis, including carbon dioxide snow, caustics and abrasives.

### PIGMENTED TUMOURS OF THE SKIN

These include moles, melanomata, Mongolian spots, basal cell carcinomata, keratoses, juvenile and senile (seborrhæic) warts, leiomyomata, fibromata, Darier's disease and acanthosis nigricans (*q.v.*).

## VASOMOTOR DISORDERS

### ERYTHEMA PERNIO (CHILBLAINS; PERNIONES; ERYTHROCYANOSIS; ACROCYANOSIS)

A condition of bluish-red, cold skin of exposed parts with swelling and itching, caused or aggravated by exposure to damp cold.

*Ætiology and Pathology.*—The chief cause is damp cold operating on a skin which is by inheritance oversensitive to its influence. Arteriolar vascular spasm results, with anoxæmia of the affected parts, at first intermittent, later chronic. The blood stagnates in the statically dilated venules, leading to œdema, degeneration and fibrotic thickening of the connective tissue and of the vascular endothelium itself.

Puberty is the time of worst involvement. Insufficient exercise is an important factor (or paralysed muscles as in poliomyelitis). The outward application of heat to the chilled surface aggravates the condition. Thromboses or extravasation of blood may occur, leading to ulceration.

**Clinical Picture.**—Perniosis may affect any area exposed to cold, particularly the distal parts of the limbs, the nose and the ears. Involvement of the upper limbs is usually confined to the digits but on the lower limbs the calves are affected as often as the feet.

Chilblains are far commoner in females than in males, a fact only partly explained by their more scanty clothing. The more sedentary tasks often carried out by women in cold, draughty or even damp surroundings are also partly responsible, and it is probable that some unexplained endocrine factor is of importance. Chilblains present as bright pink or bluish, swollen, non-pitting areas of skin. Blotchy redness is present at one area, blueness at another. The blue areas become red temporarily after gentle massage from the periphery. Chilblains often itch severely and may feel warm to the finger in this red, swollen stage; but later when the vessels have become statically dilated, as on the legs of young women (*erythrocyanosis crurum puellarum frigida*), the affected parts feel cold and are deep blue in colour except where casual contacts have emptied the superficial vessels. Often the blue discoloration is most marked around the hair follicles. If the oedematous process is marked, bullæ may develop and on rupturing leave ulcerated chilblains. Fissures (chaps) form on the fingers and hands, and infection may lead to cellulitis.

**Course and Prognosis.**—Individual attacks resolve with the coming of more clement weather or with better precautions against damp cold; but each attack leaves the tissues less able to withstand cold in subsequent winters.

**Diagnosis.**—On the face and hands chilblains have to be differentiated from lupus erythematosus profundus (lupus pernio of Hutchinson). This may be extremely difficult, except after a period of observation. Lupus erythematosus persists in warm weather, chilblains do not.

On the face and hands chilblains also have to be differentiated from sarcoidosis (lupus pernio of Besnier), a persisting, doughy, bluish swelling of the nose, ears or digits. The histology will help if doubt exists on clinical grounds.

On the legs, perniosis has to be differentiated from Bazin's disease and from Darier-Roussy subcutaneous sarcoids. Both of these conditions occur in individuals with pernicious circulations, but in addition there are extensive areas of hard, bluish nodulation, perhaps with deep and extensive ulceration.

Erythema multiforme may cause lesions resembling chilblains on the fingers but the palms are also often affected and characteristic "target" lesions may be seen.

**Treatment.**—Once it is known that there is a tendency to chilblains, every effort should be made to prevent aggravation; by suitable warm clothing all over the body as well as to the affected part; by proscribing the sudden application of heat to the affected part; by attention to bad housing by draught elimination, duck-boarding on stone floors, etc.; by adequate exercise and the avoidance of standing or sedentary jobs; by warming the affected parts by exercise of the whole body, or by the gradual and diffuse application of warmth with massage to help the venous blood flow. An electric blanket is preferable to a hot-water bottle.

Drugs hold a minor place in the treatment of chilblains and it is important to make the patient realise that alleviation depends much more on the correction of faulty habits than on medicines. Thyroid may be prescribed if there is any evidence of hypothyroidism. A temporary increase in the blood flow to the extremities may be brought about by tablets of nicotinamide 50 mg. or, of tolazoline hydrochloride (Priscol) 25 mg. Calcium has for long had a reputation for relieving chilblains by some means as yet unexplained: it is best prescribed in tablet form with vitamin D<sub>2</sub>. The use of massive doses of vitamin D<sub>2</sub> for the control of chilblains is

inadvisable in view of the possible serious side-effects. General ultra-violet and infra-red irradiation may help.

For unbroken chilblains, calamine liniment may be rubbed in from the periphery. For fissures, the ointment of wool alcohols is comforting. Appropriate antibiotics may be required to control secondary infections.

## ROSACEA (ACNE ROSACEA)

This condition is primarily erythematous and secondarily papular; it is characterised by lability of the facial blood vessels going on to persistent static dilatation and to congestive hypertrophy and inflammation of the pilosebaceous follicles, sometimes ending in necrosis.

**Ætiology and Pathology.**—Rosacea is essentially a state of vasolability of the face, particularly the centre of the forehead, the nose, the fronts of the cheeks and the chin. The vessels respond excessively to emotional stimuli, to changes of temperature and to gastric irritants. The gastric vessels and musculature tend to be hypotonic but there is no uniform change in gastric secretion as shown by test meals. Hormonal (menopausal) influences are sometimes important.

The rosaceous patient is characteristically obsessional, with very high standards of conduct and much resultant anxiety if these standards are not maintained. Excessive (often self-imposed) activities and insufficient time for meals result in a sense of hurry, flatulent dyspepsia and flushing of the face. Anger, if habitually repressed, may also cause flushing of the face, as may feelings of shame or embarrassment. A seasonal exacerbation in the early spring is sometimes noted.

Histologically there is vascular dilatation and focal inflammatory nodules either of lymphocytes or of tuberculoid type with lymphocytes, epithelioid cells and giant cells. There may be some perifolliculitis and abscess formation and all degrees of hyperplasia of the sebaceous glands, from a moderate degree in papular rosacea to an extreme degree in rhinophyma. In the latter condition there is also fibrous hyperplasia.

**Clinical Picture.**—The patient is usually a woman aged between 30 and 50, but men also are often affected and adolescents of either sex may suffer from this malady. The patient complains of redness and pimples of the face, with aggravation from exposure to extremes of temperature, from hurry, anger, embarrassment, or general anxiety, from hot drinks or indigestible foods, or in the premenstrual tension phase. There may be a flatulent dyspepsia. At first there is only a tendency to flush or blush easily; later the redness becomes persistent, telangiectases being visible; and finally red pimples form which may suppurate or necrose, giving rise to crusted papules which end in depressed scars. There are no comedones but sometimes acne vulgaris coexists; more commonly acne at puberty is succeeded by rosacea some years later. Patients with rosacea usually show evidence of the seborrhœic state, with all its consequences. Conjunctivitis, blepharitis, keratitis and corneal ulceration may all complicate rosacea.

Rhinophyma is a rare disorder and much more common in men than in women. Irregular fleshy masses develop on the distal two-thirds of the nose, with visibly enlarged follicular orifices.

**Course and Prognosis.**—Rosacea is amenable to treatment provided the patient is willing and able to co-operate with the physician. A variable amount of scarring may be left. The eye lesions may cause serious impairment of vision.

**Diagnosis** is from acne vulgaris, lupus erythematosus, contact eczematous dermatitis and polycythæmia. In acne vulgaris the distribution is different, the face is muddy, not red, and comedones are present. In the rosaceous form of lupus erythematosus, atrophy can be discerned and the eruption is worsened by exposure to the



sun. Contact eczematous dermatitis may coexist. It presents with ill-defined areas of redness and peeling at various sites on the face, particularly the eyelids, around the mouth and on the neck. In polycythæmia the whole face is persistently plum-coloured.

**Treatment.**—All circumstances that are likely to bring about flushing of the face have to be avoided. Exposure to cold winds, fires or, for that matter, the kitchen stove, have to be avoided as far as possible. Hot drinks, too, are harmful, particularly excessive hot tea-drinking; and they are a more common cause of exacerbation than alcohol, condiments or indigestible food. Obsessional traits have to be moderated if possible. Adequate time must be allowed for meals, which should have ample protein and vitamin content with no excess of fats or carbohydrates. The patient must be encouraged to express hostility more naturally. More fundamental psychological factors are, on the whole, best left undisturbed because the patient with rosacea usually cannot tolerate this line of approach.

Rosacea is not related to nutritional deficiency except secondarily, through the associated gastric disturbance. Vitamin B complex and iron are sometimes indicated, and it is always wise to estimate the hæmoglobin content of the blood. Internal treatment also consists of sedation, gastric "tonics" and, when necessary, œstrogens. A useful medicine before meals is sodium phenobarbitone gr.  $\frac{1}{2}$  in either the acid or the alkaline gentian mixture. Sometimes an acid mixture seems to be more helpful; sometimes an alkaline one. Fractional test meals show marked variations from one rosaceous patient to another and, for that matter, in the same patient on different occasions: hence they are of little value in deciding on the best medication. Bromides and iodides should not be given to rosaceous individuals as they may grossly aggravate the condition.

œstrogens are sometimes indicated, for example, ethinyl œstradiol 0.05 mg. twice a day for 10 days preceding each monthly flow; or the same remedy may be given once daily for up to 3 months to post-menopausal women.

Local treatment is relatively a secondary matter. Zinc sulphate lotion or calamine lotion with 1 per cent. of sulphur, or of ichthammol, may be used. The patient must not wash the face in very hot or very cold water and should not manipulate the lesions. Occasionally the lesions become infected, and then need treatment with the appropriate antibiotic.

In patients with sebaceous hypertrophic nodules X-ray exposures, 150 r weekly on up to four occasions, may help.

In rhinophyma the large masses may be reduced by X-ray exposures of 250 r each, up to a total of 1000 r, but surgery is better, the lesions being pared down with a scalpel or razor under general anæsthesia until the normal contour of the nose has been regained, bleeding being controlled with the galvano-cautery.

For the conjunctivitis the zinc and boric eye lotion is useful. Keratitis needs the attention of an ophthalmologist. Bright light must be avoided. Homatropine drops are indicated and cortisone drops give great relief.

## RAYNAUD'S PHENOMENON

This is described on p. 922. It may occur with perniosis, lupus erythematosus or scleroderma.

## ERYTHROMELALGIA

This is a persistent, painful, warm redness of the extremities. It is dealt with elsewhere (see p. 924).

## DERMATITIS DUE TO PHYSICAL CAUSES

Dermatitis may be caused by heat or cold, maceration or drying, ultra-violet irradiation, X-rays, thorium-X or radium; and by mechanical causes, including friction and pressure.

### DERMATITIS DUE TO HEAT

**ACUTE HEAT EFFECTS.**—These are those caused by dry heat (burns) and moist heat (scalds) and are dealt with at length in surgical textbooks. Suffice it here to say that a first degree burn (*erythema only*) arises when the heat causes drying of the surface but insufficient damage to lead to exudation into the skin. The treatment consists of the application of a bland animal fat such as lanolin, preferably mixed with mineral oils, as in the ointment of wool alcohols.

In a second-degree burn there is erythema and blistering, with a risk of infection once the blisters are broken and of loss of protein and electrolytes if the blistered area is extensive. Intact blisters should be punctured under aseptic conditions, allowed to collapse and then covered with a gauze dressing. The roofs of ruptured blisters should be cut away and the raw area swabbed with a 1 per cent. solution of cetrimide, in a sweeping centrifugal action. Tulle-gras dressings enable healing to proceed with the minimum of trauma to the young granulation tissue.

The treatment of third degree burns is a surgical matter.

**ELECTRIC BURNS.**—Electric burns are often painless, aseptic and dry, but slow in healing. The treatment is similar to that of other burns.

**CHRONIC OR RECURRENT HEAT EFFECTS.**—This causes the condition known as erythema ab igne, often seen on the legs of women. There is a pigmentary network corresponding with the sites of anastomoses between adjoining venous areas.

**CLIMATIC HEAT EFFECTS.**—Miliaria rubra (prickly heat). (See Anidrosis.)

### DERMATITIS DUE TO COLD

**PRURIGO HIEMALIS.**—An itching eruption occurring only in the winter, usually confined to the legs, sometimes affecting the forearms and thighs. Changes of temperature, for example undressing, hot baths, sitting near fires, precipitate the itchy episodes. The lesions are inconspicuous, patchy, mild lichenification and scratch marks and marked dryness of the skin.

Treatment consists of the avoidance of extremes of temperature and of the excessive use of soap. Calamine liniment is helpful.

**LIVIDO RETICULARIS.**—This is a condition in which the legs show a livid network of venules, the network corresponding to the anastomoses between the adjoining venous areas.

**CHILBLAINS.**—A chilblain is a static dilatation of venules secondary to anoxia caused by arteriolar spasm (see Vasomotor Disorders).

**IMMERSION FOOT (TRENCH FOOT).**—This is due to prolonged exposure to cold water, insufficient to cause frostbite. The feet are white, red or cyanotic. The patient complains of numbness and cramp. Minor injuries may cause gangrene. On removal from the cold, a red, swollen, blistering hyperæmic stage develops unless the parts are very slowly warmed.

Treatment is by gradual warming, cleansing and elevation of the limb, followed by exercise and the application of salicylic acid dusting powder.

**FROSTBITE (DERMATITIS CONGELATIONIS).**—This is due to freezing of the soft tissues with cessation of the blood flow. On thawing, there is an erythematous, a bullous or a gangrenous reaction.

**Treatment** is by very gradual defrosting and treatment of the damaged tissue on recognised surgical lines.

## DERMATITIS DUE TO ACTINIC RAYS

**ACUTE SOLAR DERMATITIS.**—This arises from excessive exposure to the sun and may occur in all degrees of intensity as with heat burns. It is treated on similar lines.

**CHRONIC SOLAR DERMATITIS.**—Repeated exposures to the sun cause premature changes of ageing in the skin. The physical signs consist of atrophy with telangiectasia, pigmentation and depigmentation, and a tendency to form keratoses. It is sometimes called "farmers' skin" or "sailors' skin" and is seen on the face and on the backs of the hands; rarely also on bald heads. Another condition, sometimes known as "peasants' skin", occurs on the back of the neck in the form of lozenge-shaped, pink, thickened areas of skin (see *Dermatitis rhomboidalis nuchæ*).

**ECZEMA AB SOLARE.**—This condition of hypersensitivity to light may present in many forms: hence the term "polymorphic light eruption". The same individual in one attack may show eczematous features and in another pruriginous ones. The lesions are on the forehead, cheeks, ears and exposed parts of the neck and limbs. Many substances applied to the skin have a light-sensitising effect. These include tar, bergamot oil, acriflavine, sulphonamides and eosin. *Dermatitis bullosa striata pratensis* is a bullous dermatitis of exposed parts coming on after contact with a light-sensitising plant followed by exposure to the sun (*phytophoto dermatitis*). Various plant juices including lime, figs, rue, wild parsnips, etc., may have this effect. Some drugs also have light-sensitising effects, particularly sulphonamides, and other drugs having hepatotoxic properties.

**PRURIGO ÆSTIVALE.**—This occurs in children and is a papulo-erythematous rash on the exposed parts which recurs only in summer months.

**HYDROA ÆSTIVALE VEL VACCINIFORME (HUTCHINSON'S SUMMER PRURIGO).**—This severe bullous eruption of the exposed parts recurs each summer most commonly in boys and is associated with congenital hæmatoporphyria. It results in pock-like scarring.

**XERODERMA PIGMENTOSUM.**—In this rare malady there is an inborn over-sensitivity to ultra-violet and visible rays and, as a result, senile atrophic changes resembling radiodermatitis develop at an early age and the sufferer may in adolescence begin to develop keratoses and skin cancers on the face, backs of the hands or on the legs.

**Treatment.**—The skin can be protected from ultra-violet irradiation by a cream containing 15 per cent. of para-aminobenzoic acid, 10 per cent. salol or 5 per cent. tannic acid, in hydraous ointment; or a particulate screen against ultra-violet and visible rays can be provided by the compound paste of titanium dioxide. Only calamine liniment is necessary to soothe any severe reaction.

## DERMATITIS DUE TO RADIOACTIVITY

X-rays and radium may cause acute changes in the skin, from one large exposure or several, or chronic changes from repeated small exposures.

**ACUTE EFFECTS.**—Kienböck classified X-ray burns as:

First degree: latent period 3 weeks; no visible inflammation; temporary shedding of hair.

Second degree: latent period 2 weeks; redness and swelling of the skin lasting 1 to 2 weeks; falling of the hair.

Third degree: latent period 10 days; redness, superficial erosion and vesiculation; parts restored to normal in 3 to 4 weeks.

Fourth degree: latent period under a week; necrosis with ulceration; healing takes 6 weeks or longer.

Treatment of X-ray burns is similar to that of other burns.

**CHRONIC EFFECTS.**—These are similar to those of repeated and long-continued over-exposure to the sun. There is atrophic scarring with pigmentation, depigmentation and telangiectasia. Keratoses develop and squamous carcinoma may be the final result.

## DERMATITIS DUE TO MECHANICAL CAUSES

Continuous pressure on the skin tends to cause pigmentation and atrophy.

Intermittent pressure causes corns and callosities.

The acute effects of friction include blistering and epidermolysis bullosa; the more chronic ones lichenification and hyperkeratosis.

Excessive wetting of the skin causes the epidermis to become sodden and prone to fungous and coccal infection. Excessive dryness of the atrophic skin causes a condition resembling a dried-out mud bank with irregular or rounded areas, peeling at their margins and with shallow fissures between them (eczema craquelé) or deep fissures, perhaps with secondary infection.

## DERMATITIS ARTIFACTA

Hysterical personalities sometimes produce blisters and sores on the skin by physical or chemical means and in so doing gain the sympathy, freedom from work, and (sometimes) pecuniary gain that they so much desire. Of these motives, the desire for attention, loving care and sympathy is the strongest. The lesions may be produced by sharp instruments, friction, constricting bandages, hot coins, cigarette ends, caustic liquids and in various other ways.

**Clinical Picture.**—The patient is usually a young woman. Usually there is a trivial wound or burn which does not heal as soon as might be expected; on the contrary, it extends with blistering or sloughing ulceration. The lesions are bizarre, discoid or linear, sometimes with straight edges. Hot coins cause round blisters, cigarette ends cause small sloughing ulcers and caustic liquids cause linear discolourations, dermatitis or sloughing, often with a gravitational trickle where the caustic has flowed over the surface. The lesions are always at sites easily reached by the right hand in right-handed persons and at sites easily reached by the left hand in left-handed persons; the face, breasts, forearms and hands are favourite sites.

The patient shows the "belle indifférence" of the hysteric and examination reveals Charcot's triad of anaesthesia of the cornea and pharynx, with suggestion anaesthesia of the skin, perhaps in glove and stocking distribution.

Hysteria cutis is also seen in other guises. When compensation claims remain unsettled, occupational dermatitis may continue as lichenified dermatitis long after the patient has been removed from the irritant. This occurs particularly at the bends of the elbows in what may be called "maintained dermatitis".

In several other skin reactions, particularly pompholyx, eczematous dermatoses, pruritus vulvæ, infective dermatitis, and psoriasis, the persistence of the dermatosis or its exacerbation often seems to serve the purpose of enabling the patient to avoid some repugnant task or action and to receive care and attention. The psychodermatological mechanisms of these conditions has not yet been explained.

**Treatment** of all these hysterical reactions is extremely difficult. It is one thing to understand the psychological mechanism but quite another to help the patient towards a better and more positive attitude to life. It is useless to accuse the patient: it will be indignantly denied. A reasonable level of self-esteem must be maintained. Often the physician has to be satisfied with relief of the current manifestation by a modicum of sympathetic care and occlusive dressings, knowing very well that the hysterical personality persists and will continue to react in this fashion to sundry future life situations. Care should be given to finding suitable occupations, when work-shyness is a factor. The home conditions should be investigated and an attempt made to modify any unsuitable attitude of relations.

## DERMATITIS DUE TO CHEMICAL SUBSTANCES

Chemical substances may come into contact with the skin in gaseous, liquid, particulate or solid form, and in so doing may cause dermatitis. Two types of contact dermatitis are recognised:

(1) **DERMATITIS DUE TO PRIMARY IRRITANTS.**—These are substances that cause dermatitis in everyone if they are applied to the skin in sufficient concentration and for sufficient time. They cause physio-chemical alterations in the structure of the skin and act in various ways, mechanical, physical or chemical. They may abrade the surface, destroy keratin, abstract fat or mix with skin fat, macerate or desiccate, precipitate protein, oxidise or reduce, hydrolyse, form toxic nitro-derivatives, or stimulate keratin formation. Primary irritants include inorganic acids and alkalis, certain inorganic elements and salts, organic acids, solvents, essential oils, certain dyes and tar and petroleum products.

(2) **DERMATITIS DUE TO SENSITISERS.**—These are substances which provoke dermatitis only in a few hypersensitive persons. They consist mainly of complex organic chemicals, certain vegetable and animal products, and a few inorganic chemicals which are able to take on sensitising properties when they are combined with protein. They include plants, dyes, developers, rubber accelerators and antioxidants, soaps, insecticides, cosmetics, oils, resins, coal-tar derivatives and explosives. Certain chemicals and plants have a photo-sensitising effect on the skin, for example, tar, eosin, acriflavine, sulphonamides and various plants, including wild parsnips, figs, rue and many others. Some substances can act both as primary irritants and as sensitisers. For example, soap has a primary irritant effect from its alkalinity and may have sensitising potentialities from the fatty acid part of its molecule. Traces of chromium in cement may be responsible for sensitisation dermatitis from contact with this substance. Bacteria, fungi and parasites may cause or complicate occupational dermatitis.

**Ætiology and Pathology.**—*Predisposing causes of dermatitis.*—Race, complexion, sex and age all modify the tendency to dermatitis. White races are, on the whole, more susceptible than dark races, and blondes more than brunettes. Women are more susceptible than men, and children and the aged are more susceptible than young or middle-aged adults. But there are exceptions to these generalisations. Sweating may leach out irritants from solids touched; hairiness may carry with it some follicular vulnerability; and although a greasy skin enables a person better to withstand contact with degreasing agents, it also may expose him to greater peril from irritants that are miscible with skin fat. Seasonal effects of sweating in the summer and chapping in the winter may be important. An inherited susceptibility, lack of cleanliness or reckless methods of cleaning up after work, fatigue, emotional instability or an anxious, obsessional temperament and malnutrition, may all play a part.

*Precipitating causes.*—The primary irritants most commonly responsible include soda and alkaline soaps, cement and lime, paraffin oil, petrol, diesel oil and turpentine

or turpentine substitutes, lubricating, cooling and cutting oils, glue, formalin, phenol, ultra-violet or X-irradiation, or friction from gritty particles. The sensitisers are many and include medicaments such as sulphonamides, benzocaine, penicillin, flavine, streptomycin, formalin, Lysol, Dettol and adhesive dressings; plants, particularly *Primula obconica*, chrysanthemums and many others, teak, ebony and other woods; cosmetics including paraphenylenediamine hair dye, eosin in lipsticks, nail varnish, bergamot oil andorris root powder; clothes and jewellery including dyed furs, wool and rubber, chromium and nickel plating; occupational hazards involving work with mercury, chromium or nickel, dyes and explosives, flour improvers, rubber antioxidants and very many others. Occupations with more than average dermatitis hazards include bakers, carpenters, cleaners, dentists, doctors, dustmen, dyers, florists, french polishers, garage hands, gardeners, housewives, labourers, machine hands, miners, nurses, painters, photographers, platers, rubber workers and tar workers.

The development of dermatitis from primary irritants depends, *inter alia*, on the possession of skin secretions with poor alkali-neutralising properties; on some degree of xeroderma, with insufficient sebum production to replace that removed by fat solvents and emulsifiers; and on thinness of the horny layer.

The cause of eczematous eruptions is the sensitisation of the epidermal cells to a continuously or repeatedly encountered agent. It is possible that a heightened excitability of the nervous system as a whole (of which the skin is an end organ) is one important factor. Sufferers from eczematous eruptions often show emotional lability which is more marked during exacerbations of the dermatosis; and outbreaks may coincide with events causing emotional conflict.

The mechanism of spread of eczematous sensitisation is far from settled. There is some evidence that the lymphocytes convey antibodies to remote areas of the skin. The manner of spread of eczematous processes also suggests nerve transmission as being partly responsible. Sensitisation often spreads at first locally and then to a similar site on the opposite limb and to the comparable situation on the other two limbs, before becoming generalised. Examples of this include eczema of one leg spreading to the other and then to the forearms; and ringworm of the feet with its manual mycoid eruption.

The incubation period, from the first application of a substance to the development of sensitisation, is variable and often indeterminable. Flavine and sulphonamides may sensitise after 4 days, penicillin after 8 to 10 days and some other substances after a longer interval. Traumatic breaks in the continuity of the surface of the epidermis are most important. The prickle cells of the Malpighian layer are normally protected from external noxae by an intact horny layer and they react violently if they are exposed to primary irritants or to sensitising substances.

In the acute stage there is spongiosis (intercellular and intracellular œdema) in the prickle cell layer, causing microscopic or macroscopic vesicles and a variable degree of disintegration of the epidermis. In the dermis a lymphocytic infiltrate surrounds the dilated vessels, the sweat glands and the pilosebaceous follicles. In the subacute and chronic forms there is parakeratosis (nucleated horn cells), acanthosis and a chronic inflammatory infiltrate in the dermis.

The histopathology of dermatitis due to primary irritants differs from that of sensitisation dermatitis in that the infiltrate is more polymorphonuclear in the former and lymphocytic in the latter.

**Clinical Picture.**—In the most acute forms due to caustics there is destruction of the epidermis before an inflammatory reaction can develop. In less acute forms there is smarting, redness and swelling, going on to vesiculation and blistering, and a raw surface. In subacute forms there is papulo-vesiculation with abnormal scaling. Milder and chronic forms present as redness and pathological scaling with lichenification, increase of pigmentation and a tendency to fissuring.

The reaction usually remains localised to the site of contact, sometimes with an

overlap of up to 0.5 cm., apparently from a local reflex: but if the irritant or sensitiser is in liquid or semisolid form, as often applies with contact medicaments, the dermatitis tends to spread up to and just beyond the limits of each application. If the irritant or sensitiser is miscible with sebum, the reaction may be mainly follicular, and discrete follicular papules may develop beyond the zone of confluent dermatitis.

Dermatitis varies in appearance according to the stage at which it is seen. Erythema, papulation or vesiculation predominate in the earlier stages; later, according to the degree of secondary infection or of rubbing and scratching, it may go on to pustulation with moist infected scabs on an exuding surface, or to lichenification and blood scabbing. If neither complication develops, resolution follows on the moist exuding surface by serous scabbing, decreasingly coarse scaling, diminution of redness and a return to the original state. If at any stage a further contact with the causal agent takes place, the whole process may recur.

**Course and Prognosis.**—This depends on the discovery of the cause and the possibilities of its subsequent avoidance. Sometimes a trade irritant can be replaced by something harmless; sometimes a process can be modified so as to lessen the exposure of the workman; sometimes protective clothing, better ventilation and washing facilities are all that are needed. "Hardening" by continuous re-exposure is not likely to be successful. With some specific sensitisers (for example streptomycin) desensitisation can be carried out; with others there may be a group sensitivity to chemically similar substances (for example sulphonamides, flavine, benzocaine, paraphenylenediamine) or there may be a nonspecific broadening of sensitivity to many substances probably accompanied by increased emotional lability. In this last form the prognosis is poor, the causes often being undiscoverable.

Diagnosis of primary irritant and sensitisation dermatitis on the face has to be made from solar dermatitis, facial prurigo, urticaria, infective dermatitis and erysipelas; on the body from ringworm, seborrhoeic dermatitis, pityriasis rosea, lichen planus, psoriasis and parapsoriasis; on the hands from nummular eczema, mycides, erythema multiforme and psychogenic pompholyx.

Solar dermatitis affects the forehead and malar ridges; contact dermatitis more characteristically affects the eyelids, lips and neck; facial prurigo is accompanied by hay fever, asthma or flexural dermatitis; urticaria is not accompanied by peeling; erysipelas has a brawny, spreading edge and there are constitutional symptoms; on the body the other diseases and reactions are usually more circumscribed; on the hands nummular eczema affects the backs, but adjoining areas escape entirely, whereas with dermatitis the clefts are more typically affected and the eruption is more diffuse. Psychogenic pompholyx is symmetrical, whereas eczematous dermatitis of the hands may be asymmetrical. At all sites frictional dermatoses (lichenification) have to be differentiated from spontaneous eruptions (eczema-dermatitis).

The label "contact (eczematous) dermatitis" having been affixed on the basis of the morphology of the lesions, the physician's more difficult task is to find the cause. For this purpose it is necessary to know the ways in which sensitising substances may come in contact with the skin, and the likelier causes of eczematous dermatoses affecting various parts of the body. The problem is easier in dermatitis produced by primary irritants than when sensitisers are responsible. The history is all-important, with possible seasonal fluctuations, relief at week-ends or on holiday, and other significant evidence that the patient alone can supply. Leading questions are necessary to uncover possible occupational causes, including hobbies, hygienic practices, clothing, cosmetics, jewellery, plants and other volatile agents, day by day contacts and past treatments. Sometimes the history can be supplemented by a diary of daily contacts kept by the patient, after which patch tests can be performed with suspected sensitisers. The distribution suggests the likely causes.

On the scalp the likely causes include paraphenylenediamine hair dye, permanent

waving solutions, brilliantine and perfumes, hair lacquers, hat-bands and, occasionally, medicaments. On the face, air-borne and inadvertently hand-transferred substances have to be considered, also topical medicaments and cosmetics. The eyelids are particularly affected by vapours and plant pollens; thus, formalin vapour, primulae, chrysanthemums, streptomycin are common causes, as are also eye lotions, drops and ointments, and occasionally nail varnish and other hand-transferred agents. On the neck, hair dyes, fur collars and other dyed materials are suspect; also hand-transferred irritants and dusts having a primary irritant action such as lime or cement. Dusts also affect sites of pressure from clothing and within the socks, as well as the hands. Clothing, when occasionally it is causal, tends to affect the neck, the axillary folds, the belt line, the buttocks, hips and perineum, the sock areas and the dorsa of the feet. Nickel-plated fittings and jewellery may affect many sites, including the neck, lobes of ears, mid-line of back, wrists and thighs.

The pattern of contact dermatoses on the hands depends on the physical nature of the contactant, solid, particulate or liquid, as well as on its chemical properties. Liquids tend to affect the fronts of the wrists and the clefts of the fingers; powders have a more diffuse action; inserting the hand into containers of powders or liquids may cause an eruption on the back of the hand; and objects handled may occasionally cause eruptions at various sites, depending on the type of grip.

The accurate recognition of sensitisers depends to some extent on patch tests. These are helpful if the results are interpreted correctly. For success there should be: adequate control; suitable concentrations of the suspected sensitisers; no patch testing with primary irritants; inspection at 48 hours and reinspection at 3 to 5 days. Contact eczematous responses (erythematous-vesicular) must be differentiated from follicular obstructive effects (folliculo-papulo-pustular) and noted at the time of removal and from the trauma of removal of the adjoining adhesive (erythematous-folliculo-papular occurring within a few minutes of removal). The conditions of patch testing and those in which the sensitiser is met in everyday life can never be identical (site, sweating, abrasions, fissures, friction, etc.) and allowance has to be made for this. A positive patch test does not of necessity prove that the dermatosis was produced by this substance, and a negative patch test does not completely rule out that the tested substance has been the cause of the original dermatitis. Patch tests are best performed on the back of the chest. The patient should not know which patch is which, but suitable identification marks should be made on the adhesive dressings. Patch testing should not be performed in the presence of active dermatitis; and if the dermatitis has been severe, patch testing should only be performed after complete clearance and with expert supervision, the patient being instructed to remove the patches at once if a severe reaction occurs. If this is not done, an acute relapse may result at the sites of the original eruption.

**Treatment.**—This consists of prevention, desensitisation when possible and symptomatic treatment.

The essentials in the prevention of occupational dermatitis are selection of the most suitable workers, their protection at work, their periodic inspection and supervision to see that precautionary measures are conscientiously carried out, and the provision of adequate washing facilities. Selection includes rejection of hyperhidrotic, seborrhoeic or xerodermatous individuals or those with prurigo, tinea pedis or acne vulgaris as far as certain trade procedures are concerned. Protection includes good ventilation, abatement of humidity, exhaust draughts, suitable clothing and goggles, and barrier creams which may have either water-repellent or oil-repellent effects and also emollient properties. Inspection covers not only the working conditions and the proper use of protective appliances but also medical inspection of the workers for minor injuries and infections that may be the precursors of something more serious. Washing facilities must be adequate and the worker must be discouraged from using paraffin, petrol, scouring agents and other primary irritants for cleaning



the skin. In some industries these are the cause of more sickness than the industrial hazards themselves.

Desensitisation can occasionally be performed, for example, in streptomycin cutaneous sensitivity, by graduated intradermal injections. This procedure is most valuable when the sensitivity interferes with a person's skilled occupation; but if the work is unskilled and there are opportunities for alternative employment, it is better to remove the patient from the irritant than to attempt desensitisation; furthermore, hypersensitivity is often nonspecific and multiple, sometimes only to similar chemical substances such as sulphonamides, but in others to dissimilar substances, and even to physical agents such as light.

Attempts at "hardening" by continuing to expose the worker to an occupational sensitiser are more likely to bring about ever-increasing sensitivity, ending in generalised eczema, than to succeed in enabling him to continue in the work.

Local treatment in the acute phase consists of applications of oily calamine lotion with light dressings of butter muslin (which gets less entangled in the scales and crusts than does surgical gauze) held in place by cotton bandages. The dressings are changed only once a day, a bland vegetable oil or liquid paraffin being used gently to remove debris from the surface of the skin before another application of lotion is made. For any infection that may develop, soaks in 1 in 6000 solution of potassium permanganate are helpful, with applications of the appropriate antibiotic, depending on the cultural findings.

As the condition gets less acute, zinc or calamine cream or hydrous ointment may be used, and when the eruption becomes scaly Lassar's paste or the ointment of wool alcohols are more useful. Finally, if lichenification is tending to develop, a 2 per cent. tar paste makes a useful antipruritic application. It is most unwise to use tar in the earlier stages and its use should be abandoned at once if there seems to be any tendency to the development of folliculitis. At no stage should benzocaine anaesthetising substances be used in local applications as they have a great tendency in themselves to cause eczematous dermatitis. Similarly, antihistamines are best avoided because eczematous dermatitis develops in about 3 per cent. of cases in which they are used. X-irradiation in fractional exposures is valuable in the chronic phase if the eruption persists in spite of nonexposure to the irritant.

General treatment consists of rest, to the body as a whole in widespread cases and to the affected part in local cases. Sunlight, heat and cold should be avoided. Ample sedation to relieve the pruritus should be given. In generalised cases due to sulphonamides, flavine and other hepatotoxic substances, the course may be shortened by intramuscular injections of a crude liver extract 4 ml. daily.

## INFECTIVE (SEBORRHŒIC) DERMATITIS

This is one of the commonest and most important of skin diseases. The term applies to many dermatoses, differing in situation and pattern, but in all of which there is a qualitative abnormality of the sebum. The patient's skin is unduly susceptible to bacterial and fungous infection, chemical and physical injury and emotional stress.

**Ætiology and Pathology.**—The triad of organisms found in seborrhœic dermatoses are the pityrosporon of Malassez (bottle bacillus), the acne bacillus and the *Staphylococcus saprophyticus*. The organisms do not fulfil Koch's postulates in their relationship to seborrhœic conditions and they must be regarded as secondary invaders of the abnormal sebum, follicles and horny layer.

Histologically, there is parakeratosis, hyperkeratosis and spongiosis (intra- and intercellular œdema of the prickle cell layer). In the dermis, there is a lymphocytic infiltrate of moderate degree, with dilatation of the vessels.

The seborrhœic individual is often obese and may indulge in fats and carbohydrates to excess, while taking insufficient exercise. The diet is often deficient in foods containing protein and vitamins. Drugs taken internally (for example sulphonamides) and various chemicals applied externally (for example flavine, sulphonamides, penicillin, antihistamines and some occupational irritants) may provoke an infective outburst; and emotional disturbances causing fear and loss of self-esteem may have a similar effect.

**Clinical Types.**—There are three grades of intensity in infective dermatitis. In the first and mildest there is a fine grey, dry scaling showing on the scalp as dandruff or scurf (pityriasis simplex, seborrhœa sicca) without reddening of the underlying skin.

In the second grade, the scales are coarser and look and feel greasy (pityriasis steatoides). (This is due to a cellular infiltrate amongst the cells; their fat content is not increased.) The lesions may be solitary and pinhead sized; grouped or confluent, and are found particularly where pilosebaceous follicles are most abundant.

In the third grade, there are moist red, shiny exuding areas of skin with a seropurulent exudate and frank follicular pustules around. The flexures are particularly affected and the horny layer of the opposing surfaces gets partly rubbed off and, with the white sodden portions of epidermis remaining around a red, shiny centre zone, gives the picture of intertriginous dermatitis. Greasy crusts of seborrhœic impetigo may occur on the face and elsewhere. Pyogenic staphylococci or hæmolytic streptococci may be found on culture; or there may be a mixed infection with Gram-positive cocci and Gram-negative faecal contaminants.

The sites commonly affected by infective dermatitis, either alone or in combination, are the scalp, brows, lashes, eyelids, conjunctivæ, inner and outer canthi, nasolabial folds, the vestibule of the nose, postauricular folds, outer ears, aural meati, vermilion surface of lips, angles of the mouth, beard, sweat grooves of centre of trunk, submammary region, axillæ, navel, pubis, glans penis and coronal sulcus, vulva, genitocrural folds, intergluteal cleft, toe clefts and, in discoid form, on hairy areas of arms, forearms, thighs and legs, as well as on the trunk.

The possibility of an underlying infective dermatitis has to be considered in many cases of contact dermatitis, and the converse also applies; the diagnosis of infective dermatitis should not be made lightly without giving much thought to a possible contact cause for the attack.

*On the scalp*, there may be simple scurf (pityriasis simplex) on skin of normal colour, or there may be profuse and widespread greasy scaling (pityriasis steatoides) on a reddened itchy skin, the condition often extending a little on to the forehead as the *corona seborrhœica*. The hair tends to fall more rapidly. When the scalp becomes further infected with pathogenic cocci, a condition of golden-crusts and purulent seborrhœic impetigo arises.

*On the ears*, there may be a scaly and inflammatory condition of the meati, perhaps with exudation or with folliculitis and perifolliculitis of the ceruminous glands, giving rise to much pain and to varying degrees of meatal stenosis and deafness (meatitis), or the skin of the external ears may be inflamed (otitis externa) and scaling or exuding. Above, behind and beneath the ears the inflamed skin is very liable to crack, and the painful fissures may form a portal of entry for streptococci, causing streptococcal dermatitis or cellulitis (erysipelas). The ears are often contaminated with Gram-negative faecal organisms as well as with pathogenic cocci.

*The eyes* may be affected in various ways—folliculitis of the brows or of the lashes (blepharitis) or styes; inflammation of the skin and folds of the upper lids; conjunctivitis with chemosis and a slight sticky discharge, or scaling and fissuring of the outer canthi.

*The nose* may have greasy scales and follicular plugs on the nostrils and at the nasolabial folds. There may be a vestibular folliculitis.

The vermillion surfaces of the lips, particularly the lower, may show scaling and a tendency to crack (cheilitis exfoliativa) and angular stomatitis with fissuring is common.

The beard area may be affected with a frank folliculitis (seborrhœic sycosis) or there may be patchy or diffuse redness and exudate or scaling. Occasionally impetigo is superimposed. "Seborrhœic" individuals are very susceptible to the haphazard and uncontrolled use of antibiotics and antiseptics on the skin; this is partly because they are very liable to become sensitised to topical agents, either the active component or the vehicle, and partly because the use of antibiotics without previous culture and antibiotic sensitivity testing of the organisms grown often means that an unsuitable antibiotic is applied, with the result that the causal organisms thrive, perhaps even being helped by the removal of competitors relatively harmless to the host.

On the trunk, pityriasis simplex and steatoides are common in the mid line "sweat grooves". In the obese, intertriginous dermatitis may occur in all grades of severity in the axillary domes, under the breasts, at the navel, in the genitocrural folds and between the buttocks, even under pendulous abdominal folds of fat. Satellite follicular papulo-pustules are grouped around the main lesions. The coronal sulcus may be inflamed and balanitis supervenes (infective balano-posthitis). Folliculitis of the pubis in varying degrees of intensity is present in the most intractable forms of this malady.

Discoïd or petaloid lesions of infective dermatitis may occur on the trunk and on the limbs, particularly across the scapular region and on the extensor aspects of the limbs, even involving the backs of the hands or feet. These lesions may be scaly, sharply demarcated discs and ovals with a few discrete guttate papular lesions or, in the more acute form, there may be eczematous papulo-vesicular discs going on to exudation and crusting (seborrhœic, nummular or discoïd eczema, staphylococcide).

Intertriginous dermatitis between the toes makes an ideal medium for the growth of monilia and is a commoner cause of "foot rot" than is pathogenic fungus infection in this region.

In addition to all these patterns of infective dermatitis, there are "seborrhœides" or "eczematides", conditions in which the use of one or other of various topical remedies sets off an explosive outburst of a papulo-vesicular nature, at first near the site of application, later contralaterally and, finally, in widespread fashion. This condition is thought to be due to the development of sensitisation to bacterial or fungous products or the patient's own disintegrating epidermal cells, or to the topical agent used (see autolytic eczema). It only occurs when there is profuse exudate or maceration at the primary site affected.

Course and Prognosis are uncertain, owing to the constitutional factors concerned. If the causal factors—dietetic, drug, contact, emotional—can be altered or removed, there is a reasonable prospect of success; in cases where this is impossible for reasons of age, environment or disposition, the outlook is proportionately bad.

Diagnosis.—On the scalp, the diagnosis is made from ringworm in children by examination for broken hairs, microscopy and Wood's light examination. Psoriasis of the scalp causes palpable discoïd lesions, with heavy scaling, whereas in seborrhœic dermatitis the lesions are impalpable except when impetiginised. On the trunk, the diagnosis is from pityriasis versicolor, pityriasis rosea, ringworm, psoriasis and parapsoriasis (q.v.).

Treatment.—The general treatment consists of dietetic adjustment, the withdrawal of any harmful contact or drug irritants, and emotional adjustments where necessary or possible.

The diet should be low in carbohydrates and fats and sufficient in protein and vitamin content. The urine should be tested for albumin and sugar. Alcohol, chocolate, fried and spiced foods should be taken in strict moderation. Vitamin B

complex and crude liver injections may help in cases with a history of dietetic imbalance or with evidence of hepatotoxic effects from a drug or other cause.

*Local treatment for the scalp*—a shampoo of 1 per cent. cetrimide is most useful and this substance may be used for cleansing other affected areas of the skin.

For pityriasis simplex, a lotion such as that of salicylic acid and perchloride of mercury (N.F.) is useful, rubbed in daily and gently with the finger-tips.

For pityriasis steatoides of the scalp, the ointment of salicylic acid and sulphur (N.F.) is most useful, but the strength should be reduced to 1 per cent. when using it on children's scalps.

For impetiginised lesions, it is advisable to have a culture made and to use the best antibiotic according to the findings. Until this result is to hand, the use of 1 per cent. cetrimide, followed by zinc and copper lotion (D'alibour water) as a local application, should help.

For infective dermatitis on the *trunk*, the emulgent base in salicylic acid and sulphur ointment is likely to aggravate and recourse should be had to 1 per cent. of sulphur or ichthammol or to 0.1 per cent. of pyrogallol in calamine liniment or, if there is more obvious infection, Vioform cream (3 per cent.) (Ciba) is often helpful.

For *intertriginous dermatitis*, antibiotics are best held in reserve until the cultural findings are known and recourse should be had to fungistatics such as magenta paint or to brilliant green 1 per cent. in zinc paste, or to Vioform cream. When the moist phase has passed, the patient should apply a bland dusting powder, for example boric tale powder, or salicylic acid dusting powders, and keep the opposing skin surfaces apart with uplift breast supports and suitable clothing, or gauze dressings.

## OTHER FORMS OF ECZEMATOUS DERMATITIS

The term "eczema" implies a "boiling over" of the skin, and should be confined to spontaneous eruptions characterised clinically by papulo-vesiculation and microscopically by spongiosis. This definition excludes all primarily frictional dermatoses such as lichen simplex (neurodermatitis circumscripta) and disseminated neurodermatitis (atopic dermatitis).

A condition of uncertain status is *exudative neurodermatitis*, in which extensive areas of exudation and crusting are present, chiefly on the more distal parts of the limbs. It is found in persons with hysterical traits and appears to be an exudative response to emotional stimuli, particularly self-pity.

## NUMMULAR ECZEMA

Nummular (discoïd) eczema (infectious eczematoid dermatitis) is an outbreak of papulo-vesicles, often confined to the more hairy surfaces of the limbs, particularly the forearms and legs, but sometimes becoming more generalised. Sometimes discrete shotty vesicles appear as well. A chemical contactant cannot be incriminated and the malady is probably related more to sensitivity to skin-resident organisms, particularly *Staphylococcus saprophyticus* and monilia.

Infectious eczematoid dermatitis is a disorder closely related to nummular eczema, in which the discharge from an area of infective dermatitis produces a mixed eczematous and infectious (impetiginous) reaction wherever it touches.

**Treatment.**—Nummular eczema responds best to nonsensitising bacteriostatic and fungistatic remedies, such as chlortetracycline ointment, chloramphenicol cream, Vioform cream, magenta paint, or brilliant green in zinc paste. Symptomatic treatment should also be given to relieve depression, if present, by dextroamphetamine 5 mg. in the morning; and insomnia from itching by barbiturates or promethazine

hydrochloride in the evening. In resistant forms a course of intravenous T.A.B. 25 million, 50 million and 100 million organisms at 5 to 7 days' intervals may bring about a remission. X-irradiation in fractional doses is often effective.

### POMPHOLYX (DYSIDROSIS)

This is a vesicular eruption of the palms, and of the palmar and lateral aspects of the digits and of the under-surfaces of the feet. It is often recurrent.

**Ætiology and Pathology.**—This is a skin reaction which may be secondary to fungous infection of the feet (mycide); it may be a manifestation of eczematous dermatitis, exogenous or endogenous; or it may be of psychogenic origin, an hysterical phenomenon serving the purpose of preventing the sufferer from performing some task which is distasteful.

Histologically there is spongiosis as in eczematous dermatitis elsewhere. The vesicles remain intact owing to the thick horny layer above them. There is no evidence of obstruction of the sweat ducts, except secondarily through pressure from the adjacent vesicles, but clinical experience of the seasonal incidence and of aggravation by heat, exertion or anxiety suggests that some abnormality of the sweat apparatus (so far unexplained) plays a part in the pathogenesis.

**Clinical Picture.**—There are vesicles of uniform size, resembling frog spawn in the skin of the palms and fingers and on their lateral aspects. The backs of the hands may be quite normal. The feet may show a similar condition in a comparable distribution. The affected areas do not sweat. There is considerable itching until the fluid is either reabsorbed or discharged by rupture of the vesicles. Coarse peeling follows and resolution may occur, or the whole process may be repeated.

**Course and Prognosis.**—This depends on the cause, whether it be fungous infection, eczematous hypersensitivity, or an hysterical personality. The form due to fungous infection does well when the infection is controlled. The other two forms tend to recur unless a sensitising substance can be found and subsequently avoided, or unless the patient can be brought into better adjustment with life situations.

**Diagnosis** is from pustular psoriasis, erythema multiforme and tinea pedis. The former presents with golden yellow pustules from the beginning, whereas in pompholyx the vesicles are skin-coloured at first.

In erythema multiforme there may be large bullæ and there is also erythema, which is absent in pompholyx.

**Tinea pedis** presents with large bullæ in the roofs of which mycelial threads may be found on microscopy; but the same foot may also have on it many small vesicles of pompholyx type (mycide) in which fungus cannot be found. **Tinea pedis** is often asymmetrical, its mycide symmetrical; idiopathic eczematous and psychogenic pompholyx are symmetrical, but contact eczematous dermatitis is often asymmetrical.

**Treatment** is bland and supportive by Lassar's paste, hydrous ointment or calamine lotion, while the fungous infection is being controlled, while irritants and sensitisers are being avoided, or while the patient is receiving psychotherapy. If infection becomes superimposed—and this often occurs, with purulent blebs, lymphangitis and lymphadenitis—the part should be elevated and kept at rest. Soaks for 10 minutes in a 1 in 6000 solution of potassium permanganate are useful and sulphonamides or penicillin may have to be used systemically.

In many patients it is necessary to give sedatives, for example phenobarbitone in a dose sufficient to control itching and to provide sleep.

### AUTOLYTIC ECZEMA (ECZEMATIDE)

This is a widespread papulo-vesicular eruption arising from absorption of products from an area of erosion or of ulceration. The absorbed products may originate from

organisms on the skin or they may result from the breakdown of body cells. The process is more likely to occur with the use of certain substances on the skin, particularly sulphonamides, flavine, paraphenylenediamine, benzocaine, mercurials, etc.; but it may even develop from the occlusion of a moist area by soft paraffin, which suggests that the substances applied are not primarily responsible but that they hasten cellular disintegration or encourage infection. Autolytic eczema typically arises from faulty treatment of ulcers or eczema (eczematide) on the legs but it also arises from over-treatment of extensive abrasions, second-degree burns, herpes simplex, eczematous or infective dermatoses.

**Prevention and Treatment.**—This condition is preventable by avoidance of the use of powerful sensitising agents on the surface, such as sulphonamides, flavine, picric acid, mercurials and benzocaine; also by not using occlusive soft paraffin dressings over moist areas.

It is best treated by application of oily calamine, the use of sedatives and intra-muscular crude liver extract injections.

## ENDOGENOUS ECZEMA

A widespread papulo-vesicular eruption for which no immediate contact cause can be found. Sometimes the epidermal sensitisation has arisen from the administration of a drug (for example sulphonamide) previously used topically; but often the most careful history fails to elicit any cause in the form of a focus of infection, drug, food or metabolic disorder. Such patients are often tense, over-active, obsessional personalities, and this make-up seems to be of aetiological significance.

**Treatment.**—Bed rest is advisable in the more severe forms. Suspected foci of infection are treated and the patient is given a diet of high protein and vitamin content which is not water-retaining. The intake of fats and carbohydrates, alcohol, coffee and condiments is reduced. Sedatives are given by mouth and bland local applications are used. T.A.B. injections are sometimes useful. If the condition is believed to be an exudative neurodermatitis, the patient should be encouraged to lead an active life and to discard feelings of self-pity if, as often happens, these are present. Dextro-amphetamine 5 mg. after breakfast is a useful remedy for this type of patient.

## INFANTILE ECZEMA

The term covers infective eczema of infants and the earliest papulo-squamous stages of the condition called "Besnier's prurigo" later in life. Both forms may coexist.

*In the infective variety there is greasy scaling of the scalp and sometimes of the face, chest and flexures. The child is usually overweight.*

*In the pruriginous form there is a widespread erythematopapulo-squamous rash with exudation and crusting affecting particularly the face and parts of the limbs and body most accessible to the infant's efforts at scratching and rubbing, that is, the shoulders, elbows, wrists and hands, knees, legs and feet. The trunk is only slightly affected, with a blotchy erythematopapular eruption.*

**Ætiology.**—Infantile eczema is in part due to inherited abnormalities, in part to an unfavourable emotional environment and in part to faulty feeding practices. It is seldom due to allergy to foodstuffs.

*In the infective form, an excess of fat or carbohydrate in the diet is often an important factor. This may occur because the child is weaned at an early age on to a full cream milk because of failure of lactation. It may also occur at or about 6 months because the child is given excess of cereal foods. The skin as a result becomes*

susceptible to infection by organisms resident on the skin (monilia and *Staphylococcus saprophyticus*).

In the rare allergic form, milk (lactalbumin) or cereal products are usually responsible.

The more common pruriginous form (atopic eczema) is in part due to an inherited predisposition and in part due to an unsatisfactory mother-child relationship, in which an emotionally labile mother, who is unable to give the child the steady and unselfish affection it needs, clashes with a child of higher than average intelligence and peculiarly prone to itching and frenzied rubbing and scratching whenever deprived of pleasurable activities or of affection. Pruriginous eczema sometimes complicates xeroderma.

**Course and Prognosis.**—The infective type tends to clear up with suitable dietetic adjustments and local treatments, but it may relapse.

The allergic form responds to the withdrawal of the proven allergen provided this is the only cause.

The pruriginous form tends to get better at 1½ to 3 years when the child can do more for itself in exploration of its environment. There is, however, often a recrudescence at or about puberty, this time with a preponderance of facial and flexural involvement (Besnier's prurigo).

**Diagnosis.**—The affixment of the label "eczema" offers no difficulty; the problem is to apportion blame to inheritance, environment, diet and infection, and this depends on a careful review of the history and signs.

**Treatment.**—In the infective form, the protein, vitamin and mineral content of the diet should be rendered adequate but fats and carbohydrates should be reduced. Thus, egg yolk, bone broth, sheep's brains, tripe and pounded fish may be recommended, with spinach purée and other sieved vegetables; cereals, full cream milks or addition of sugar are best avoided, half-cream milk being offered instead.

Local treatment depends on the degree of infection. If this is severe, the most suitable antibiotic should be applied. If milder, the skin may be cleaned with a 1 per cent. solution of cetrimide, and 1 per cent. of salicylic acid and of sulphur in an emulgent base applied. Later, oily calamine lotion can be substituted.

The child should be cleaned as a routine with olive oil, and a superfatted soap used when necessary.

The diagnosis of allergic eczema is made by elimination diets. Cow's milk is first omitted. If there is improvement lactalbumin of milk is suspected as the cause. If there is no improvement, cow's milk is given alone for 24 hours and then one item is added each day until any aggravating factor or factors are found. Those are then omitted from the diet. If cow's milk is the cause, goat's milk can be substituted or a lactalbumin-free product (for example Allergilac).

Pruriginous eczema depends for its control on adjustments in the mother-child relationship as well as on all the physician can do by bland local applications, restraining appliances and sedatives. The mother and all around the child should be encouraged to generate a calm and unselfishly affectionate atmosphere. The child should be kept fully occupied with suitable toys on which he can relieve his aggressive urges; but in infancy it may be necessary to tie the limbs with broad crepe bandages to the sides and foot of the bed, providing adequate protection to the skin where they are applied, so that damage cannot occur. It is only in this way, and with sedation pushed to the limit, that the child can be kept from rubbing and scratching its face and limbs until they are raw. Eczematous children tolerate sedatives such as phenobarbitone in higher doses than the more normal child, and a dose of gr. ½, three or four times a day for a child 12 months old is nothing unusual. In milder cases the elixir of Benadryl or of promethazine hydrochloride, or a chloral and potassium bromide mixture may be sufficient.

Local applications should be bland and free from sensitising properties. The

watery or the oily calamine lotion, zinc cream, zinc paste or hydrous ointment are all useful at times. Hydrocortisone ointment 1 to 2.5 per cent. has been reported to be effective.

Where treatment is not proving successful at home, a period in hospital is sometimes of great value but this has to be balanced against the risk of these children getting widespread pyogenic or virus skin infections to which they may succumb.

### ERYTHEMA INFANTUM (NAPKIN ERUPTION)

Erythema of the napkin area may be due to infection or to chemical irritation. The infective form involves the depths of the folds of skin. It may be a part of pemphigus neonatorum. The chemical irritative form affects the summits of the folds of skin, buttocks, thighs, etc. Sometimes the cause is urea-splitting organisms in the infant's feces. The resultant ammoniacal urine causes a contact dermatitis (Jacquet's erythema). In other cases, excesses of fat or sugar in the infant's diet may result in stools that irritate the skin. Occasionally, insufficient rinsing of the napkins after they have been washed is responsible for an alkaline or detergent dermatitis.

**Treatment.**—In the infective form, cleansing with 1 per cent. cetrimide and the application of an inert dusting powder is often sufficient, or the appropriate antibiotic can be applied after cultural examination.

In the chemical irritant form, treatment depends on the cause, but further aggravation must be prevented by the application of zinc and castor oil cream to the infant's buttocks.

Dietetic adjustments may be necessary, or greater care in rinsing the napkins. In Jacquet's erythema soaking the napkins in a quaternary ammonium compound or in saturated boric acid solution before use is effective. The napkins should be rinsed thoroughly after these procedures before use.

### HYPOSTATIC ECZEMA AND ULCERS ON THE LEGS

Defective venous return of blood from the legs leads to a gradual deterioration of the vitality of the skin of the lower parts of the calves and ankles, resulting in the various clinical conditions known as hypostatic eczema. Minor wounds of the legs are always apt to take longer to heal than similar wounds on the upper limbs, even in healthy youths. This tendency to poor healing is accentuated if there is any deficiency of the veins either through incompetent valves or deep thrombosis, each of which may be responsible for the development of varicosities; but varicosities in themselves are not the cause of eczematous and ulcerative changes: eczematous changes are due in the first place to chronic congestion and anoxæmia, while ulceration is due to superficial venous thrombosis causing a focal necrosis in the dermis.

The congested anoxic legs tend to itch; scratches or other minor injuries do not heal but tend to exude. Mild secondary infection causes an aggravation of the condition and many patients treat themselves not by rest, with elevation of the limbs or by suitable supports to the legs, but by local applications, one or other of which in time sets off a contact eczematous reaction. Further misguided treatment with antiseptics and other potential sensitisers results in the picture of chronic exuding eczema of the legs.

With appropriate treatment the exudation stops and is replaced by coarse peeling from the swollen, reddened skin. Gradually the peeling becomes less conspicuous and provided lichenification does not develop, ultimately it stops, the leg being left pigmented and possibly somewhat indurated, but dry.

Ulcers may develop from abrasions, scratch marks, cuts or bruises on the leg.



The skin below and behind the medial malleolus is a specially vulnerable area, no doubt in part because there may be a downward back pressure from the pumping action of the calf muscles and in part from the poor support and lack of rest supplied by the underlying tendons. Stasis and local œdema are the most important factors in the non-healing of ulcers of the leg, and secondary infection is usually a minor feature; but sometimes healing is prevented by a heavy mixed infection of cocci, *Ps. pyocyanea* and *Proteus*, or streptococci may gain entry and cause cellulitis, followed by chronic solid œdema of the part (*elephantiasis nostras*).

**Diagnosis.**—Most ulcers on the legs are hypostatic and related to thromboses, varicosities and chilblains, but some are arteriosclerotic, as shown by absence of pulsation in the dorsalis pedis artery and radiographic evidence of calcification. This may occur with or without diabetes.

Gummatous ulcers are often higher up the calf, serpiginous in outline, ham-coloured and appear as if punched out. Lupus vulgaris, sporotrichosis and halogen granulomata can all cause leg ulcers.

Rodent ulcers occasionally form on the legs and nodes of Hodgkin's disease or some other reticulosis may break down in that situation.

Pseudoepitheliomatous hyperplasia is a warty condition clinically and histologically resembling carcinoma but due to over-treatment of an ulcer with sensitising local applications. It clears up when the irritant is withdrawn.

Ecthymatous ulcers are moist, with dirty sloughs and no signs of granulations.

**Treatment** of hypostatic eczema is supportive by suitable elastic hose or bandages, with bland, non-absorbable local applications, for example calamine liniment.

If the exudation persists in spite of this, an ointment of 12½ per cent. of solution of aluminium acetate, with 37½ per cent. of zinc paste and 50 per cent. of lanolin may prove effective. In the scaling, lichenified stage, X-irradiation in fractional exposures may help. Unna's gelatin paste or zinc paste bandages are useful in the subacute or chronic stages, but adhesive bandages should not be used. The patient needs to wear a support to the leg indefinitely, or in suitable cases, provided the deep veins are patent, the varicose veins may be given surgical attention by injections and ligations.

Treatment of hypostatic ulcers aims at reducing local œdema. Tulle-gras is applied to the ulcerated area with an overlying gauze, orthopaedic felt or sponge rubber pad covering the ulcer and the skin around, the whole leg being firmly bound with an elastic bandage. The patient is encouraged to take exercise and is warned about the bad effects of prolonged standing. Massage to the surroundings of the ulcer and to the limb as a whole is helpful. Any infective element is controlled by the appropriate antibiotic. Any excessive granulations are reduced by a silver nitrate pencil.

Surgical treatment of any varicose veins is carried out in selected cases.

## COCCAL INFECTIONS

In health the intact skin is able to resist invasion by organisms falling upon its surface. Infections result either from breaks in the surface of the skin or from some abnormality of its "acid mantle". This mantle is formed by the continuous, slow extrusion of sebum from the sebaceous glands through the pilo-sebaceous orifices and the emulsification and spread of the sebum over the surface by means of the sweat.

Dehydration of the surface is another important factor in the prevention of infections. Sweat retained on the surface, particularly in body folds, provides ideally moist, warm conditions for bacterial growth; and sweat when decomposing by bacterial growth, becomes alkaline, which further encourages the bacteria.

Coccal infections of the skin are encouraged by anything that causes breaks in the surface, such as clumsy hair cutting or shaving, rough clothing, scratching, or

dermatitis leading to fissuring; also of importance are the qualitative and quantitative abnormalities of the sebum which occur in seborrhœic dermatitis and xeroderma, and excessive sweating, particularly in obesity when skin surfaces chafe and rub off the superficial epidermal cells.

Skin infections are more common with diabetes mellitus, in toxic states such as uræmia, in states of nutritional deficiency and in blood diseases, for example leukæmia.

Before considering infections at various anatomical situations in the skin, it is well to remember that in all cases of severe or widespread coccal infection, a cause must be looked for locally (infestations, itchy dermatoses) and generally (diabetes, uræmia, leukæmia, anxiety neurosis, etc.). Attention must also be paid to potential carrier sites of staphylococcal infection, especially the hairy vestibule of the nose.

### IMPETIGO VULGARIS (IMPETIGO CONTAGIOSA)

Impetigo is a coccal infection of the epidermis, sometimes involving the ostia of the pilosebaceous follicles (follicular impetigo) or of the sweat ducts (infected miliaria rubra, Bockhart's impetigo).

**Ætiology and Pathology.**—Impetigo vulgaris is usually a disease of children but may occur in adults with the "seborrhœic" diathesis (seborrhœic impetigo). It usually follows some break in the skin's surface, caused by insect bites, scratching or the rupturing of herpetic bullæ. Purulent discharges from the nose, ears or eyes are often responsible, or the infection may be transferred to the face and other exposed parts from a paronychia whitlow. Nasal diphtheria may be complicated by impetigo.

**Clinical Picture.**—The lesions of impetigo consist of golden or dirty greenish-grey "stuck on" crusts, discoid, polycyclic or annular, scattered over the face, scalp or limbs amongst areas of normal skin. Occasionally there are intact bullæ containing thin pus. Similar lesions may be present in the nostrils. It is not possible on clinical grounds alone firmly to differentiate between staphylococcal and streptococcal impetigo. Although streptococci may be present in the early stages, *Staphylococcus pyogenes* usually predominates in any culture that is made and is often grown in pure culture.

At the angles of the nose or mouth and behind the ears, fissures may form with exuding, red, sodden or crusted skin nearby.

**Course and Prognosis.**—Without treatment, impetigo may continue for several weeks. In every case the precipitating cause must be dealt with, for example, pediculosis, otorrhœa, rhinorrhœa or scabies, because once this is under control the elimination of the coccal infection is a simpler matter. Use of the appropriate antibiotic then leads to clearance in 3 to 7 days. Occasionally impetigo is complicated by nephritis. Impetigo should be investigated epidemiologically in order to control the outbreak in a family or school. Contacts should be examined for banal lesions, septic fissures, running noses, etc.

**Diagnosis.**—It is important to differentiate impetigo from herpes simplex and from eczematous dermatitis on the face, whether infected or not.

In herpes simplex the vesicles often remain intact for a while; they are grouped and contain clear fluid. Impetigo may originate from infection of ruptured herpes vesicles but eczematous dermatitis may also begin from the faulty treatment of herpes simplex with antiseptics or antibiotics.

In eczematous dermatitis the lesions at first spread in continuity from the site of application of the irritant, but later they may erupt symmetrically in explosive fashion. In impetigo the spread is more irregular and impetuous, skipping areas of normal skin, with the effect that individual lesions develop rapidly by peripheral spread at several sites of skin inoculation.

**Treatment.**—If pediculosis or scabies is present it should be dealt with first. Any residual infection that persists may then receive attention.

If an intensely itchy skin disease, such as prurigo, coexists, it should be controlled by suitable sedatives by mouth and the superimposed impetigo only treated for as long as is necessary before proceeding to suitable treatment of the underlying dermatosis.

Ideally a culture should be made and the organisms tested for their susceptibility or resistance to various antibiotics; but with a short-term disease such as impetigo the usual practice is to apply the antibiotic believed by the prescriber to be most effective. Chloramphenicol, chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) are all effective in many cases, but, in common with penicillin, they are unsuccessful in those infections due to resistant strains, which are becoming more common.

Antibiotics are far from being the *sine qua non* in the treatment of impetigo. Simple desiccation may be quite effective, and for this purpose calamine lotion is effective with the addition of 0.1 per cent. of mercuric chloride if desired. Calamine liniment may also be used, or zinc paste with 2 per cent. of salicylic acid (Lassar's paste). To the last named may be added 1 per cent. of ammoniated mercury or of brilliant green.

Loose crusts and intact bullæ should be removed before any remedies are applied. For this purpose normal or slightly hypertonic saline may be used, or a 1 per cent. solution of cetrimide which has the added advantage of its antiseptic properties.

No antibiotic should be persisted with for more than 3 days if it is not giving satisfactory results. Failure to respond implies resistant organisms and continuing the use of the antibiotic may lead either to a spread of infection or to the development of eczematous hypersensitivity. Two per cent. of silver nitrate in spirits of nitrous ether is useful as a paint for application to fissures.

#### PEMPHIGUS NEONATORUM (IMPETIGO NEONATORUM)

This is a form of staphylococcal impetigo affecting newborn infants, highly infectious and having a considerable mortality rate.

**Ætiology.**—The infection begins from an extraneous source, for example a cutaneous or nasal infection or carrier state in a medical or nursing member of a maternity unit, a visitor, a lay worker or one of the patients. One attendant may infect several infants.

**Clinical Picture.**—Large bullæ containing thin pus cover the body surface and pink, shiny, moist areas indicate where bullæ have ruptured. The widespread, severe and often fatal form of the condition resembles exfoliative dermatitis (dermatitis exfoliativa neonatorum of Ritter). It has recently been suggested, however, that Ritter's disease is caused by the application of napkins which have previously been soaked in boric acid.

**Course and Prognosis.**—Premature and inadequately treated infants may succumb to the infection but, as a rule, patients respond to antibiotic therapy. A careful search must be made for the primary source, for carriers and possible conveyance by fomites. As a precaution, all in attendance on newborn infants should wear efficient surgical masks.

**Diagnosis** is from congenital syphilis in which the pemphigoid lesions occur on the palms and soles as well as elsewhere. Other signs of congenital syphilis may be present, including rhagades, snuffling, etc.

**Treatment** is by the appropriate antibiotic locally, also systemically if this seems advisable. Good nursing is essential and protection of the child from chilling when dressings are being done.

#### IMPETIGO PITYROIDES (PITYRIASIS ALBA)

This consists of scaly depigmented discs which occur on the faces of children. The lesions are believed to be streptococcal and mildly infective, but drying winds

and the excessive use of soap seem to play an equally important part in their production.

**Treatment.**—The lesions usually respond to the application of weak ammoniated mercury ointment, or to 2 per cent. of solution of coal tar in Lassar's paste.

### PYOGENIC PARONYCHIA (see Diseases of the Nails)

#### ECTHYMA

This is a coccal infection, originating from the surface and affecting the dermis, leading to necrosis, ulceration and scarring. Trauma is an important predisposing factor.

**Clinical Picture.**—This malady is more common amongst under-nourished, ill-cared for children and amongst individuals of low intelligence than among clean and normally intelligent persons. It usually affects the legs, where one or several areas of dirty grey crusting may be seen, with a purulent discharge and red surrounds. Later, the crusts become detached, leaving shelving ulcers with an inflammatory rim and a sero-purulent base. There may be regional lymphadenopathy. Ecthyma may also occur in adults suffering from pediculosis or from infection of traumatised legs (for example, desert sores).

**Course and Prognosis.**—If untreated, the condition may persist indefinitely and it may spread, as impetigo or furunculosis, on other parts of the body.

**Diagnosis.**—An ecthymatous syphilide must be excluded.

**Treatment.**—Having excluded any parasitic infestation, attention is directed to any malnutrition and uncleanness that may exist.

For local treatment, cleansing with 1 per cent. cetrimide is indicated, followed by application of the antibiotic most suitable according to the cultural findings. This is likely to prove effective more rapidly than nonspecific remedies such as eusol compresses or a lotion of sodium hypochlorite. Desiccating measures may also be employed. The nails should be kept closely trimmed and attention paid to any infective foci in the nostrils or paronychial folds.

#### FOLLICULITIS

Coccogenic folliculitis is one form of sycosis barbæ (folliculitis profunda), the other being mycotic folliculitis. Folliculitis may also be superficial (ostio-folliculitis, Bockhart's impetigo).

#### FOLLICULITIS BARBÆ

**Clinical Picture.**—Folliculitis barbæ is a chronic staphylococcal inflammation of the depths of the hair follicles in the beard region. Folliculitis profunda may also occur at other sites, for example, the nucha and the pubis.

Discrete follicular papules and pustules are present and from them hairs protrude. The lesions may be grouped or diffusely confluent all over the beard area. Tender nodules may form. In long-standing cases due to antibiotic-resistant strains, the efforts at cure with sundry medicaments may end in a mixed condition of folliculitis and dermatitis, presenting as diffuse redness and exudation or scaling interspersed with follicular pustules.

**Ætiology and Pathology.**—Shaving trauma and staphylococcal infection.

**Course and Prognosis.**—The progress of folliculitis depends on the susceptibility or resistance of the causal organisms to antibiotics. In the majority, relief can be obtained with one antibiotic or another, but it is always wise to have a culture made and the antibiotic sensitivity of the organisms investigated before starting treatment, especially as antibiotic-resistant strains of staphylococci are becoming more

common. Furthermore, many individuals with folliculitis show other signs of the "seborrhæic" diathesis which indicates that they are susceptible to infection of the skin. Sycosis in them may present with less frankly purulent lesions, the organisms responsible being less potent strains of *Staphylococcus aureus* or even *Staphylococcus albus* and not the coagulase-positive *Staphylococcus aureus* usually met in folliculitis.

If folliculitis relapses in seborrhæic individuals, it may be because of invasion by a different strain of organisms with different antibiotic sensitivities. For this reason, it is advisable to repeat the culture and antibiotic sensitivity tests in any relapse.

In every case of staphylococcal folliculitis it is essential also to take a swab and to culture the organisms from the nasal vestibule and to treat this carrier site of staphylococci with the appropriate antibiotic. It is not necessarily true that the organisms cultured from lesions on the skin are alone responsible for the development of that lesion. A coccal infection may be superimposed on a syphilide; and organisms such as *Staphylococcus saprophyticus* and Gram-negative organisms of the coli group, *Ps. pyocyanea* or *Proteus*, may be secondary invaders of devitalised tissue. Faecal contaminants do, however, seem to play a significant rôle in some cases.

Diagnosis has to be made from impetigo, mycotic folliculitis, chemical folliculitis, foreign body reactions due to ingrowing hairs, infected acne and syphilis. In impetigo the lesions are superficial and not necessarily follicular. In mycotic sycosis the patient gives a history of contact with cattle, the lesions are much more acute and œdematous, and hairs can easily be pulled out from the follicles: fungus spores may be found (often with some difficulty) on removing infected hairs.

Chemical folliculitis is usually due to over-treatment or to faulty treatment of a non-infective dermatosis of the beard area with antibiotics or antiseptics. It is recognised by the presence of diffuse dermatitis and much serous exudate, as well as folliculitis.

Foreign body reactions due to ingrowing hairs are most common in coloured men with curly hair running in every direction, which, on shaving, tends to become embedded in the skin. This especially occurs on the sides of the neck under the chin line but may also occur on the face. It occasionally occurs in white men, particularly those who shave very closely "against the grain". Embedded hairs are visible on inspection with a hand lens and their free ends can be extracted with a needle. Culture in such a case usually grows saprophytic organisms or coliforms.

Infected acne occurs in the skin immediately adjoining the beard area but may coexist with folliculitis barbæ. The presence of comedones is an essential feature in the diagnosis of acne.

Syphilis may in the secondary stage present with pustulation and frambœsiform crusts at the cleft of the chin. Its presence should be suspected from any atypicality of the lesions and any signs of syphilis elsewhere. Lupoid sycosis is differentiated from lupus vulgaris by the presence of atrophic scarring with occasional pustules, and by the absence of apple-jelly nodules.

Treatment consists of the application of the appropriate antibiotic to the lesions and, if necessary, to the nostrils three or four times a day. This treatment should be persevered with for a fortnight after apparent clinical cure: even after that interval, relapses are common in seborrhæic individuals. With penicillin, a lotion is often more effective than a cream and less likely to sensitise the skin but it may prove too drying. With chloramphenicol, chlortetracycline and oxytetracycline, ointments or creams are usually effective and they are pleasant to use.

Other applications which may prove relatively effective include quinolor ointment, Vioform cream and ammoniated mercury, but they all have, in varying degrees, a tendency to sensitise the skin. Zinc and copper lotion (D'alibour water) is useful as an after-shave lotion. In very severe or resistant forms of folliculitis barbæ it may be advisable for the patient to use an electric razor. Growing a beard is a satis-

factory alternative. The use of X-rays in folliculitis barbæ is contraindicated both in fractional and epilatory doses.

### OSTIO-FOLLICULITIS (BOCKHART'S IMPETIGO)

Ostio-folliculitis is a staphylococcal infection of the orifices of the follicles.

**Ætiology.**—Ostio-folliculitis is caused by stimulation of the epidermis by oil, adhesive plasters or other surface irritants. It is often a complicating feature of prickly heat (*miliaria rubra*).

**Clinical Picture.**—Discrete, superficial pustules are present at the orifices of hair follicles. Hairs penetrate the pustules. On rupture, superficial erosions are left. The lesions are often grouped but sometimes extensive. There is often an associated keratosis follicularis or acne because the irritants causing the folliculitis also stimulate epithelial proliferation at the ostia. The sites usually affected are the forearms and thighs.

**Course and Prognosis.**—This depends on the future avoidance as far as possible of contact with irritants such as oil, adhesive plaster, powerful degreasers and dehydrators. The worker should be given facilities to wash parts exposed to oil immediately after work is finished: he should be discouraged from postponing washing until he gets home, perhaps after a considerable journey. The condition is then likely to clear.

**Treatment.**—Parasitic infestation must be excluded. A culture should be made and the appropriate antibiotic used. Vioform cream is sometimes effective and D'alibour water is useful, followed by lead and calamine lotion.

### PILI INCARNATI (see Folliculitis Barbæ)

**Treatment.**—The only treatment of value for this relatively mild but annoying condition is the avoidance of close shaving, particularly with the skin under tension. The shaver should aim at the sort of result obtained by one shave "with the grain". Electric razors are not necessarily an advantage.

### BOILS AND CARBUNCLES

A boil (furuncle) is a staphylococcal infection of a sebaceous gland proceeding to a perifollicular abscess, sloughing of the hair papilla and of the pilosebaceous follicle and its replacement by scar tissue.

Furunculosis is a condition of multiple localised or widespread boils. A carbuncle is a localised group of boils which by their mutual pressure cause sloughing of extensive areas of skin and subcutaneous tissue with much constitutional disturbance.

**Ætiology and Pathology.**—Boils are usually due to some local breakdown in the skin's protective mechanism. Carbuncles are usually due to some general lowering of resistance. Thus, boils may be secondary to scratch damage in an itchy skin condition, whether it be parasitic infestation, dermatitis or prurigo; or they may result from local damage arising from shaving or haircutting, rough clothing, oil or dirt. A carrier site of staphylococci in the nose is often the source from which the skin is inoculated and furunculosis may set a problem in domestic epidemiology in which the sharing of face flannels, towels, etc. may prove to be responsible for the spread of infection within the family. In every case of furunculosis and more especially with carbuncles, attention should be directed to the possible presence of diabetes, renal disease, leukaemia or nutritional deficiency, either of insufficiency or of imbalance.

**Clinical Picture.**—A boil begins as a painful, red nodule which enlarges and becomes hard and tender. At its centre a small papule or papulo-pustule is visible, penetrated by a hair. Induration and pain cause difficulty in moving the affected

part. After 36 to 48 hours the centre softens, a small scab or slough detaches and a purulent discharge begins. In another 36 to 48 hours the "core" or pilosebaceous slough is extruded, the purulent discharge and induration lessens and the boil heals with a varying amount of scar formation.

A carbuncle begins with greater constitutional disturbance. Instead of a nodule, there is a brawny plateau in which several follicular pustules can be seen. The mass enlarges and a shelving induration with œdema extends for some way around. Softening and liquefaction of the mass may (in patients treated by local application only) take days or even a week or two, but sooner or later a large slough forms and is gradually detached, or many points of suppuration develop, with subsequent extensive scarring. Smaller boils and follicular pustules around the main lesion often form as a result of auto-inoculation.

**Course and Prognosis.**—These depend on the cause and the ease or difficulty of its removal. With itching due to infestations, it is easy; with itching due to emotional conflict, it may be extremely difficult. A carbuncle in a debilitated patient is a serious and sometimes fatal condition.

**Diagnosis.**—A boil or carbuncle has to be diagnosed from a malignant pustule (anthrax). In the latter, the onset is more rapid and the constitutional symptoms are more marked, while the history of exposure to wool or hides makes the diagnosis likely. Culture or even a direct smear will usually reveal the bacilli but treatment should be started on clinical grounds alone, without awaiting cultural confirmation.

The primary tuberculous complex resembles an indolent boil but the youth of the sufferer, a history of contact, the lymphadenopathy draining the site of inoculation and the resistance to antistaphylococcal measures should arouse suspicion.

**Treatment.**—In every case the cause should be looked for and treated if possible. Glycosuria or albuminuria, malnutrition or leukæmia should all be excluded. If itching preceded the boils, this should be investigated. Occupational hazards, unsuitable clothing and faulty hygiene practices should receive attention.

Severe boils and carbuncles are best dealt with by systemic penicillin or some other suitable antibiotic depending on organismal sensitivity tests. Smaller lesions are better treated by local remedies. Penicillin injections are a passive treatment, having no value for stimulating the reactivity of the host: in fact, the converse sometimes applies, penicillin injections being followed, on cessation, by a crop of further boils of even greater severity. For this reason, it is a mistake to give penicillin at once, without first investigating the cause of the infection and the susceptibility of the organisms to antibiotics. Vaccines, staphylococcal toxoid, manganese injections and tin by mouth have a reputation for relieving furunculosis but their effects are most uncertain.

Local treatment should aim at resolution of the lesions with minimal discomfort and with the avoidance of further contamination of the skin by the pus coming from the boils. Softening or maceration of the skin must be avoided and boracic fomentations, kaolin poultices and glycerin and magnesium sulphate dressings often do more harm than good. Dry heat may be applied with precautions to prevent burning, or hot bathing may be used. In the intervals between such procedures the following paint may be applied to and around the boil to control the local infection and to keep the surface of the skin dry and hard:

Mercuric chloride	0.1 per cent.
Brilliant green	1.0 per cent.
75 per cent. industrial spirit to 100.0 per cent.	

Once the boil is discharging, dry dressings, frequently changed, are used, and chlortetracycline cream 1 per cent., or the above-mentioned paint, applied to the skin around.

Surgery, in particular crucial incisions, is contraindicated and the only justifiable

manipulative procedure is the encouragement of separation of the slough as soon as possible.

Boils on the nose and upper lip need especial care because of the risk of infection spreading by communicating veins to the interior of the skull, with fatal results. On no account should they be subjected to pressure. The patient should be rested and systemic antibiotic treatment started at once. Locally, the gentle application of warmth is justifiable.

### HYDRADENITIS SUPPURATIVA

This is an infection of apocrine glands in the axillæ or perineum, often giving rise to deep abscesses which tend to track beneath the skin.

**Ætiology.**—The condition is more common in women than in men. The apocrine glands are susceptible to psychosexual and endocrine stimuli. Infection is unlikely to arise without some other factor being present, such as chemical irritation from depilatories, deodorants, or the rubber of dress protectors.

**Clinical Picture.**—In one or both axillæ or at the perineum is an irregularly nodular surface with tenderness and areas of induration and of fluctuation. Pus may be discharged from sinuses and there is a marked tendency to tracking, irregular scarring, chronicity and recurrence.

**Treatment.**—Any chemical irritation of the region should be avoided. Culture and use of the appropriate antibiotic in a cream is usually effective, or 0.1 per cent. mercuric chloride and 1 per cent. brilliant green in 75 per cent. industrial spirit may be applied. In resistant cases X-rays, 100 r up to four times at weekly intervals may help. In the most chronic forms success has followed excision of the affected tissue, with plastic repair.

### DERMATITIS VEGETANS

This is a condition of irregular epidermal hyperplasia overlying an area of infected dermatitis where the tissue reactions are vitiated by senility or local disease, in particular lymph stasis.

**Clinical Picture.**—Over an extensive area of skin there is redness with a pustular exudate and an irregular warty or even pseudo-epitheliomatous hyperplasia of the epidermis. Culture may reveal a mixed infection in which Gram-negative organisms such as *Ps. pyocyanea* and *Proteus* are prominent.

The condition may develop as a complication of pre-existing skin conditions, for example, pemphigus vulgaris.

**Treatment** is that of the underlying condition and elimination of the causal organisms. In the form secondary to lymphatic blockage in the leg, the best that can be expected is an elephantiac leg and sometimes amputation may have to be considered, as likely to give the best results, whereas retaining the limb may bring with it much toxicity and secondary anæmia.

### PYODERMA GANGRENOSUM

This is a rare condition of burrowing colliquative necrosis and ulceration of the skin, either due to symbiosis between anaerobic streptococci and hæmolytic streptococci (Melency's ulcers) or due to the loss of fluid and electrolytes that occurs in acute exacerbations of ulcerative colitis or dysentery, or when massive intestinal hæmorrhages occur in the former disease. A similar condition has rarely been reported in prolonged cachectic states with varicella. There is leucopenia due to marrow depression.

**Treatment** is of the primary condition. Replacement of fluid and electrolytes, blood transfusions and antibiotics are necessary. With control of the loss of fluid and electrolytes, healing usually begins spontaneously.



## ERYSIPELAS (see p. 34)

## ERYSIPELOID

An infection of the cellular tissues of the fingers or hands with the organisms of swine erysipelas, from injury to the skin arising from the handling of animal or vegetable matter.

**Clinical Picture.**—This is essentially a disease of food handlers and manipulators. It starts as an erysipelas-like swelling on a finger or the hand. The swelling advances with an easily visible border and may travel up one finger on to the hand and down the adjoining finger. Constitutional disturbance is slight. If untreated, the condition persists for several weeks.

**Treatment.**—It quickly responds to intramuscular injections of penicillin.

## ANTHRAX

This is dealt with elsewhere (see p. 79).

## CUTANEOUS DIPHThERIA

This is rare. Wounds (for example desert sores) may be infected and occasionally lesions develop on the skin of children suffering from naso-pharyngeal diphtheria. The skin may also be affected without mucosal involvement.

**Clinical Picture.**—There may be only one lesion, or several. At first there is a blister which ruptures; a red zone develops around and a central slough forms. Diphtheria may cause paronychia. Constitutional symptoms are often slight but the complications serious.

**Diagnosis** is from infected eczema, impetigo and ecthyma. Direct smear and cultural examination for *Corynebacterium diphtheriae* confirms the suspicion.

**Treatment.**—Diphtheria antitoxin should be given in full dosage immediately the condition is suspected, without waiting for a bacteriological report. The patient should be kept at rest and isolation is necessary. Locally, the area should be cleaned with cetrimide 1 per cent. and an antibiotic such as chloramphenicol cream applied.

## FUNGOUS INFECTIONS

Mycotic infections of the skin may be superficial (epidermal) or deep (dermal). The former type is common, the latter rare.

## SUPERFICIAL FUNGOUS INFECTIONS

Pathogenic fungi are classified according to their morphological and cultural characteristics, macroscopically and microscopically, into *Microsporon*, *Trichophyton*, *Epidermophyton*. For the clinician it is more convenient to classify fungous diseases according to the region of the body they are affecting. The chief groups are *tinea capitis*, *tinea barbae*, *tinea glabrosa*, *tinea axillae et cruris*, *tinea pedis* and *tinea unguium*. Two or more regions on one patient can be affected by a fungus concurrently, the zonal terminology being arbitrary. For example, *Trichophyton rubrum* may affect the nails, the hands, the feet and the groins at one time.

Fungous eruptions, particularly if infected with cocci or if over-treated, often give rise to secondary eruptions or mycides which, depending on the nature of the fungus, are described as microsporides, trichophytides, epidermophytides, favides or moniliides (levurides).

## TINEA CAPITIS (TINEA TONSURANS)

## MICROSPOROSIS

Ringworm of the scalp in over 90 per cent. of cases is due to microsporon, either *Microsporon audouini* (the human form) or *M. canis vel felineum*. A much rarer form acquired from animals is *M. gypsum*. All forms only infect children, the skin at puberty acquiring fungistatic properties.

**Ætiology and Pathology.**—The human form is believed to be spread by direct contact and by indirect contacts, for example, hair clippers and caps; it may also be air-borne. The animal form is acquired by fondling kittens and puppies and may spread from child to child, for two or three transferences, before it loses its vitality, which is re-established after infection of an animal host once more.

The organisms invade the stratum corneum and the mycelium grows down the hair follicles and thence passes to the hair shafts, forming a mosaic of spores around the shafts and mycelial threads within the shafts. The hair shafts become fibrillated and break off about 3 mm. above the surface of the skin.

**Clinical Picture.**—As a general rule, *M. audouini* causes less severe reactions than *M. canis*, and is less likely to be associated with tinea of the glabrous skin. The history of animal contacts in the latter, and of a school or institutional epidemic in the former, may also help to suggest the nature of the fungus.

Characteristically there are circular areas of short, bent or broken hairs with frayed ends and having thicker shafts than those of the unaffected scalp around. The scalp itself shows a dirty scaling, without redness, or there may be slight papulopustulation. Rarely there are numerous follicular pustules with much œdema, causing a boggy, dusky, dome-shaped swelling, a condition known as kerion. This is more common with Trichophyton infections.

Sometimes the circular or annular arrangement is inconspicuous or absent, and casual inspection may suggest a diagnosis of infective dermatitis, if the whole or most of the scalp is affected, until closer inspection shows broken hairs which are not found in infective dermatitis.

Examination with Wood's light is an invaluable aid to the diagnosis and management of these disorders. It consists of ultra-violet rays passed through a nickel glass filter. With microsporon, but not with trichophyton, there is a brilliant green fluorescence of the affected hairs. As the infection persists, the fluorescence tends to become less brilliant. With Wood's light the diagnosis can be made of microsporon ringworm, affected hairs can more easily be removed for microscopy and culture, and the follow-up of patients until cure is greatly facilitated. It is often noted under the lamp that single outlying hairs are affected and even that small patches are present which were not suspected on examination by daylight. Direct microscopy is not essential if examination under Wood's light is positive. It is carried out by extracting a hair and placing it on a slide with potassium hydroxide. Heat is applied to hasten the keratolytic action of the potassium hydroxide. Microscopy then reveals a mosaic of small spores surrounding the hair shaft.

Diagnosis has now reached the stage of microsporiasis. Further differentiation is made by culture, using Sabouraud's medium. Usually the macroscopic and microscopic features of the culture are characteristic but occasionally dysgonic forms are seen.

**Course and Prognosis.**—The natural history differs in the two types of infection. *M. audouini* tends to persist indefinitely or until puberty, whereas *M. canis* usually dies out after about 3 months. It follows that local applications may be sufficient in the latter but not in the former.

**Diagnosis.**—Alopecia areata causes smooth bald patches with exclamation mark hairs at the periphery. Trichotillomania causes areas of broken off hairs, usually at one temporo-frontal region. Infective dermatitis causes redness and scaling and

loss of hair but no breaking of the hairs. Impetigo of the scalp is more exuberant and lesions are usually present elsewhere, or there is some other cause for it such as pediculosis.

**Treatment.**—Scalp ringworm is a problem in epidemiology. With *M. audouini* it is necessary to examine the contacts and to trace the infection to its source, if possible. A Wood's light is invaluable for this purpose. In residential institutions tracing the source and quelling the infection is relatively simple. In day schools it may be difficult because siblings of all the school contacts should be examined as well. Fortunately, as microsporiasis is almost unknown after puberty, it is not necessary to examine children over 14 years of age.

Treatment should be begun with local applications pending the cultural diagnosis. The choice of local application is, at present, relatively unimportant, as one is not available which will eliminate the infection from the depths of follicles, and from the hair shafts themselves, which is the essential of cure. Local applications serve the purpose of fungistatic action on the surface and at the ostia, and prevent contaminated fragments of scale or hair from being carried off in the air.

The mother is instructed to cut the hair all over the head to stubble and to make two linen closely fitting skull-caps for continual wear, on alternate days, the cap not in use being boiled. The scalp is scrubbed daily with soap and water, paying special attention to the areas known to be affected. Then the ointment being used (Whitfield's ointment, or phenyl mercuric nitrate 0.5 per cent. in emulsifying ointment, or dithranol 0.5 per cent. in emulsifying ointment) is scrubbed into the scalp with enough vigour to cause a slight erythematous reaction.

In small spore ringworm of the scalp due to *M. audouini*, it is exceptional to get a cure with local applications and recourse is had to X-ray epilation, using either a 4 or a 5 circular fields method. The hair falls after 3 weeks, when examination under Wood's light will reveal any affected hairs that may remain. These can be removed gently with epilation forceps. In the epilating stage a fungistatic ointment, for example Whitfield's, should be applied and the falling hair burned. Epilation by thallium acetate (8 mg. per kg. of body weight) in a single dose is too dangerous a method and has been practically abandoned, death having occurred from accidental overdosage.

#### RARER FORMS OF SCALP RINGWORM

Large spore ringworms of various types may affect the scalp. They include two forms contracted from animals, *T. mentagrophytes* from domestic or farm animals, and *T. discoides* from cattle. Both are ectothrix forms. In the former, filaments and spores are seen around the hairs: in the latter, large spores. Four endothrix forms, all of human origin, include *T. tonsurans*, *T. sulphureum*, *T. violaceum* and *T. schoenleinii* (favus). None of these forms of scalp ringworm causes fluorescence under Wood's light, except favus, which gives a pale bluish-green fluorescence throughout the length of the hairs which often remain unbroken.

Microscopically the endothrix ringworms show filaments and spores within the hair shafts. Favus may be recognisable at this stage by its polymorphic filaments and oval spores, with areas having the appearance of air spaces within the shafts.

Clinically the trichophyta of animal origin usually cause kerion but the endothrix forms cause much less violent reactions, perhaps some scattered broken hairs with thick scurf: with *T. violaceum* the hairs break off flush with the surface of the skin (black dot ringworm), giving an appearance that can easily be confused with alopecia areata. Microscopy after careful removal of a hair, reveals the fungus as mycelial threads and oval segments. Favus may resemble infective dermatitis, mousey-smelling, yellow, scutuliform scales may be present, or in long-standing cases where the scalp has been kept clean it may present as a slowly extending cicatricial alopecia.

Favus may also affect the glabrous skin with scutuliiform lesions in which bright-yellow cups form massive crusts, and it may cause nail deformity. Favus is usually acquired in childhood but it persists into adult life if untreated.

**Treatment** of scalp trichophyta depends on their natures. With the animal ectothrix kerionic forms, manual epilation followed by the application of Whitfield's ointment or magenta paint usually suffices. It is wise to give warning of the probability of some degree of scarring. The boggy swelling of kerion should not be incised.

In the endothrix forms X-ray epilation is usually necessary. With favus it is important to examine all child contacts under Wood's light, to find if any clinically undetectable early cases exist.

### TINEA BARBÆ

Ringworm of the beard is nearly always caused by *T. mentagrophytes* or *T. discoides* infections of animal source: hence it is found mostly amongst grooms and farm workers. It presents as irregular areas of follicular papulo-pustulation in the beard area, with considerable perifollicular swelling which gives rise to the fig-like nodular appearance of mycotic syphilis. Microscopy of an extracted hair often fails to reveal the fungus because of a secondary coccal infection, as in kerion celsi.

**Treatment** is by manual epilation and the use of fungistatics, for example Whitfield's ointment or Castellani's paint. X-ray exposures of 150 r up to four times at weekly intervals may be used to diminish the swelling and tendency to keloid formation.

### TINEA GLABROSA

Tinea of the glabrous skin may be classified for clinical purposes as: tinea circinata of body and limbs; tinea axillæ et cruris and tinea pedis.

### TINEA CIRCINATA

This form of ringworm affects children or adults and may be due to microsporon or trichophyton. The former may occur in children with tinea capitis due to *M. canis*, or in adults coming into contact with them. The latter may be of human or animal source. In nearly all forms the infection spreads peripherally and heals centrally with the result that the early macular or papulo-vesicular lesion becomes a ring with a scaly or vesicular border and a central zone of normal or discoloured skin. In infections by *T. discoides* ("cattle ringworm") groups of papulo-pustules occur on the forearms or on the backs of the hands; but the endothrix trichophyton tends to form large rings.

**Diagnosis** is from pityriasis rosea, patchy infective ("seborrhoeic") dermatitis, nummular eczema.

Pityriasis rosea begins with a herald patch followed by a general eruption, but microscopy reveals no fungus.

Discoid infective dermatitis has greasy scales, a sweat area distribution and signs of infective dermatitis elsewhere.

Nummular eczema presents with papulo-vesicular disks on the forearms and hands, calves and feet.

**Treatment.**—Tinea circinata is usually eliminated easily with fungistatic agents such as Whitfield's ointment, magenta paint or weak tincture of iodine. If the patient is a child, it is important to examine the scalp under Wood's light even in the absence of clinical evidence of involvement of the scalp.

In the pustular form, it is advisable to carry out manual removal of any hairs present.

## TINEA AXILLARIS ET CRURIS

This presents as extensive areas of erythema in the flexures, with festooned polycyclic edges showing some scaliness or slight vesiculation, from which mycelium can be recovered. The anal region, the perineum, the scrotum and the buttocks may be affected as well as the genito-crural folds. The responsible organism is usually either *T. rubrum* or *Epidermophyton floccosum*; either may also affect the hands, feet and nails, but *E. floccosum* does not affect the hair.

**Diagnosis.**—In infective dermatitis of the flexures there are numerous follicular erythematous "satellite" lesions. In ringworm of the axillæ and groins (eczema marginatum) these are not present. In doubtful cases microscopy should make the diagnosis clear. In flexural dermatitis due to hæmolytic streptococci the intensity of inflammation is much greater and in monilial dermatitis the white, sodden epidermis overlying the moist, reddened surface with fissuring in the depths of the folds makes the diagnosis clear. Contact dermatitis due to textiles is recognised by its preference for the folds of the axillæ rather than their domes.

## TINEA PEDIS

This is usually due to *T. mentagrophytes*, *T. rubrum* or *E. floccosum*. Cultural differentiation is important because eradication of *T. rubrum* is a far more difficult matter than eradication of *T. mentagrophytes* or *E. floccosum*.

**Ætiology.**—Foot ringworm is most easily spread where people mix in bare feet; hence its designation "Athlete's Foot". Sports clubs, swimming baths and bath-rooms are probably the commonest sources of contagion but individual susceptibility, because of hyperidrosis, crowded toes and minor foot deformities, is also important. Other factors include climatic and working conditions of heat and humidity, and faulty footwear, in particular thick socks and impervious footwear.

**Clinical Picture.**—On the inner surface of the foot, spreading on to the sole, groups of vesicles are present of various sizes and of skin colour. Secondary infection may cause opalescence of the vesicles. The eruption is usually somewhat asymmetrical. Other parts of the sole may be infected, especially the flexures and clefts of the toes, but when the only physical sign is white, sodden skin, with fissuring of the fourth toe clefts, monilial intertriginous dermatitis is a more likely diagnosis.

In the presence of secondary infection or over-treatment, a secondary eruption (mycide) of vesicles often develops symmetrically on the hands and feet. These vesicles do not contain fungus and the hand condition is in no way contagious. Infection may, however, spread to the nails of hands and feet.

*T. rubrum* infections behave in a different fashion. It is not unusual to find simultaneous infection of the hands, feet, nails and groins. The hands and feet usually show a diffuse, fine peeling and some redness only, perhaps with hyperkeratosis and fissuring but without vesiculation; often the condition is unilateral. One or more nails may be affected as well. On the calves there may be discrete deep follicular lesions resembling a deep coccal folliculitis, tuberculide or even erythema nodosum.

**Diagnosis.**—Microscopic confirmation by removing the roofs of suspected vesicles is essential if errors are to be avoided, as a very similar, if not identical picture can arise in pompholyx (dysidrosis) and in contact dermatitis. Contact eczematous dermatitis of the feet usually arises on the dorsa but may itself be due to over-treatment of tinea pedis. Tinea pedis is often asymmetrical whereas pompholyx is symmetrical. Sodden toe clefts may be due to excessive sweating and maceration or to monilial infection.

Pustular psoriasis of the feet presents as reddened areas with excessive scaling and brown "pustules" which are sterile on culture and microscopically show no fungus.

**Treatment.**—Footwear should be well fitting; socks should be of cotton and

changed daily, or a fresh pair of white cotton in-socks can be worn each day. Sponge-rubber soles should not be worn. The feet should be washed twice a day and magenta paint applied at night and 3 per cent. salicylic acid powder liberally shaken into the socks and between the toes each morning. Mercurial fungicides are liable to sensitise the skin, and zinc undecylenate is relatively ineffective. Whitfield's ointment is sometimes useful, or 1 per cent. silver nitrate lotion. If any secondary infection is present foot soaks in potassium permanganate 1 in 6000 for 10 minutes twice a day are useful.

### TINEA UNGUIUM

Ringworm of the nails may be due to trichophyton or epidermophyton. It may pick out one nail, one hand or foot, or both. It is unusual for all the nails to be affected and the distribution is usually asymmetrical.

**Clinical Picture.**—The nails are usually affected from their free edges and become grey or brown, thickened, rough, dull, friable and honeycomb-like. They are sometimes easily shed. To make a microscopic examination for fungus a microscope slide is used; by scraping with its edge, fine flakes of nail can be detached. The more superficial ones are discarded; the deeper ones are caught on another slide, covered with potassium hydroxide and a cover-slip, and heated to hasten the keratolytic action of the potassium hydroxide. It is usually easy to find mycelium by this method but subsequent attempts at culture often fail.

**Diagnosis.**—Ringworm of the nails has to be differentiated from psoriasis, eczema, syphilis and nail dystrophies. Psoriasis usually affects many nails in symmetrical fashion. Thimble-like pitting may be present or the nails may be thickened and yellow. In tinea unguium there may be only one or two nails affected and the discoloration is dirty grey rather than yellow. Microscopic examination for mycelial filaments is the deciding method in doubtful cases, in addition to the presence or absence of psoriasis or fungous disease elsewhere. Paronychia is rarely caused by pathogenic fungi but often in part due to monilial infection.

**Treatment.**—The eradication of fungous infections of the nails is very difficult and success is exceptional. Removal of the nail plates and the application of fungicides to the nail bed is usually followed by recurrence. X-ray exposures and thorium-X applications have sometimes been reported to give partial success. Useful local applications include ammoniated silver nitrate,  $\frac{1}{2}$  per cent. dithranol ointment and zinc undecylenate ointment; but the most that can be said for each and all of these is that they may help to check the spread of the disease on the sufferer and to others. It is important to treat concurrently any skin areas involved.

### MONILIAL INFECTIONS

*Monilia (candida) albicans* may affect the mucosæ and skin in several ways: monilial stomatitis (thrush), monilial vulvovaginitis, monilial intertriginous dermatitis, monilial paronychia.

*Monilial stomatitis* occurs as thrush in infants, with white, easily detached shreds overlying the mucosæ. In adults monilial stomatitis may follow the use of antibiotics which disturb the flora of the mouth.

*Angular stomatitis* is sometimes infected with monilia.

*Monilial vulvovaginitis* is a cause of pruritus vulvæ and usually presents as a shiny flexural erythema with a heaping up of white sodden epidermis at the margin.

*Monilial flexural dermatitis* has a similar appearance at other sites, chiefly under pendulous breasts or abdominal folds, at the umbilicus, at axillary and genitocrural flexures and between the fingers in the form known as *erosio interdigitalis mycetica*. It is a common cause of sodden skin in the toe clefts.

In all these forms of monilial dermatitis it is important to test the urine for sugar and to look for evidence of nutritional deficiency.

*Monilial paronychia*.—The cause of chronic paronychia is a break in the epidermal barrier due to the effects of alkalis, detergents, cuticle removers or excessive manicuring. Once this barrier is broken down, *Staphylococcus saprophyticus* and yeasts gain access to the folds and cause a low-grade inflammation. If the hands are repeatedly immersed in alkaline solutions or if they are exposed to beer, as with barmaids cleaning up bar counters, conditions are rendered ideal for the infection to develop.

Treatment of monilial infections consists of attention to the general health; attention to the local anatomical condition predisposing to this infection; and the application of fungicides.

Unbalanced nutrition, obesity and any associated diabetes must be controlled. Opposing skin folds should be prevented from rubbing against one another by means of suitable dressings, up-lift brassieres and abdominal supports, well-fitting socks and shoes. The affected areas should be kept clean with an unscented toilet soap and after its use a talcum dusting powder should be liberally applied to the less active areas and magenta paint to the more active ones. To any fissures in the depths of the folds a 2 per cent. solution of silver nitrate applied daily by an orange stick is usually effective.

Monilial paronychia can only be relieved with full co-operation on the patient's part. Wet work must be kept to a minimum and the handling of soda, alkaline soaps and detergents is forbidden. Magenta paint is allowed to trickle under the nail folds by means of a camel-hair brush. X-ray exposures to the folds (150 r) weekly or fortnightly on up to four occasions are often invaluable in encouraging the regrowth of the epidermis over the proximal parts of the nail plates. After cure, the patient must be reminded of the possibility of recurrence and advised to take especial care to avoid the known hazards.

### TINEA VERSICOLOR

*Malassezia (microsporon) furfur* is the organism responsible for this condition, which presents as brown, slightly scaly plaques on the body and to a lesser degree on the limbs. If the skin has been exposed to sunlight the affected areas may be paler than the normal areas adjoining (*achromia parasitica*). The affected areas are also pale in coloured people.

**Diagnosis.**—In tinea versicolor in the white man, the brown areas are "islands" in a "sea" of white and the edges of the brown are convex. In vitiligo the converse applies. In tinea versicolor there is slight scaling, made more apparent by scraping the edge of brown. Microscopic examination of these scales reveals fragments of mycelium and many spores, sometimes in clusters resembling bunches of grapes. This fungus will not grow on artificial media. Another diagnostic feature is a golden fluorescence when the patient is examined under Wood's light.

**Treatment.**—Tinea versicolor is encouraged by hyperhidrosis or sweat retention: hence it is wise to look for any tuberculous or other condition which might be responsible for the sweating. Insufficient bathing and the wearing of the same thick woollen underclothing day and night may be to blame. Bad habits of this sort must be corrected and porous underclothing worn and changed daily if the condition is to be cured. The application of 10 per cent. sodium thiosulphate is effective; or the 3 per cent. ointment of sulphur and salicylic acid may be applied. Treatment should be continued for 2 weeks after apparent cure. The bed linen and underclothes should be disinfected by laundering.

### LEPOTHRIX (TRICHO-MYCOSIS AXILLARIS)

This is a fungus infection around hairs in the axillæ, producing dark-reddish concretions and caused by *Nocardia tenuis* in symbiosis with a coccus which forms red, yellow or black pigment.

**Treatment** consists of shaving followed by the application of calamine lotion with 2 per cent. of sulphur.

### MYCIDES

These may take the form of vesiculation of the hands (pompholyx) or lichenoid, horny, follicular papules in groups on the trunk (lichen trichophytide). Erythematous, urticarial, erythema multiforme and erythema nodosum types have been described.

**Treatment** is by bland local applications while the primary focus is being got under control.

## DEEP FUNGOUS INFECTIONS

These conditions are rare in Great Britain.

### SPOROTRICHOSIS

This is caused by accidental inoculation with *Sporotrichum schencki*, a plant saprophyte. Infection usually takes place through the hand or forearm and vegetable handlers or persons attending to animals are most likely to be affected. There is a primary lesion at the portal of entry, an ascending lymphangitis and chains of nodules which break down and suppurate along the course of the lymphatics.

**Clinical Picture.**—There may be cutaneous, mucosal or systemic manifestations. There may be a chancre-like lesion with lymphangitis and lymphadenitis and multiple subcutaneous cold abscesses which break down to form gummatous or ecthymatous ulcers with little or no pain. Apart from the skin, cold abscesses may form in the mucosæ, muscles, lymph nodes, joints, bones, epididymis, lungs, gastro-intestinal tract or the central nervous system.

**Diagnosis** is from late syphilis, halogen eruptions, other fungous infections and the primary tuberculous complex. The lymphatic spread is typical of sporotrichosis. Syphilitic gummata are usually single or few in number. The primary tuberculous complex has a portal of entry and an ulcerated lymph node draining it, but not chains of ulcers along the lymphatics as in sporotrichosis. Halogen eruptions may be granulomatous and ulcerative but are usually symmetrical and do not have a distribution corresponding to a lymph drainage area. In sporotrichosis there are multiple lesions in lymphatic distribution with little constitutional disturbance.

**Treatment.**—Potassium iodide in ascending dosage up to the limits of toleration usually brings about a steady resolution.

### BLASTOMYCOSIS (GILCHRIST'S DISEASE)

In the localised form of this infection with *Blastomyces dermatidis*, papulopustulation goes on to the formation of large ulcers bordered by papillomatous vegetations and with discharging sinuses and epidermal bridges. The proliferation of the epidermis may be so marked as to resemble epithelioma (pseudo-epitheliomatous hyperplasia). In the systemic form the lungs are most commonly affected but no organ is immune.

**Course and Prognosis.**—The condition is benign but chronic.

**Diagnosis** is from syphilis, sporotrichosis, halogen granulomata, vegetating pyoderma, tuberculosis verrucosa cutis and epithelioma. Repeated microscopic and cultural search may be necessary before the budding yeast fungus is demonstrated. The histology resembles tuberculosis but with blastomyces in the centre of a nodule.

**Treatment** is by thorough curettage and cautery of the extending hyperplastic edge. X-ray therapy is usually ineffective. Potassium iodide in large doses should be given a trial.



## ACTINOMYCOSIS

This condition is due to bacteria-like fungi of genera *Nocardia*, *Actinomyces* or *Streptothrix*. The cutaneous form (cervico-facial) causes dermal infiltration leading to indurated irregular subcutaneous nodulation going on to ulceration, with sinuses from which seropurulent or sanguineous fluid, containing sulphur-yellow granules, is discharged. Further nodules form nearby with boardlike hardness. The skin may also be involved secondarily from deeper involvement in the mouth, thorax or abdomen. The tongue, lungs, intestines, urinary tract, female genitalia or bones may be affected.

**Histology.**—A granule consists of one or more colonies, each of which has mycelium and pigment granules in the central zone and club-shaped organisms in palisade arrangement at the periphery. The branching hyphae are Gram-positive.

**Course and Prognosis.**—The course is slow, the malady sometimes persisting for up to 10 years.

**Diagnosis** from syphilis, sporotrichosis, scrofuloderma and carcinoma is made from a consideration of the clinical, bacteriological and histological findings (*q.v.*).

**Treatment** is by penicillin or other antibiotic. Surgery and X-irradiation may also be of value.

## CUTANEOUS TUBERCULOSIS

The skin may be invaded by tubercle bacilli or it may be the site of reactions of hypersensitivity to these organisms (tuberculides). When the skin is invaded by tubercle bacilli its manner of response depends on the immunological state of the host at the time. If the individual has suffered no previous tuberculous infection at any site, the Mantoux reaction is negative (primary anergy) and the response will be the primary tuberculous complex: but if there has been a previous tuberculous infection in the skin or elsewhere, and the Mantoux reaction is positive, the response will be lupus vulgaris (normergy). It is believed that if a secondary anergy develops, any subsequent tuberculous infection causes the condition known as sarcoidosis, although this reaction may also be non-tuberculous. Some individuals develop an excessive sensitivity to tuberculin. In them, tuberculous infection at any site may be followed by some form of tuberculide (hyperergy).

## THE PRIMARY TUBERCULOUS COMPLEX IN THE SKIN

This consists of a tuberculous chancre on some exposed part of the body such as the face, eye, hands or knees, and enlargement of the lymph node draining the area. The chancre resembles a boil, but instead of suppurating it persists as a crusted indurated patch with a little bloodstained discharge. The lymph node draining the site enlarges, softens and breaks down through the skin, leaving an irregular scar. Subsequently the primary chancre slowly heals up, or it may form the focus from which a patch of lupus vulgaris develops. The Mantoux reaction changes from negative to positive with the development of the primary complex.

**Diagnosis** has to be made from a low-grade coccal infection.

## LUPUS VULGARIS

**Ætiology and Pathology.**—Infection of the skin causing lupus vulgaris may take place by inoculation, by lymphatic spread, by the breaking down of some underlying tuberculous focus or by the blood-stream. Either human or bovine bacilli may be responsible.

Inoculation through the skin may happen when contaminated dust is accidentally abraded into the skin, as when an infant crawls on the floor in a house in which there is a patient with open pulmonary tuberculosis. Lupus most commonly begins in the first decade but occasionally starts much later in life. The face, particularly around the orifices, is the commonest site of infection but the elbows, hands, knees, buttocks and perianal region are other relatively common sites. Local spread then proceeds by the lymphatic channels or these vessels may be the route by which an infection primarily infecting the nose reaches the skin. Involvement of the skin by spread from underlying tuberculous foci takes place in scrofuloderma (King's Evil) from the breaking down of cervical tuberculous lymph nodes; also from sinuses draining tuberculous kidneys, bones and joints. Spread by the blood-stream only occurs in states of extreme debility, which may arise with measles or pertussis. In this form, multiple foci may occur on widely separated parts of the skin. In its extreme form of severity, blood dissemination causes the rare and often fatal condition of tuberculosis cutis miliaris acuta or lupus miliaris, in which the multiple miliary areas of tuberculosis are only the outward signs of a miliary tuberculosis of internal organs.

Typical "tubercles" are seen in the dermis, with round cells surrounding a zone of epithelioid and giant cell histiocytes. There is considerable disruption of collagen with a variable amount of fibrous tissue formation. Secondary epidermal changes may include atrophy and a patchy parakeratosis, but at some sites, for example, the hands and buttocks, warty thickening may occur (lupus verrucosus).

**Clinical Picture.**—The nodule of lupus vulgaris is a flat, semitranslucent area with slight scaling—the "apple-jelly" nodule described by Jonathan Hutchinson. Subsequently the lesion may have exudative or fibrotic characters. In the former, there is some swelling and redness and no tendency to heal spontaneously; ulceration may occur. In the fibrotic form, the lesions are not raised and ulceration does not occur but the lesions tend to heal in places with much scarring, only to break out once more here or elsewhere. As a result, multiple foci of activity may remain amongst extensive areas of scarring.

Lupus around the nose and mouth is often complicated by mucosal lupus in the nose or on the gums, cheek, tongue, palate, pharynx or larynx. Mucosal lesions are different from the cutaneous ones, being dusky, granular infiltrations which bleed easily.

Lupus vulgaris may destroy cartilage but not bone. The resultant deformities that may arise include simian or parrot-bill deformities of the nose, due to destruction of the alæ and septum respectively, septal perforation and stenosis or occlusion of the anterior nares. The mouth may be narrowed by scarring (microstomia) or the upper lip may be retracted, permanently exposing the gums. Contracture of scarring below the eye often causes ectropion. The pinnae may be destroyed, irregularly or completely, or they may, as a result of the inflammatory process, become adherent to the skull. Some of these deformities are in part due to secondary infection or to the use of caustics and X-rays in treatment. Lesions on the limbs and body may be very extensive. Ulceration may be followed by scarring and contractures or lymphatic obstruction may lead to elephantiasis.

Complications of lupus include secondary infection, particularly in the nose, contractures, elephantiasis and the development of keratoses and prickle cell carcinoma. This is particularly likely to happen in patients who have received X-ray treatment for the lupus, but it may also occur in patients who have had much treatment by ultra-violet irradiation and other locally destructive procedures.

Lupus vulgaris may be associated with phlyctenular keratitis, tuberculosis of the upper respiratory tract, of bones, joints or kidneys and, rarely, of the lungs.

**Diagnosis.**—The earliest lesions may resemble moles, but on diascopy (inspection through a piece of glass firmly applied to the skin) it is clear that the brown colour is due to an exudative process and of apple-jelly appearance, whereas with moles and

freckles it is duller and without translucency. More advanced lesions have to be differentiated from syphilis, tuberculoid leprosy, sarcoidosis, lupus erythematosus, lupoid syphilis and rodent ulcers. Lupus vulgaris usually starts in the first decade, affects skin and cartilage and takes years to develop, showing characteristic apple-jelly nodules. Syphilitic gummata develop much more rapidly, usually in the 30 to 50 age group, and may ulcerate and destroy in weeks or months to an extent that would take lupus several years. Bone may be destroyed as well as cartilage and skin, and it is not unusual for a gumma to form deeply and to ulcerate rapidly with the formation of a large cavity perhaps involving the maxilla. Tuberculoid leprosy may closely mimic lupus but there is anaesthesia to light touch, and heat and cold; the nerves in the area may be thickened and tender and the patient has lived in an area of endemic leprosy.

Sarcoidosis presents as raised, pinkish-yellow, translucent nodules about the face or on the shoulders and arms, or as indurated erythematous lesions on the legs. Histological study may be necessary in the differentiation.

Lupus erythematosus is often symmetrical and involves the "bat's wing" area of the face, the scalp (which is seldom affected by lupus vulgaris), the vermilion surface of the lips and perhaps the backs of the fingers. There is redness with follicular plugging, scaling and central atrophic scarring but without apple-jelly nodulation. A very important differential point from lupus vulgaris is that lupus erythematosus never involves cartilage, so that no matter how long it has been present there is no serious deformity of nose or ears, and no loss of tissue other than the skin.

Rodent ulcer may be simulated by ulcerated lupus but it has a hard pearly edge, whereas ulcerated lupus is ragged. Lupus vulgaris may be complicated by squamous cell epithelioma.

Ancillary aids to differential diagnosis include biopsy, the Wassermann reaction, the Mantoux reaction, the Kveim test and the lepromin test.

Treatment of lupus has been revolutionised in the last few years. Isoniazid in a dose of 300 to 400 mg. a day leads to disappearance of the nodules and of scaling within 2 to 6 months, almost without exception. Time alone can tell of the permanency of this effect because with all treatments of lupus vulgaris "cure" can only be considered a possibility after 5 years' uninterrupted clinical clearance. In the present state of knowledge, a course of 6 to 12 months seems necessary. There is no evidence of the development of drug-resistant organisms. Toxic reactions are slight and rare. Histologically the nodules gradually become nonspecific and finally disappear. Under an "umbrella" of isoniazid it is possible to-day for the surgeon to carry out plastic repairs with far greater confidence than in the past.

Calciferol either by local injection (300,000 units once a fortnight) or orally (150,000 units daily) is also effective, but in a different way. The lesions at first become worse, redder and more swollen, then become less conspicuous with much fibrosis. Histologically the tubercles remain but they are surrounded by an increased fibroblastic and fibrotic reaction. Toxicity is a far greater hazard with calciferol. The urine should be tested fortnightly and blood urea estimations carried out. If the blood urea rises above 70 mg. per 100 ml. it is advisable to suspend the treatment. Early symptoms of intoxication are euphoria, capricious appetite, vomiting, diarrhoea or constipation, headaches and vertigo.

The general health, domestic and occupational surroundings, and nutrition of the lupus patient should always receive attention. The diet should include ample milk, butter and eggs. Coexistent tuberculosis in other organs is not uncommon, particularly in lymph nodes, bones, joints and kidneys; rarely in the lungs.

Before the introduction of calciferol and isoniazid, the local treatment of lupus vulgaris mainly consisted of destructive measures, with the Finsen-Lomholt lamp, the Kromayer lamp and by chemical caustics such as the acid nitrate of mercury. General ultra-violet irradiation is also valuable. It has an unexplained "tonic"

effect as well as helping by the formation of vitamin D in the skin. Light treatment still has its uses to-day when dealing with solitary resistant foci, for which a course of isoniazid may be considered unjustifiable.

### LUPUS VERRUCOSUS (TUBERCULOSIS VERRUCOSA CUTIS)

This is usually due to inoculation from without. It most commonly occurs on the hands or buttocks as a violaceous, warty excrescence, with a reddish halo and a sero-purulent discharge. One form of it is the verruca necrogenica, the anatomical tubercle or post-mortem wart, acquired from a human or bovine cadaver, but the infection can also occur from a patient's own tuberculous sputum. The lesions may be secondarily infected but they do not ulcerate. Dissemination of tubercle bacilli may occur from them through the lymphatics to lymph nodes and the blood-stream. The histological appearance is of a nonspecific inflammatory reaction with overlying papillomatosis: or there may be a tuberculoid appearance.

Diagnosis is from warts, lichen planus verrucosus, syphilis, vegetating pyoderma and blastomycosis. Warts do not show dusky discoloration. Lichen planus verrucosus usually occurs on the shins or on the forearms, and itches intensely. Syphilis is much more actively inflammatory than the indolent lupus verrucosus. Vegetating pyoderma and blastomycosis can only be differentiated by histological and cultural methods.

Treatment is by surgical excision, curettage and cautery, or by oral treatment with isoniazid.

### TUBERCULOSIS COLLIQUATIVA (SCROFULODERMA)

This is tuberculosis of the skin secondary to tuberculosis of underlying lymph nodes, joints or bones.

**Clinical Picture.**—The commonest form is in the neck, secondary to tuberculous cervical adenitis. Subcutaneous nodules become attached to the skin which becomes dusky and indurated; finally the mass breaks down and a crusted sinus is exposed, or ragged, undermined ulcers form with intercommunicating sinuses. When the condition heals, irregular scarring is left.

Diagnosis from syphilis, actinomycosis and sporotrichosis is on clinical grounds and by cultural, serological and histological methods.

Treatment is by attention to good feeding, housing and fresh air, general ultra-violet irradiation and isoniazid by mouth 300 to 400 mg. daily. Surgical intervention is sometimes necessary.

### TUBERCULOSIS CUTIS ORIFICIALIS

This is a form of painful tuberculous ulceration in or around the orifices, usually secondary to tuberculosis of internal organs; thus tuberculous ulcers of the nose, palate, tongue, floor of mouth or the lips arise from infection by sputum from a pulmonary or laryngeal focus; ulceration of the external genitalia in both sexes may occur from tuberculosis of the genital or urinary tracts. Perianal ulcers may occur in persons with intestinal tuberculosis. The ulcers are painful, shallow and ragged, with undermined edges and dirty grey bases from which there is a mucopurulent secretion.

Diagnosis is from chancre, epithelioma or chancroid, by bacteriological examination from the base of the ulcer.

Treatment is by electro-cautery or chemical cautery with acid nitrate of mercury, and with isoniazid by mouth.

### TUBERCULIDES

These are skin reactions which are due to hypersensitivity (hyperergy) to tuberculin. In some forms this relationship is clearly established; in others it is suspected but not proven.

## ERYTHEMA NODOSUM

This is a nonspecific reaction of hypodermal vascular hypersensitivity, one of the causes of which is a recently developed tuberculin hyperergy (see Erythema Nodosum).

## ERYTHEMA INDURATUM

Erythema induratum or Bazin's disease is a condition of dusky, painful nodulation on the lower halves of the legs of young women with pernicious "billiard table" legs. A faulty peripheral circulation seems to predispose to this malady which is rarely, if ever, seen in males or in women with an efficient peripheral circulation. The indurated areas are painful and tender and may break down and form ragged ulcers with undermined edges: secondary coccal infection may follow. The malady is usually bilateral. The Mantoux reaction may be hyperergic, normergic or hypergic.

**Pathology.**—There is a heavy infiltrate in the hypoderm replacing the fat. The infiltrate also involves the deeper parts of the dermis. It may be specifically tuberculoid in some areas and nonspecific in others. The vessels show marked proliferative changes, and obliterative thromboses are seen. Caseating necrosis may extend upwards from the hypoderm and lead to ulceration.

**Clinical Picture.**—The bluish calves show in their lower thirds, on their postero-medial and postero-lateral aspects, irregular, hard, dusky, painful, plaque-like nodulations, which often necrose centrally and leave depressed scars. There may be no other sign of tuberculosis or there may be a history of a pulmonary infection or of the presence of tuberculides elsewhere, for example of the papulonecrotic variety.

**Course and Prognosis.**—The changes in the hypoderm are, to some extent, irreversible, and some degree of scarring is inevitable.

**Diagnosis** is from subcutaneous (Darier-Roussy) sarcoids, erythema induratum of Whitfield and syphilitic gummata. In sarcoidosis there are often other lesions elsewhere on the skin and ulceration is unusual. In Whitfield's erythema induratum middle-aged women are mostly affected and the lesions are multiple. Syphilitic gummata are painless, often single, ham-coloured, serpiginous, "punched-out" ulcers.

**Treatment** is by elastic supports; good food, housing and fresh air; general ultra-violet irradiation (provided there is no pulmonary focus) and isoniazid 300 mg. daily. Calciferol is contraindicated. It may cause rapid softening of the lesions and extensive ulceration, or an outcrop of papulonecrotic tuberculides. Ulcerated lesions may need appropriate antibiotics to control secondary infection: apart from this they should be treated in the same way as hypostatic ulcers (*q.v.*).

## LICHEN SCROFULOSORUM

This is a rare form of tuberculide, consisting of lichenoid papules, which usually occurs in children with tuberculous lymph nodes, bones or joints.

**Clinical Picture.**—There are brownish-red, lichenoid, follicular papules scattered or grouped in circles, sometimes with a spiny tip, slight scaling, crusting or even pustulation. The lesions mostly appear on the trunk and there is slight itching. The Mantoux reaction is strongly positive.

**Diagnosis** is from lichen planus. This is rare in children and usually causes severe itching. The lesions are violaceous, polygonal papules with a waxy surface. In doubtful cases the histology is diagnostic, the papules of lichen scrofulosorum having a tuberculoid structure.

**Treatment** is of the underlying tuberculous condition.

### ACNE SCROFULOSORUM

This also affects children and adolescents who have some form of tuberculosis elsewhere. The lesions especially appear on the buttocks and thighs; they are red, acuminate, follicular papules and pustules. The Mantoux reaction is positive.

**Diagnosis** from staphylococcal folliculitis is by the more prolonged course of the tuberculous lesions, and their lack of response to antibiotics.

**Treatment** is of the primary condition, and general measures to raise the resistance.

### PAPULONECROTIC TUBERCULIDES

Papulonecrotic tuberculides have various forms and distributions: some are truly tuberculous but others may in fact be virides. Superficial forms have been called "follicles", deeper ones "acnitis". Papulonecrotic tuberculides of the extremities consist of discrete, inflamed papules which undergo central necrosis, ulcerate, form scabs and heal with scarring. They occur on the extensor aspects of the forearms and legs, and on the backs of the hands and feet. The whole process may take some 8 weeks but there may be successive crops. The Mantoux reaction may be normergic or hypergic.

Lupus miliaris disseminatus faciei consists of multiple, pinhead sized, flat, discrete, semitranslucent lesions which occur symmetrically on the posterior halves of the cheeks. They are probably tuberculous, the Mantoux reaction being strongly positive.

### ACNE AGMINATA

This is a condition in which acneiform, apple-jelly-like nodules occur on the nose, eyelids and face, often grouped together. They may also occur on the genitalia. After a variable persistence they may disappear, with slight pock-like scarring. The Mantoux reaction is usually hypo- or anergic and the condition is not proven to be tuberculous: it may be of virus origin (see Acneiform Eruptions).

### ROSACEOUS TUBERCULIDE OF LEWANDOWSKY

This condition of translucent, pink papules on the forehead, cheeks and chin resembles rosacea. The Mantoux reaction is strongly positive. It may be a tuberculide localised by a rosaceous circulation.

**Histopathology of the Tuberculides.**—All these lesions show a tuberculoid structure, but this does not of necessity prove a tuberculous aetiology. A tuberculoid structure is often seen in acne vulgaris and in rosacea.

### SARCOIDOSIS (BENIGN LYMPHOGRANULOMATOSIS)

This is an infiltrative and nodular disease affecting the skin and internal organs.

**Ætiology and Pathology.**—Controversy persists as to the cause of sarcoidosis. It appears to be an unusual type of reaction to the tubercle bacillus; but it may also occur in relationship to leprosy, syphilis, foreign bodies, or beryllium. The Mantoux reaction is negative, an acquired anergy to tuberculin; it is probable that this anergy is sometimes more general.

Histologically there are "naked tubercles", well-defined concentric aggregates of epithelioid cells without any necrosis or marked surrounding inflammatory reaction. There may be a few giant cells. Tubercle bacilli cannot be found. In older nodules fibrosis predominates.

**Clinical Picture.**—Most patients are middle-aged adults, women more often than men. There is often very little disturbance of general health but there may be slight pyrexia. Sarcoidosis has extremely variable cutaneous manifestations. There

may be raised, dome-shaped nodules with an apple-jelly appearance on diascopy, or more deeply situated lesions causing purplish or skin-coloured opaque nodules or plaques, with fine vessels coursing over the surface. The more superficial lesions (sarcoidosis of Boeck) appear especially on the nose, cheeks, lips, shoulders and upper limbs. The deeper lesions (Darier-Roussy sarcoids) appear on the face and extensor aspects of the limbs, including the sarcoid variant of erythema induratum on the legs. Diffusely infiltrating, erythrodermatous, annular and serpiginous forms of sarcoidosis are also described.

In one form (lupus pernio of Besnier) the nose, ears, hands and feet are dark blue, swollen and doughy, but not cold. Sarcoidosis may affect practically any organ in the body, causing mucosal lesions, uveoparotitis, hilar glandular enlargement or pulmonary infiltrations, enlargement of lymph nodes, tonsils, spleen, liver, breasts, testes, etc., disturbances of the gastro-intestinal, genito-urinary systems, peripheral or central nervous systems. The iris and the choroid may be affected, sometimes accompanied by swellings of salivary glands (uveoparotitis). Involvement of the bones of the hands or feet may cause absorption of bone and a radiographic picture of cyst-like rarefactions. Radiography may also show hilar glandular enlargement, radiating, peribronchial infiltrations or a diffuse mottling.

**Course and Prognosis.**—Sarcoids may heal spontaneously or may steadily progress with increasing disability. Sometimes tuberculosis develops, the Mantoux reaction becomes positive and the sarcoid lesions disappear. Some patients die from tuberculosis and some from right heart failure secondary to fibrosis of the pulmonary lesions: others die from destruction of the bone marrow by sarcoid infiltrations.

**Diagnosis.**—Sarcoidosis has to be differentiated from perniones, lupus vulgaris, the deep and erythematous forms of lupus erythematosus, tertiary syphilis, leprosy, drug granulomata and cutaneous reticuloses. Reliance is placed on the morphology of the lesions, the sarcoid histology, the negative Mantoux reaction, the raised serum globulins and inverted albumin/globulin ratio, and X-ray evidence of sarcoidosis in the bones or in the chest. Radiographic findings in the lungs may suggest a diagnosis of tuberculosis, pneumoconiosis or carcinomatosis. The Kveim test is sometimes used. This consists of the injection of an extract of proven sarcoid lymph nodes into the dermis. Some 6 to 8 weeks later an indolent nodule develops which shows a typical sarcoid histology.

**Treatment.**—It is difficult to assess the value of treatment owing to the possibility of spontaneous remission. A 3-months' course of calciferol 150,000 units a day is worth a trial.

The urine should be tested for albumin and the blood urea estimated periodically for evidence of toxicity from calciferol. The skin lesions tend to improve more than the systemic ones with this treatment. Isoniazid (300 to 400 mg. daily) is worth a trial. It has to be borne in mind that any treatment that hastens fibrosis of sarcoid lesions may, in fact, shorten life by producing pulmonary fibrosis and right heart failure. Intralesional injections of hydrocortisone (25 mg. in 1 ml.) at weekly intervals can be used to cause shrinkage and flattening of individual nodules, if this is desired for cosmetic reasons or because of discomfort, as for example, beneath spectacle frames.

## VIRUS INFECTIONS

### HERPES SIMPLEX (RECURRENS) (FEBRILIS)

A malady, often recurrent, consisting of outcrops of papulo-vesicles which run their course in 10 to 14 days and end in scabs with minimal scarring.

**Ætiology and Pathology.**—The cause is a delicately balanced host-virus relationship, easily disturbed in favour of the virus. Infection with herpes virus takes place in infancy and the immunological state that results usually prevents outbreaks of herpes except when there is a severe upper respiratory infection.

Histologically, there are intra-epidermal, unilocular or multilocular vesicles with swollen, grossly degenerate epidermal cells.

**Clinical Picture.**—Outbreaks may occur occasionally with severe infections or frequently, and from insignificant or even undetectable stimuli. Precipitating causes include coryza, slight pyrexia, exposure to sunlight, menstruation, digestive upsets and emotional stimuli. Genital herpes may occur after intercourse with one partner but not with another.

The outbreak begins with the appearance of a group or groups of painless red-dened papules, rapidly becoming vesicular. The lesions may be bilateral. The vesicles may remain intact or rupture, forming golden scabs on an erythematous base. The lesions occur most commonly on the vermilion surface of the lips, around the mouth or on the cheeks, ears or nose; they may occur on the buttocks or on the external genitalia. There is no enlargement of the regional lymph nodes unless secondary infection occurs, as is not unusual. An associated oral aphthosis is uncommon.

Uncomplicated lesions pass through their various stages and resolve in 10 to 14 days. Recurrences may occur as often as once a fortnight or only very occasionally, the lesions recurring at the original sites or nearby, especially on the cheeks, lips, genitalia or buttocks.

**Course and Prognosis.**—The condition is not amenable to present methods of treatment and may recur indefinitely.

Diagnosis is from zoster and from impetigo.

Zoster is a nonrecurrent, unilateral, painful malady, with enlargement of the regional lymph nodes. The lesions conform to a posterior nerve root (or roots) distribution.

Impetigo is characterised by golden "stuck on" crusts or by purulent blebs, and usually there are other lesions on the face, in the nostrils or at the paronychia folds. This differential diagnosis is one of the most important and recurrent problems of dermatology, the misdiagnosis of herpes simplex as impetigo often being followed by unsuitable treatment and the development of a contact eczematous dermatitis.

Herpes preputialis forms shallow ulcers which do not enlarge. This helps to differentiate them from syphilis and soft sore, but a dark ground examination should be made in any suspicious circumstances.

**Treatment.**—There is, at present, no specific treatment for herpes simplex. Precipitating factors should receive attention when discovered. Local applications should be bland, for example, calamine liniment; antibiotics are best avoided. An individual attack can be shortened by a single X-ray exposure of 100 r, but this procedure should not be used except for some special occasion. It has been claimed that repeated vaccination with calf lymph sometimes checks recurrences.

### ZOSTER (ZONA, HERPES ZOSTER, SHINGLES)

An eruption of vesicles in unilateral, segmental distribution.

**Ætiology and Pathology.**—The cause is an infection of the posterior nerve roots and corresponding area of the skin with the virus of varicella. The virus may be activated by infections, neurosyphilis, neoplasms, Pott's disease of the spine, Hodgkin's disease and other reticuloses, certain drugs, particularly arsenic, or deep X-irradiation, but usually no such cause is apparent.

Zoster may coincide with one or several vesicles of varicella elsewhere on the



skin; it may occur 10 to 14 days after exposure to varicella, or varicella may follow at a similar interval after exposure to zoster.

Histologically, there are intra-epidermal, mostly unilocular vesicles, with swollen, grossly degenerate epidermal cells and an underlying inflammatory infiltrate proceeding to necrosis.

**Clinical Picture.**—There is a unilateral and segmental eruption consisting of grouped erythematous vesicles, with enlargement of the regional lymph nodes and a variable degree of pain in the area affected. This pain may precede by a few hours the outcrop of vesicles. It is severe in proportion to the patient's age, being practically nonexistent in adolescents but often severe and persistent in the elderly. Sometimes the pain develops its full intensity when the eruption is resolving and persists for months or years after the cutaneous manifestations have ended in scars. This post-herpetic neuralgia is most common in elderly patients.

The lesions of zoster are at first erythematous, then vesicular with erythematous margins. The vesicles proceed to necrosis and dark crusts and secondary infection may then become superimposed. When the scabs detach, depressed scars are left.

Zoster is more serious in some sites than in others. The first (ophthalmic) division of the fifth cranial nerve is often affected and the eye may then become involved, with resultant opacity of the cornea and impaired vision, or even with perforation of the cornea. Involvement of the second division of the fifth cranial nerve causes palatal lesions in addition to those on the skin, and involvement of the third division of this nerve produces lesions on the anterior two-thirds of the tongue, the floor of the mouth and buccal mucosa, as well as on the chin. When the seventh cranial nerve (geniculate ganglion) is affected, there is pain and vesiculation on and behind the pinna, the fauces and the posterior third of the tongue and, in addition, facial palsy. Involvement of the ninth cranial nerve (petrous ganglion) causes pharyngeal lesions.

**Course and Prognosis.**—Zoster, once it has begun, inevitably proceeds through its various phases and ends with scarring, in proportion to the intensity of the tissue reaction and amount of secondary infection, in 2 or 3 weeks.

Second attacks rarely, if ever, occur. The prognosis as regards post-herpetic pain is bad in direct proportion to the age of the patient.

**Treatment.**—There is no specific treatment for zoster. The patient should rest in an equable temperature and a bland but not occlusive application should be applied, such as calamine lotion or liniment. Occlusive dressings encourage maceration and secondary infection of the lesions. Suitable antibiotics, locally applied, are of value to control secondary infections but are no use for controlling the zoster itself. For ocular involvement, homatropin should be instilled and antibiotics used to control or prevent secondary infection. For pain, compound codeine tablets may be sufficient, or a preparation such as the following:

Soluble phenobarbitone	..	..	..	gr.	$\frac{1}{2}$
Tincture of gelsemium	..	..	..	m.	10
Phenazone	..	..	..	gr.	4
Syrup of lemon	..	..	..	dr.	$\frac{1}{2}$
Peppermint water to	..	..	..	oz.	$\frac{1}{2}$

$\frac{1}{2}$  fl. oz., t.d.s.

For more severe pain, opiates may be necessary, particularly at night.

### VARICELLA (CHICKEN POX)

This is characterised by a polymorphic rash appearing in crops, with some constitutional disturbance and residual scarring.

**Ætiology.**—The virus is closely related, if not identical, to that of zoster. The incubation period is 12 to 21 days.

**Clinical Picture.**—Without prodromal symptoms or with slight malaise, the eruption begins with pink macules, rapidly becoming vesicular. The vesicles often show little or no erythema. They may become slightly purulent or become broken and form blood scabs which detach in a few days, leaving slightly depressed scars. With the occurrence of further crops of lesions for the first few days of the illness, all varieties of lesion—macules, papules, vesicles, scabs and scars—can be seen in the one patient at the same time. Itching is moderately severe. In adults and sometimes in children, there may be malaise and fever. The distribution is widespread with involvement of the trunk more than the limbs, also the scalp and the oral mucous membranes.

Diagnosis is from papular urticaria, in which the lesions appear mostly on the extensor surfaces of the limbs and consist of firm, shotty, itchy, erythematous, often golden-scabbed, papules, sometimes much excoriated.

From variola, the diagnosis may be simple or extremely difficult. Small-pox in the unvaccinated is a malady with serious constitutional disturbance, a heavy affection of the exposed parts, marked sensitivity to light, and all the lesions in the same stages of development; but smallpox modified by vaccination, and the milder variant of the malady, known as alastrim, may present with only one or a few lesions, from which a diagnosis on clinical grounds may prove impossible. Reliance must then be placed on virological and serological studies.

**Treatment.**—Varicella needs no treatment except rest in bed and calamine lotion, with a normal or restricted diet depending on the presence or absence of fever.

### KAPOSI'S VARICELLIFORM ERUPTION

This is a generalised infection with the virus of herpes simplex. It occurs in infants with eczema who have been exposed to a sufferer from herpes simplex.

**Clinical Picture.**—There is a generalised eruption of varicelliform lesions, high fever and general malaise.

**Course and Prognosis.**—There is a considerable mortality. In those who survive, the malady clears up in 2 to 3 weeks.

**Treatment.**—The best nursing is essential. Secondary infection is common and possibly in part responsible for the mortality. The use of antibiotics, both systemically and locally, is advisable. The lesions should be dressed with bland applications such as calamine liniment.

### VACCINIA

Vaccinia is the result of deliberate or accidental inoculation with calf-lymph. The accidental form may follow deliberate vaccination and transference may take place on the same individual or to someone else. The lesions are the same as those caused by vaccination in the susceptible, and go through stages of erythema, papulation, vesiculation, necrosis, crusting and scarring. The diagnosis is easy if the possibility is thought of and confirmed by enquiry.

Individuals with Besnier's prurigo (atopic dermatitis) or infantile eczema are liable, if accidentally or deliberately vaccinated, to develop a generalised vaccinia with high fever and considerable malaise. The condition has been called eczema vaccinatum and may be indistinguishable, apart from the history and virological studies, from Kaposi's varicelliform eruption due to the herpes virus. Eczema vaccinatum may be further complicated by a severe coecal infection.

**Treatment.**—None is needed apart from protective dressings and topical antibiotics if secondary infection occurs. Eczema vaccinatum needs rest in bed with good nursing and, if secondary infection occurs, appropriate antibiotics, systemically and locally.

## WARTS (see Tumours of the Epidermis)

## MOLLUSCUM CONTAGIOSUM (see Tumours of the Epidermis)

## ORF (CONTAGIOUS PUSTULAR DERMATITIS OF SHEEP)

A virus infection resulting from the handling of infected sheep's heads.

**Ætiology.**—The malady may affect all handlers of sheep's heads and carcasses—shepherds, meat porters, butchers, cooks and housewives. The histological picture resembles that of cowpox, but virological studies differentiate the two conditions.

**Clinical Picture.**—The lesion usually occurs on a finger, on the hand or on the face as an oedematous inflammatory nodule. The inflammation attains its maximum intensity after 7 to 10 days, some central necrosis occurs, and the lesion gradually shrinks, disappearing after several weeks, leaving a scar. Constitutional symptoms are slight.

**Diagnosis** is from vaccinia and milkers' nodes.

**Treatment.**—No treatment is effective in shortening the course. Topically applied antibiotics are helpful to control secondary infection.

## MILKERS' NODES

These are red nodules, occurring on the hands of milkers and probably due to the cowpox virus acting on someone with partial immunity. In the absence of such immunity, more typical cowpox develops, with bullous lesions on the hands or face.

## LYMPHOGRANULOMA VENEREUM VEL INGUINALE

This is a venereal disease caused by a virus.

**Clinical Picture.**—After an inoculation period of 7 days, a genital papule or vesicle or urethritis develops, followed in 2 weeks by enlargement of the inguinal lymph nodes which break through the skin, with multiple sinuses. Involvement of the ano-rectal glands from vaginal lesions may cause rectal stricture and genital elephantiasis. The infection may start as a proctitis.

**Diagnosis** is from syphilis, soft sore, granuloma venereum and carcinoma of the rectum. The Frei test is positive.

**Treatment** is by chlortetracycline or chloramphenicol, gr. 3 every 8 hours for 14 days.

## GRANULOMA VENEREUM VEL INGUINALE

An infection with Donovan's granulomatosis, mostly of coloured people, venereally acquired, of the anogenital region, causing nodules or vesico-pustules, with slowly spreading ulceration and vegetations with serpiginous outlines and ending in extensive scarring. The Frei test is negative. *Donovania granulomatis* is responsible. The incubation is one or a few weeks.

**Diagnosis** is from syphilitic, tuberculous and carcinomatous ulcers.

**Treatment** is by antimony injections, streptomycin or chloramphenicol.

## PARASITIC INFESTATIONS

## SCABIES

Scabies is an acarine parasitic infestation of the stratum corneum caused by *Sarcoptes (Acarus) scabiei*.

**Ætiology.**—The adult female is about 0.4 mm. long, just visible to the naked eye, oval in shape, with two anterior pairs of limbs which bear suckers and two

posterior pairs which bear trailing bristles. The gravid female burrows in the horny layer where she deposits up to 30 eggs and then dies. The larvæ hatching from the eggs have only two hind limbs until, by repeated moulting, they develop to mature males and females. The larvæ and males burrow into hair follicles, the males dying after impregnation of the females. The complete life cycle takes 10 days. Infection is by intimate skin contact; the infestation is either a familial and household or a venereal complaint of bedfellows. It may rarely spread by more casual contacts, as in hand-holding. Itching begins about 3 weeks after infestation, apparently due to the development of allergic hypersensitivity.

**Clinical Picture.**—Scabies may present as pruritus, widespread eczema or infected dermatitis, urticaria, impetigo or furunculosis. Itching may be intolerable or inconspicuous, depending on the integrity of the sensory tracts and on the mental alertness of the individual. Thus, in lepers, imbeciles or in senile dementia there is no obvious discomfort from itching in individuals very heavily infested. Secondary infection may then result in a picture resembling infective dermatitis or exfoliative dermatitis (Norwegian or crusted scabies). Nurses are very liable to become infested as a result of attending to these patients whose scales and even nails show an enormous acarine population.

A history of familial incidence or of venereal exposure makes the diagnosis probable. In any widespread itchy eruption, the physician should examine for scabies. The sites involved and the presence of burrows should make the diagnosis clear. Scabies affects thin skin areas below the collar line: thus, the anterior axillary folds, the inner sides of the elbows, the ulnar sides of the wrists and hands, and the clefts of the fingers are sites commonly affected on the upper limbs. On the trunk, the sites most affected are the female breasts, the abdomen, male external genitalia and the buttocks; and on the lower limbs the thighs, ankles and feet; in infants, palms and soles are characteristically affected.

The burrow is a linear, slightly sinuous elevation in the skin, at one end of which a darker speck marks the site of the parasite. In cleanly individuals the burrows may be inconspicuous and it is best to search for them by oblique, almost tangential lighting in order to make minor elevations in the skin more obvious. In less cleanly persons, accumulations of dirt beside the burrows make their recognition easier. Skin-coloured or red follicular papules are also observed at the sites of election and elsewhere. Both these types of lesion may be masked by scratching, secondary infection or eczematous dermatitis. In doubtful cases the diagnosis can often be made by finding adult parasites, larvæ or ova. This is best done by scraping open suspect burrow-like lesions with a Harrison's scarifier, through potassium hydroxide. Microscopic examination may then reveal one or more of adult parasites, larvæ, unhatched eggs or eggshell fragments.

Scabies may be caught from cats and dogs, but the parasites do not burrow, there are only itchy papules and the disease dies out if the animal is avoided.

**Course and Prognosis.**—If untreated, scabies infestations go on indefinitely. This is only likely to occur in individuals of low intelligence in whom itching may be slight or absent. By concurrent treatment of all members of the household, scabies can be eliminated quickly; but if any one member of the household remains untreated, or is treated at some other time, recurrences are likely.

**Diagnosis** is from pediculosis and from other causes of widespread itching eruptions associated with urticaria, eczema-dermatitis, furunculosis and impetigo. The manual lesions by themselves may suggest a contact dermatitis and a more general examination should be made in all such cases if there is the least cause for suspicion. The diagnosis of scabies is made from a consideration of the history and the distribution and nature of the lesions, and from microscopic examination. Involvement of the penis and scrotum with itchy red papules is characteristic.

*Pediculosis corporis* mostly affects the upper trunk and shoulders with scratch

marks, excoriations and patchy pigmentation. *P. capitis* may also cause scratch marks on the shoulders. Parasites are found on the seams of underclothes and eggs on coarse body hairs or attached to underclothing.

**Treatment.**—The patient and all contacts must be treated concurrently. Self-treatment is difficult and the treatment of patients by each other is best. In extensive family infestations and in epidemics, or if home amenities are inadequate, treatment at special cleansing stations is preferable.

The full course of treatment takes 3 days. On the first day the patient takes a warm bath and lathers and scrubs the body and limbs thoroughly all over, with particular attention to the sites known to be most heavily involved. After the bath, the skin is not dried but benzyl benzoate 25 per cent. is applied all over from the neck downwards, using a paint brush 2 or 3 in. wide. Having made certain that every square inch of skin has been covered, including the genitalia, perineum and toe clefts, the patient dries in front of a fire, puts on the previously worn nightwear and goes to bed between the previously used sheets. On the second day the patient dresses in the previously worn underwearer. That day, a second application of benzyl benzoate is made, but without a preceding bath; then the patient dries before a fire and puts on clean underwear. That night clean nightwear is worn and the patient goes to bed between clean sheets. On the third day the patient takes a bath and the treatment is then at an end.

If there is any further itching, calamine lotion is applied, and on no account must further applications of benzyl benzoate be made. Patients sometimes give themselves repeated applications because itching often persists for a while after the two treatments, and they interpret this as meaning that the infestation persists. Repeated applications of benzyl benzoate may cause dermatitis medicamentosa. For infants under 2 years of age, a half-strength emulsion may be used. Sulphur ointment (B.P.) (10 per cent. for adults, 2½ per cent. for infants) may be used instead of benzyl benzoate emulsion, but it is more liable to irritate the skin. Underclothing, nightwear and sheets are best dealt with by laundering and ironing. *Sarcoptes* essentially lives on and in the epidermis and does not, like the louse, move away from the host; hence it is unnecessary to disinfest bedding, blankets and the outer clothing.

## PEDICULOSIS

Three forms of lice live on man: *Pediculus capitis*, *Pediculus corporis* (vestimenti) and *Pediculus (phthirus) pubis*.

### PEDICULOSIS CAPITIS

**Clinical Picture.**—The parasite is about 3 mm. long with an oval head having two antennæ, a powerful mandible and a proboscis. The narrow thorax supports three pairs of legs, each of which has a hook-like extremity. The abdomen is much wider than the thorax. The eggs (nits) are laid on hairs, being affixed by a cement-like substance. The larvæ hatch out from the egg by means of a movable lid. *P. capitis* may be asymptomatic and found during the course of routine examination of the scalp, or it may present as itching of the scalp, neck or shoulders, with scratch marks, or as impetigo or pyoderma of the scalp. On examination, ova are found, obliquely attached to hair shafts, especially in the occipito-parietal region. In light infestations there may be eggs on a few hairs, but in heavy infestations several eggs may be seen attached to one hair shaft. The discovery of adult parasites on clinical examination is difficult except in heavy infestations. Secondary infection causes matting of the hair, an offensive odour, pyoderma, cervical lymphadenitis and sometimes œdema of the orbital tissues causing closure of the eyes.

**Treatment.**—Infestation may affect the family. It is of no use treating the

individual without investigating home conditions with the aid of a health visitor. All infested individuals should be treated concurrently.

The hair is combed thoroughly with a fine-mesh comb to unthread the nits (ova) by force. In severe infestations it makes things easier if the hair is cut short. D.D.T. application, 2 per cent. (B.P.C.), is then rubbed into the scalp and not washed out for the next 24 hours; the parasites are not killed immediately and may survive for a day or two: or medicated (lethane) hair oil (N.F.) may be used in a similar way. With either preparation a second application is made after an interval of 3 days. Benzyl benzoate emulsion can also be used and is said to make it easier to remove the nits. Lorexane, a benzene hexachloride concentrate, is also effective. Any coccal infection that remains is dealt with afterwards by antibiotics. Heat disinfection of the bedding and headwear should be carried out.

**Prophylaxis.**—Of great importance in the prevention of scalp infestation is daily brushing and combing of the hair and a weekly shampoo. This régime is often neglected when expensive permanent waving and setting is performed, hence scalp infestation to-day occurs mostly in young women, apart from outbreaks in uncleanly families. A low intelligence is common in adults with scalp infestation.

### PEDICULOSIS CORPORIS

The parasite is structurally similar to *P. capitis* but slightly larger (4 mm. long). *P. corporis* is rare in peace-time, except among vagrants and inhabitants of common lodging-houses. In war conditions it tends to become more widespread.

**Clinical Picture.**—Itching of the body and scratch marks, excoriations and patchy pigmentation with areas of eczematization and lichenification sometimes with secondary infection, suggest the diagnosis. Exposed parts escape and the trunk is mostly affected, especially the backs of the shoulders, the waist and the buttocks and the proximal parts of the limbs. The parasites visit the skin to feed and to deposit eggs on coarse hairs, but spend most of their existence on the underclothing and bedding, a completely different mode of life from sarcoptes. Eggs are also affixed to fibres of textiles. If the host is pyrexial the parasites move to the outer clothing and occasionally transference takes place of louse-borne typhus in this way. More common is transference from one person to another under overcrowded and unhygienic conditions.

**Course and Prognosis.**—Pediculosis is important not only in itself but also as the means of spread of more serious conditions, such as typhus.

Diagnosis is from scabies, senile or general pruritus, and dermatitis herpetiformis. Scabies has a different distribution, pathognomonic signs in the form of burrows, and sarcoptes or ova may be found on scraping. Senile pruritus may present with scratch marks and excoriations but parasites are not found on inspecting the clothing. The physician must remember, however, that the patient may have put on clean underwear for his visit to the hospital. *Dermatitis herpetiformis* affects the shoulder and pelvic girdles chiefly, also the genitalia, elbows and knees. The physical signs are flaccid vesicles, easily ruptured, excoriations and patchy pigmentation. There is a characteristic histology and a brisk response to treatment with sulphapyridine.

**Treatment.**—D.D.T. powder (N.F.), 10 per cent. liberally dusted on the patient's skin beneath the underwear is effective in controlling the personal infestation. The underclothes and bedding should be heat disinfested and the seams of more superficial garments run over with a hot iron.

### PHTHIRIASIS PUBIS

*Phthiriasis pubis* or crab louse infestation is usually acquired venereally. *Phthirus pubis* is a short, wide, almost triangular louse 1.5 mm. long and about the same width,

with three pairs of legs having hook-like ends. Infestation may also take place in the axillæ, on coarse body hairs and, rarely, on the eyebrows, eyelashes or beard. The brownish parasite hides in follicular orifices attached to hair shafts, or suspends itself from two hairs, and the females deposit ova on the hairs. The bites of these parasites cause tiny blue spots known as "*maculæ cærulæ*".

**Clinical Picture.**—There is itching of the pubis and the sufferer often recognises the presence of the lice. Bluish macules about 0.5 cm. in diameter are observed but few, if any, scratch marks can be seen.

**Treatment.**—Shaving the pubis is a great help. Then D.D.T. application, medicated (lethane) hair oil, or benzyl benzoate application may be applied—all preferable to mercury ointment which often causes severe dermatitis. Parasites on the eyelashes should be removed with forceps.

### INSECT BITES AND STINGS

The flea (human or dog), bed bug and gnat may cause urticarial papules with central puncta, or large blisters may develop. Bee, wasp and ant stings may cause more violent allergic reactions in the susceptible individual.

**Treatment.**—Antihistamine creams may be applied and antihistaminic drugs taken by mouth. A bee sting should be extracted if possible and weak ammonia applied. Wasp and ant stings are also best treated with ammonia. Dimethyl phthalate cream makes a useful repellent against gnats.

## ERYTHEMATOUS CONDITIONS

Erythema is a transient redness of the skin due to vasodilatation.

### SIMPLE ERYTHEMA

A transient redness of the skin from physical causes such as heat, cold and friction.

### INTERTRIGO

A shiny, pink condition of opposing skin surfaces due to erosion of the superficial cells of the epidermis by mutual friction. Secondary infection with monilia and cocci is common, giving rise to intertriginous (infective) dermatitis, often with fissuring.

**Treatment** of intertrigo is by suitable clothing, uplift brassieres, etc., to prevent friction of the opposing surfaces and maceration from retention of sweat. For simple intertrigo a dusting powder such as boracic talc powder is suitable. If fungous infection is superimposed, magenta paint is often helpful and if coccal infection develops, the appropriate antibiotic. Silver nitrate solution (2 per cent.) is a useful application to fissures at the depths of the folds.

### TOXIC ERYTHEMA

A widespread reddening of the skin believed to be due to toxic agents: of virus origin in measles and rubella; of streptococcal origin in scarlatina; due to drugs in morbilliform and scarlatiniform drug eruptions and some examples of urticaria, erythema multiforme, erythema nodosum, etc., or due to unknown causes.

**Diagnosis** depends on a careful history and examination; on the presence of fever, coryza, photophobia and Koplik's spots in measles; occipital lymphadenopathy in rubella; fever, tachycardia, headache, vomiting, circumoral pallor, exfoliation of the tongue and sore throat in scarlatina; drug eruptions and idiopathic toxic ery-

themata may occur with or without fever; they do not spread over the body surface in the same order as the exanthemata, and some areas may escape. In scarlatiniform toxic erythema the pattern may be coarse and the peeling more marked than in scarlatina, but mouth lesions may be absent. Milian's ninth-day erythema is a scarlatiniform rash thought to be due to activation of a latent infection by a drug, for example, arsphenamine or sulphonamides. The phenomenon is known as "biotropism".

Treatment is by finding and removing the cause. Septic foci may need attention. Often a cause cannot be found.

### FIXED ERYTHEMA

A localised and circumscribed recurrent erythema erupting in the same situation every time one particular drug is taken (see Drug Eruptions).

### URTICARIA

A transient redness and swelling of the skin, causing characteristic weals in the dermis or large hypodermal swellings.

**Ætiology.**—Urticaria is caused by dilatation of the capillaries and small arterioles and transudation therefrom. Capillary dilatation may arise from the release of histamine or H-substance and arteriolar dilatation from acetylcholine. Urticaria may arise from external or internal causes. The external causes include nettle stings (from their histamine and acetylcholine content), insect or jellyfish bites, contact with "woolly bear" caterpillars, or infestation with scabies. In certain individuals friction causes wealing within a few seconds (dermographism or factitious urticaria). In such persons, too, scabies may present as urticaria. In others, heat is responsible and these persons also urticate from exertion or excitement (cholinergic urticaria). Urticaria from cold or from light (the yellow band of the spectrum) are both very rare. Among internal causes are certain foods and drugs, foci of infection, intestinal parasites and hydatid cysts, cutaneous reticuloses and emotional causes, particularly resentment and masochism. Urticaria may be dermal and present with itchy papules or with weals; or it may be hypodermal and present with large, non-itchy swellings (giant urticaria; angioneurotic œdema; Quincke's œdema).

**Clinical Picture.**—Urticaria is conveniently divided on clinical grounds into two forms; acute or subacute, single attacks; and chronic or recurrent attacks.

The acute form presents as itchy, pink papules and weals—elevated pink areas with blanched centres brought about by the obliteration of the dermal vessels by the pressure of exudate. The lesions appear suddenly with intense itching, and disappear just as rapidly, with the result that when the patient attends for examination physical signs may be absent. Urticaria from the nettle may have pseudopodia, apparently due to lymphatic spread of the injected histamine and acetylcholine. Non-itchy hypodermal, skin-coloured or pink swellings may also appear, particularly around the eyes or mouth. Swellings within the mouth are rare but potentially lethal at the back of the tongue or on the larynx, where they may cause obstruction of the respiratory tract. The lesions may recur at intervals for a few hours or days and then cease. Constitutional symptoms are usually slight or absent but the patient may be very anxious about the significance of the rash and depressed by the severe itching which interferes with sleep. An emotional disturbance may lower the threshold of reaction to some antigen. Sometimes a gastro-intestinal disturbance precedes the eruption, or foods such as shellfish or strawberries may have been eaten. In other patients a drug is responsible, usually aspirin, a barbiturate, halogen, codeine, phenolphthalein or quinine, although many others can give the same effect. The injection of sera, for example diphtheric antitoxin, or penicillin, may be followed by urticaria within 10 to 14 days in the first instance or within a few hours after subsequent injections. Acute local urticaria is usually caused by nettle stings, mosquito, bug or flea



bites; it may also occur around sites of injections. Dermographism, too, tends to be localised to sites where clothes rub or press.

Chronic or recurrent urticaria presents as itchy papules and weals and subcutaneous swellings which usually occur more in the evening but sometimes in the morning. Foods and drugs are seldom found to be responsible for this type of urticaria, and the most careful search for foci of infection or of infestation is often unrewarded with success. Resentment, fear or ungratified libido may precipitate the condition, or cause exacerbation, and fatigue is often the immediate precipitant.

**Diagnosis.**—The recognition of urticaria is usually easy; even if there are no physical signs at the time of the examination the history of transient swellings, perhaps with itching, can only mean urticaria. Dermatitis herpetiformis presents with vesicles, excoriations, crusts and pigmentation. The lesions of erythema multiforme are more persistent than those of urticaria but less itchy.

Giant urticaria is differentiated from erysipelas and contact eczematous dermatitis by the absence of fever and a dusky, brawny swelling which are found in erysipelas, and by the absence of vesiculation and peeling which occur in eczematous dermatitis. Discovery of the cause is another matter. This is often simple in the acute form but in chronic cases it necessitates the most careful history and examination directed towards the discovery of allergens, toxic foci, infestations, physical causes or faulty attitudes of mind. Further, the urticarioid lesions of the reticuloses must be borne in mind and a white cell count is always advisable in the chronic form of the malady.

**Treatment** consists of removal or avoidance of the cause; and symptomatic relief by means of antihistaminic drugs while looking for the cause. The patient should be instructed to stop taking any drugs that are not essential. Suspected foods should be avoided and foci of infection treated. Of the antihistaminic drugs, promethazine hydrochloride 25 mg. in the evening or twice a day, is perhaps most useful owing to its powerful soporific effect, but sometimes this action is not desired and then mepyramine maleate, 100 mg. up to three times a day, may be more suitable. The dose of any antihistaminic drug should be adjusted so as to give the best control with a minimum of unwanted side-effect: the dose is reduced and the drug finally withdrawn as the symptoms are relieved. This particularly applies to urticaria from injected drugs such as penicillin. An aperient is sometimes useful. In severe forms rest in bed is advisable.

In the psychogenic variety, barbiturates or bromides may be as useful as antihistaminic drugs, but if the urticaria is believed to have an allergenic basis it is wise to avoid all drugs except the antihistamines. Relief of the psychogenic type depends on helping the patient to understand the significance of the symptom in relation to his attitude of mind. Dextro-amphetamine is a valuable sympathomimetic drug for these patients, in a dose of 5 mg. each morning. Local treatment consists of calamine lotion, to which 1 per cent. of phenol or 12½ per cent. of weak lead subacetate solution may be added.

### LICHEN URTICATUS (PAPULAR URTICARIA)

This is a form of urticaria which occurs in children.

**Ætiology and Pathology.**—The malady tends to occur more in the summer months and may recur for several years. The cause is unknown, but something in the home environment is important: it has repeatedly been shown that removal of the patient to hospital without any other alteration in treatment may bring about a prompt remission. Insect bites are responsible in a proportion of cases but in many patients a tense emotional environment seems to be another important factor.

Histologically there is acanthosis, spongiosis and oedema with a chronic infiltrate around the vessels of the dermis.

**Clinical Picture.**—Itchy, pink or skin-coloured, shotty papules appear in crops, mostly on the extensor surfaces of the limbs but also on the buttocks and trunk. The papules soon acquire vesicular tops which may become crusted and excoriated.

**Course and Prognosis.**—The malady may persist for several weeks.

**Diagnosis** is from scabies, varicella and insect bites. Scabies affects the flexor surfaces and the elementary lesions are burrows and follicular papules. Penile, scrotal and mammary lesions are characteristic. The history may reveal other cases in the family. Varicella presents with a polymorphic eruption of macules, papules, vesicles and crusts. The scalp is often affected and the trunk more than the limbs. There are often vesicles on the buccal mucosa. Insect bites may show puncta or there may be large bullæ on the legs; but papular urticaria may sometimes be a generalised reaction of hypersensitivity to insect bites, and puncta will not then be seen.

**Treatment.**—Any drugs being taken should be withheld and careful enquiry should be made into the child's diet, with particular reference to fruits and sweets. Any imbalance or excess should be adjusted. An examination at the home may reveal bug infestation or flea-infested animals. Antihistaminic drugs in syrup form are useful, for example, elixir Benadryl 1 to 2 dr., or elixir Phenergan in a similar dosage. Removal of the child into hospital may succeed after all else has failed.

### URTICARIA PIGMENTOSA (XANTHELASMOIDEA)

A pigmented macular eruption with urtication.

**Ætiology and Pathology.**—The cause is unknown.

Histologically there are numerous mast cells in the upper dermis in the infantile form, but few or none in the adult form.

**Clinical Picture.**—In the first year of life brown macules, urticarial papules and small weals are seen. The lesions appear anywhere on the skin, in crops, each lesion starting as a papule or weal and proceeding to pigmentation. The pigmented macules urticate on friction. Weber has described a form in which there are telangiectatic, red macules with very slight pigmentation.

**Course and Prognosis.**—In the infantile form the lesions may disappear after several years. In the adult form they are said to be more persistent and the telangiectatic form may end fatally as a mast cell reticulosis.

**Diagnosis** from papular urticaria in infancy is by the marked pigmentation and the presence of mast cells in the dermis. The adult form may be mistaken for secondary syphilis but is recognisable by the urtication.

**Treatment** is symptomatic by calamine lotion and a trial of antihistaminic drugs.

### ERYTHEMA MULTIFORME

An eruption with a marked tendency to recurrence, of well-defined, reddened areas of skin which mostly appear on the extremities.

**Ætiology and Pathology.**—Erythema multiforme is a reaction of hypersensitivity to a variety of known or suspected causes, in particular bacterial and virus infections, and drug intoxications. It is characteristically recurrent and is sometimes preceded by herpes simplex. It is a rare complication of the X-ray treatment of Hodgkin's disease.

Histologically there is dilatation of the dermal blood vessels with a cellular, mainly lymphocytic, infiltrate around them, and some serous exudation. There may be some spongiosis.

**Clinical Picture.**—Erythema multiforme usually affects young adults. There is no obvious seasonal incidence but a marked tendency to recurrence. The distal parts of the limbs and the face are most affected and often the vermilion and mucous surfaces of the lips and the mucosæ of the mouth and genitalia are also involved.

Lesions on the trunk are relatively rare. An attack may be ushered in by malaise for 48 hours before the characteristic outbreak.

The lesions are polymorphic; and maculo-erythematous, papulo-vesicular, bullous and hæmorrhagic varieties occur. They persist in one situation throughout an attack and do not show the evanescent properties of urticaria. The central part of the lesions may be paler or darker than the periphery; the former indicates early bulla formation; the latter is due to hæmorrhage or to brown pigmentation. In either case the picture of erythema iris results.

When the exudate in these cutaneous lesions has been absorbed they take on a dry, superficial, fissured and scaly, brownish-red discoloration, followed by peeling and resolution. The mucosal orogenital lesions differ from those of the skin in that erosion occurs more easily, with the result that a moist ulcerative, pseudomembranous condition results along the vermilion surface of the lips, in the mouth, or on the glans penis or mucosa of the vulva. There may also be pain and swelling of joints, fever and albuminuria; but usually subjective symptoms, including itching, are slight.

The Stevens-Johnson syndrome is a severe variant of erythema multiforme with exudative, bullous and erosive cutaneous lesions, extensive and distressing involvement of the mouth, and lesions on the conjunctiva and cornea of the eye which may go on to pannus and blindness. This malady is accompanied by fever and malaise.

**Course and Prognosis.**—Attacks of erythema multiforme usually clear spontaneously after 2 or 3 weeks, but recurrences after intervals of months or years are common. The common form leaves no sequelæ but the severe form may lead to dimness of vision or blindness.

**Diagnosis** is from other bullous conditions on the hands and elsewhere and from other erythematous conditions. Thus, pompholyx, dermatitis herpetiformis, pemphigus and pemphigoid, lupus erythematosus and urticaria, may all, at one time or another, have to be excluded. Pompholyx may present with large bullæ, but there is no marked erythematous component unless secondary infection occurs. Dermatitis herpetiformis presents with intensely itchy vesicular and eroded lesions on the shoulders, buttocks, elbows, knees or elsewhere, but there is little or no erythematous halo to the lesions. In pemphigus the bullæ are flaccid and extend when lateral pressure is applied to them (Nikolsky's sign). They may arise from normal-coloured skin. In pemphigoid the bullæ are tense, but Nikolsky's sign is positive. There may be pink areas around the bullæ. This malady may, in fact, so closely conform to the clinical and histological pattern of erythema multiforme as to be regarded as senile erythema multiforme perstans. Subacute and cutaneously disseminated lupus erythematosus may resemble erythema multiforme but the distribution is more on the face and upper part of the chest. In doubtful cases, a raised erythrocyte sedimentation rate, leucopenia and increased serum globulins, will support the diagnosis of lupus erythematosus. Urticaria is characterised by the short-lived and recurrent nature of its lesions which come and go, first at one site, then at another.

**Treatment** is supportive, by rest (in bed in severe forms) and bland local applications such as calamine lotion or Lassar's paste. Internally antihistaminic drugs such as mepyramine maleate or promethazine hydrochloride may prove helpful. In the severe Stevens-Johnson form, active measures must be taken to avert the serious eye conditions that can result. The administration of corticotrophin is an urgent measure to help the patient through the severest phase. A dose of 50 mg. every 6 hours is advisable for 4 days, after which the drug is gradually withdrawn.

#### ERYTHEMA ANNULARE CENTRIFUGUM (DARIER)

This is believed to be a variant of erythema multiforme, though some examples have seemed to be more akin to dermatitis herpetiformis. The conditions called erythema simplex gyratum (Jadassohn), erythema chronicum migrans (Lipschultz)

and erythema figuratum perstans (Wende) are generally regarded as closely related, if not identical.

In this malady there are large annular and polycyclic, pinkish-grey lesions with slightly scaly borders usually with a free edge centripetally. The lesions may slowly extend in one direction and fade out in another.

**Treatment.**—In some cases Fowler's solution has been reported to bring about a remission. Apart from this, only symptomatic measures can be employed.

### PURPURA

Purpura, or the extravasation of blood in the skin may be due to many causes; one of three pathological abnormalities is usually responsible. There may be a defect in the vessel walls due to bacterial or chemical toxins or malnutrition; there may be a deficiency of platelets or some defect in the complex process of clotting; or there may be an increase of capillary pressure.

In the first group is purpura in meningococcal septicæmia or in subacute bacterial endocarditis; also the purpura of fulminating exanthemata—scarlet fever, measles, smallpox, typhus, etc. Certain drugs, for example iodides, barbiturates, sulphonamides may cause purpura. The purpura of scurvy is due to a deficiency of the ground substance between the endothelial cells. Schoenlein-Henoch's purpura or "allergic" purpura is thought to be brought about by damage to the endothelial cells by circulating antigens.

In thrombocytopenic purpura the absence of thrombocytic plugs to fill any gaps in mildly traumatised cutaneous vessels is responsible for the purpura.

Purpura may also arise on the legs from hypostasis, and in widespread eczematous conditions it is not unusual to see a purpuric component to the lesions on the lower extremities while those on the upper extremities show eczematous features only.

**Diagnosis.**—Purpura is differentiated from erythematous lesions by the persistence of the dark-red colour on diascopy—examination through a glass spatula, slide or watch-glass with which pressure is applied so as to expel blood from the vessels.

Discovery of the cause of the purpura depends on a full and careful clinical investigation with particular attention to the diet, drugs, fever, enlargement of the spleen and manifestations of non-cutaneous allergy or purpura, such as joint swellings, hæmaturia, intestinal colic, etc. A full blood and platelet count is essential and an estimation of the clotting and bleeding times. In the rare cryoglobulinæmic purpura, the plasma undergoes gelification at room temperatures. It chiefly affects exposed parts.

**Treatment** is of the cause. (This subject is dealt with more fully elsewhere.)

### THE TOXIC CAPILLAROSSES

In addition to frank purpura the skin may be affected by pigmentary and telangiectatic conditions which have been given various clinical descriptions but which all show a similar histological picture suggesting some damage to the endothelium of the vessels.

**Ætiology and Pathology.**—In all types the cause is unknown.

The histological picture is one of dilatation of superficial capillaries with intimal proliferation and degeneration and a perivascular infiltrate. Extravasated blood cells may be seen and depositions of hæmosiderin. There may be some epidermal atrophy.

**Clinical Picture.**—This varies according to the type of capillarosis.

In Majocchi's disease (purpura annularis telangiectodes) the patients are usually young women and the eruption consists of discs or rings of telangiectasia with brown discolouration due to slight extravasations of blood. The lesions form on the thighs or legs, and very slowly extend peripherally and heal centrally with a slight residuum of atrophy.

In Schamberg's disease (progressive pigmentary dermatosis) men are usually affected, on the legs more often than elsewhere, but sometimes at sites of pressure. Dark reddish-brown puncta, the "cayenne pepper" spots, are visible in a zone of brownish skin. The lesions may itch and they slowly enlarge but may ultimately resolve spontaneously, leaving some pigmentation. A similar condition is sometimes seen on the legs of patients with varicosities.

The pigmented lichenoid purpuric dermatitis of Gougerot and Blum presents with discrete and agglomerated papules, with petechiæ, pigmentation and telangiectasia. The lesions may appear on the trunk or on the limbs.

Angioma serpiginosum (Hutchinson) presents with telangiectasia which by clearance at one site and spread at another comes to acquire an annular or a serpiginous arrangement. The body or limbs may be affected.

**Treatment.**—As no cause is at present known for these conditions, none other than supportive treatment can be offered. The patient should be investigated for foci of infection, diabetes and vascular hypertension.

### OTHER FORMS OF CAPILLAROSIS

Occasionally extensive eruptions of capillarosis are seen on the lower extremities, buttocks, trunk, shoulders, elbows and elsewhere of young men. It has been shown in some cases that textiles are responsible, but the exact cause, whether it be dye mordant or something else, has not yet been determined. The eruption usually persists for several months. No treatment is effective in bringing about earlier remission.

### ERYTHEMA NODOSUM

This is an outbreak of tender nodules on the legs and sometimes on the forearms, which in their healing stage have the appearance of bruises (erythema contusiforme).

**Ætiology and Pathology.**—The cause is a reaction of hypersensitivity in the subcutaneous vessels of the limbs which bring about an inflammatory reaction in and around the vessel walls (nodular vasculitis). The sensitising causes include tubercle bacilli, streptococci and occasionally meningococcal and other infections. In the United States a common cause is coccidioidomycosis. The lesions may also develop when chemotherapeutic and antibiotic drugs release organismal products to which the patient is sensitised.

Histologically there is a focal dense infiltrate of neutrophil leucocytes and lymphocytes in the more superficial hypoderm. The infiltrate invades the vessel walls (venules) and there is endothelial proliferation and thrombosis.

**Clinical Picture.**—Often after a sore throat or an upper respiratory infection the patient, usually a child or young adult, complains of tender swellings on the fronts of the legs and perhaps on the forearms. The lesions are at first red and later brownish-blue, or even greenish, obtuse nodes with somewhat ill-defined limits. There may be a dozen or more lesions on the two limbs. The natural course of the lesions is to undergo slow resolution, disappearing in a few weeks without visible permanent change. The nodules do not break down (except a rare form occurring with severe exacerbations of ulcerative colitis).

**Course and Prognosis.**—Erythema nodosum clears spontaneously after a few weeks. The lesions in themselves are of no import but they are of great significance in that they may indicate the presence of a primary tuberculous infection with hypersensitivity. Other manifestations of tuberculosis may follow and every patient with erythema nodosum should be kept under periodic observation for some months. In cases due to hypersensitivity to streptococci the prognosis is better. The erythrocyte sedimentation rate is a useful guide in following the progress of erythema nodosum.

**Diagnosis** is from erythema induratum (Bazin), erythema induratum (Whitfield) and periarthritis nodosa. In the first-named the lesions are larger and usually arise

on pernioic legs of young women. Ulceration is common, with considerable scarring and disfigurement. In some cases the differential diagnosis may prove impossible except after a period of observation.

In *erythema induratum* (Whitfield) (*q.v.*) the patients are usually women between 30 and 45 years of age. This malady, sometimes called nodular vasculitis, is probably a variant of *erythema nodosum*, but the lesions, which come out in crops, are more persistent than those of *erythema nodosum* and leave discoloured, hard areas in the skin. Ulceration is uncommon. In *periarteritis nodosa* the lesions are more persistent and necrotic and they may appear anywhere on the body or limbs.

**Treatment.**—The patient should be kept in bed until the nodules have subsided. Chemotherapeutic and antibiotic drugs are best withheld because their administration may be followed by an exacerbation of the skin condition. Symptomatic treatment is best, with the minimum use of drugs of all kinds excepting aspirin, which may be given with benefit. Vitamin supplements, an adequate diet and subsequently a period of convalescence and return to good housing conditions are desirable. A bland local application, for example calamine lotion or titanium dioxide paste, is suitable.

If the Mantoux reaction is undergoing or has recently undergone conversion, it is important that the patient should not come into contact with tuberculous individuals except inadvertently and unavoidably, for some months at least. If the patient is a nurse, she should not be allowed, even after convalescence, to take up nursing of tuberculous patients. Every patient with *erythema nodosum* should be investigated by clinical and radiographic means for evidence of tuberculosis elsewhere.

### ERYTHEMA INDURATUM

This is of three types: *erythema induratum* of Bazin, a subcutaneous tuberculide; the *subcutaneous sarcoid* of Darier-Roussy; and *erythema induratum* of Whitfield (nodular vasculitis).

#### BAZIN'S DISEASE

This affects the unshapely calves of young women with pernios. It is believed to be a tuberculide localised to the calves because of the defective circulation (see p. 1244).

#### DARIÉ-ROUSSY SUBCUTANEOUS SARCOID

This is similar to Bazin's disease in appearance but does not ulcerate. The Mantoux reaction is negative, there is a sarcoid histology, and the condition reacts sluggishly, if at all, to antituberculous drugs (see p. 1246).

### ERYTHEMA INDURATUM OF WHITFIELD (NODULAR VASCULITIS)

This presents as recurring, tender, hard subcutaneous nodules in the legs of women of 30 to 45 years of age. The condition is not a tuberculide but is a variant of *erythema nodosum*, possibly of streptococcal origin. There is no specific treatment; elastic supports often give relief.

### LUPUS ERYTHEMATOSUS

An erythematous and atrophic malady presenting in two forms, the first circumscribed, benign, cutaneous and chronic; the second malign, systemic and acute. An intermediate form occurs—chronic or subacute disseminated lupus erythematosus.

#### CHRONIC DISCOID LUPUS ERYTHEMATOSUS

**Ætiology and Pathology.**—The cause is unknown.

The characteristic features of the histology include, in the chronic discoid variety,

hyperkeratosis with keratotic follicular plugging, atrophy of the prickle cell layers, liquefactive degeneration of the basal cell layer and basophilic degeneration of the collagen and elastic tissue, with a lymphocytic infiltrate mainly distributed around the vessels and cutaneous appendages.

**Clinical Picture.**—This form affects the face, particularly across the nose and malar ridges (bat's wing lupus); also on the forehead, chin, lower lip and ears. Young and middle-aged women are more often affected than men, and the condition is not seen in children. The lesions are well defined, red rings, ovals or irregular shapes, with marked thickening peripherally and paler atrophic centres. On the surface are white or grey closely adherent scales, and horny plugs may be visible in the ostia of the follicles. The patches remain stationary or slowly extend at one site while atrophic scarring develops at another. Other sites characteristically affected include the vertex of the scalp (scarring, baldness with redness and follicular plugging); the mucosæ of the cheeks (leucoplakia and reddened areas with erosions); the hands (red, scaly, thickened patches on the backs of the fingers between the joints, chilblain-like redness around the nail folds; lupus pernio of Hutchinson); and the arms and upper part of the trunk. In chronic or subacute disseminated lupus erythematosus many of these sites may be affected in the one patient.

**Course and Prognosis.**—In patients in whom the diagnosis of chronic discoid lupus erythematosus is firmly established by pathological as well as clinical means, the course is usually of intermittent clearance and relapses on the skin with, on the whole, a gradual extension. Sometimes the disease becomes inactive and scarring alone remains. Transition from the chronic discoid to the acute systematised form rarely occurs but there are examples of the systematised form which present with lesions apparently so benign and chronic that the incorrect diagnosis of the chronic discoid form is made unless examination of the blood is carried out.

**Diagnosis** is from lupus vulgaris and other granulomatous processes, from carcinoma, cutaneous reticulosis, rosacea and light sensitisation dermatitis.

Lupus vulgaris usually begins in childhood, lupus erythematosus in adult life. Lupus vulgaris shows translucent, yellowish nodules which may be scattered around the edge of the scarred area; lupus erythematosus is characteristically a centrifugal process with adherent scaling and central, atrophic scarring. Lupus vulgaris may destroy the cartilage of nose or ears and cause great disfigurement. Lupus erythematosus does not affect cartilage but is confined to the skin.

Syphilitic gummata characteristically break out on the surface following the destruction of cartilage and bone, but they may also present as infiltrated, irregular, soft, reddish-brown nodulations. Psoriasis of the face may resemble lupus erythematosus but the scales are white, mica-like and easily detached and typical psoriatic lesions are present elsewhere. Seborrhoeic dermatitis causes greasy scaling on a reddened background but the lesions itch and are more numerous and less well defined than in lupus erythematosus. Sarcoidosis nodules more closely resemble lupus vulgaris but may mimic lupus erythematosus profundus. In these circumstances biopsy is essential. Lymphomata (Spiegler-Fendt sarcoids) are dome-shaped, dusky nodules with little or no epidermal change.

Lupus erythematosus on the *ala nasi* may resemble carcinoma cutis. The redness may be slight, the border markedly raised, the centre ulcerated; but follicular plugging is present and there is no pearly edge. If the diagnosis cannot be established on clinical grounds alone, biopsy will decide it. One form of lupus erythematosus resembles rosacea in distribution but the lesions are persistent and associated with some degree of atrophy and there is no vasolability. Light sensitisation dermatitis may resemble the less infiltrated form of lupus erythematosus but the lesions are more diffuse, eczematized and itchy. Chilblains on the fingers resemble lupus erythematosus but they only occur with cold weather, whereas lupus erythematosus persists throughout the year.

**Treatment.**—When the clinical diagnosis of lupus erythematosus has been made it is wise to have the erythrocyte sedimentation rate estimated because if this is within normal limits it is most probable that the condition is in fact the benign cutaneous form of the malady; but if the erythrocyte sedimentation rate is increased and particularly if there is also leucopenia, the condition is probably systematised and potentially malign, no matter how benign the cutaneous manifestations may seem to be. An estimation of the serum protein may then reveal an increase of globulins and an albumin/globulin ratio of less than unity.

The treatment of discoid lupus erythematosus is, in the present state of knowledge, empirical and the clinician can only treat every case on its merits, giving whatever remedy, in his experience, produces the best results.

Mepacrine 0.1 g. up to three times a day is successful in many cases in bringing about a remission. It should be taken until the lesions fade or until the skin becomes yellow, whichever is the sooner, and then the dose is gradually reduced, a course lasting anything up to 3 months. Periodic urinary examinations are a sensible precaution, and the patient should be examined at regular intervals so that the drug can be withdrawn at once should a toxic eruption begin to show itself. Alternative oral remedies include mercury with potassium iodide, and quinine. Sulphonamides are contraindicated. Vitamin supplements may be indicated and crude liver injections sometimes bring about relief. Isoniazid has not been found of value in lupus erythematosus.

Another valuable treatment in some cases is weekly injections of bismuth oxychloride 0.2 g. in 1 ml., intramuscularly into the upper quadrant of the buttock, the course extending up to 8 or 12 injections. Injections of gold (sodium aurothiomalate) have been advocated, but the risks of gold dermatitis are too considerable to justify the use of this remedy except for some very good reason. If used, the dosage should be low (10 to 25 mg.), the urine should be tested and the body surface inspected before each injection; and the course should comprise a total dosage of not more than 250 mg. in about 12 weeks. The drug is cumulative.

Local treatment is also of great importance and value. Local applications have no healing action but they can protect the lesions from mechanical injury, screen them from light, and provide cosmetic camouflage. Titanium dioxide paste can fulfil all these functions, or the patient may prefer the more æsthetic make-up preparations of the cosmetic firms. As an ultra-violet screening cream, salol 10 per cent. or para-aminobenzoic acid 15 per cent., can be incorporated in a vanishing cream base, but must be reapplied frequently if sweating is heavy.

Local therapeutic practices include applications of carbon dioxide snow ( $-78^{\circ}\text{C}.$ ) or slush, the former being compressed into a pencil and applied for about 10 seconds to thickened, red areas, and the latter made by adding acetone to carbon dioxide snow and then applying it for one or two brief freezes by means of a camel-hair brush or cotton wool on a probe. The aim is to bring about an inflammatory reaction which will be followed by the formation of smooth and supple scarring. Snow has a deeper action than slush, and is more suitable for localised thickened lesions.

Contraindicated in lupus erythematosus are sulphonamides by mouth and ultra-violet irradiation, X-rays or radium locally; the former because an exacerbation may result; the latter because exacerbation or even malignant changes (epithelioma) may be initiated by these means.

#### SYSTEMATISED LUPUS ERYTHEMATOSUS

**Ætiology.**—The cause is unknown. Over 90 per cent. of cases occur in women, usually between the ages of 20 and 40. The disease may arise in a patient with chronic discoid lupus erythematosus, or it may follow exposure to sunlight or the exhibition of drugs such as sulphonamides, iodides, thiourea and organic arsenicals.



**Pathology.**—The commonest findings at necropsy are chronic obliterative pleurisy, pericarditis, perihepatitis and perisplenitis. There are small warty endocardial vegetations in one-third of the cases.

Histological examination shows proliferation and fibrinoid degeneration of collagen in the supporting tissues of the serosal surfaces, myocardium, mediastinum, retro-peritoneal tissues and skin. There is fibrinoid degeneration and necrosis of the connective tissue of the media of small arteries and arterioles, with proliferation of the endothelium, sometimes leading to thrombotic occlusion of the vessel; these changes are usually found in the kidney, spleen and skin.

In the kidney there may be focal necroses of capillary loops, and the basement membrane of glomerular capillaries may be thickened and eosinophilous. In the spleen the central artery of the Malpighian bodies may be surrounded by concentric rings of connective tissue.

**Clinical Picture.**—The manifestations of the disease are those of a febrile, wasting illness with inflammation of serous membranes, depression of the bone marrow and, finally, symptoms of vascular changes in viscera, especially the skin and kidney.

The joints are frequently affected, usually with a slowly shifting polyarthritis. There may be swelling of the joints, but permanent deformity is uncommon. Pleurisy with effusion and pericardial effusion occur. Hypertension is uncommon, but albuminuria and microscopic hæmaturia are frequent. The spleen and lymph glands may be enlarged; anæmia is common and purpura may be found. Diarrhoea is the commonest gastro-intestinal symptom, and there may be vomiting, abdominal pain and jaundice. Mental changes are common; they vary from anxiety to toxic confusional states and delirium. Involvement of the nervous system may cause epilepsy and rarely lymphocytic meningitis, encephalomyelitis or peripheral neuritis. Examination of the fundus oculi may show hæmorrhages, exudates and papilloedema. Cutaneous manifestations may be marked, slight or absent, temporary or persistent. On the face and chest there may be erythematous patches resembling erythema multiforme. There may be red petechiæ or telangiectases on the tips of the fingers, splinter hæmorrhages under the nails and a condition resembling chilblains on the fingers. The palms may show ill-defined erythematous blotches. There may be redness and leucoplakic changes in the mouth, on the lips or in the ano-genital region.

Laboratory findings include an increased red cell sedimentation rate, leucopenia and the discovery of the "L.E." cell on mixing the patient's plasma with her own or someone else's blood cells. This cell is a polymorphonuclear leucocyte which has ingested degenerate nucleoprotein material and it is rarely seen except in systematised lupus erythematosus.

**Course and Prognosis.**—The course varies considerably. The illness may be acute and fulminating from the beginning, with high remittent fever, prostration and joint pains; alternatively there may be acute exacerbations in a subacute or chronic form of the disease, which may be precipitated by exposure to sunlight or exhibition of the drugs previously mentioned. Death may occur in a few weeks. The disease more usually runs a subacute course of many months or a chronic course of 5 or even 10 years. Relapses and remissions are common, the remissions rarely lasting longer than a year. Death is usual within 5 years. Spontaneous cure of the disease has been described but must be very rare. Patients are often seen with chronic discoid lupus erythematosus who have a raised blood sedimentation rate, leucopenia and hyperglobulinæmia, who nevertheless continue in a reasonable state of well-being; the number of these patients who develop the florid manifestations of systematised lupus erythematosus is unknown, but the long-term prognosis is unfavourable.

**Diagnosis.**—The facial lesions may resemble erysipelas, erythema multiforme, or dermatomyositis. When the joint manifestations are prominent the disease will have to be differentiated from acute rheumatism and rheumatoid arthritis. Systemat-

ised lupus erythematosus must be considered in all cases of inexplicable pyrexia or when there is wasting, anæmia, albuminuria, purpura or lymphadenopathy; also in the presence of acute neurological episodes. The diagnosis is confirmed by the presence of a raised blood sedimentation rate, leucopenia, hyperglobulinæmia, albuminuria and the discovery of the "L.E." cell.

**Treatment.**—Corticotrophin or cortisone may bring about a remission and prevent relapse. The effect on the ultimate prognosis is less favourable, although a few apparent cures have been reported. An initial dose of 50 mg. of corticotrophin intramuscularly 6 or 8 hourly should be given and gradually reduced. Renal involvement is a contraindication as renal failure may be precipitated, presumably due to ischæmic changes following healing of the arterial lesions.

The patient with chronic discoid lupus erythematosus and laboratory evidence of systematised lupus erythematosus should avoid sunlight, extremes of temperature and the drugs mentioned previously.

## DRUG ERUPTIONS (DERMATITIS MEDICAMENTOSA)

Almost any drug may cause a skin eruption at one time or another, but some drugs have this property to a much greater extent than others; and certain individuals are unduly susceptible to drugs. Drugs may produce ill effects from their external or from their internal use, in several ways.

**External use :** Drugs applied externally may give rise to toxic effects in the following ways—(a) Contact eczematous dermatitis, as from the topical use of sulphonamides, antibiotics, surface anæsthetics, antiseptics, antihistaminics, etc. (b) Light sensitisation, as from sulphonamides, tar, quinine, etc. (c) Toxic effects on various organs after absorption, as from sulphonamides, flavine, mercury (liver, kidney), resorcin (thyroid), etc.

**Internal use :** Drugs taken internally may cause toxic effects by—(a) Toxic action on the skin, immediate or accumulative. (b) Induction of allergic hypersensitivity in the cutaneous vessels. (c) Toxic action on bone marrow, liver, kidneys, thermosstatic centre, etc., causing purpura, skin infections, nutritional deficiency, hæmaturia, albuminuria, fever, etc. (d) Indirect toxic or allergic action through the destruction of bacteria and the release of their toxins. (e) Destruction of organisms capable of synthesising vitamin B in the gut. (f) Interference with absorption from the gut. (g) Destruction of competitors of monilia in the gut. (h) By competing for enzymes that are essential for cellular welfare. (i) Aggravation of a pre-existing dermatosis. (j) Activation of virus infections, herpes simplex, zoster.

Drug eruptions may also be of mixed external and internal origin. A drug (for example penicillin, sulphonamide) may be used topically in the first instance and cause an eruption from its subsequent internal use: or it may be used internally in the first instance and cause an eruption when it is subsequently used by local application.

**Clinical Pictures.**—Many drugs cause nonspecific eruptions and a few have specific effects.

The nonspecific eruptions in their simplest forms are morbilliform and scarlatiform erythema. In greater degrees of intensity there may be a resemblance to erythema multiforme, with or without bulla formation, or the toxic action on the bone marrow or cutaneous blood vessels may be sufficient to cause purpura. Urticaria implies vascular hypersensitivity. More specific effects include fixed erythema, pruritus, exfoliative dermatitis, pigmentation, eczematoid, psoriasiform, acneiform, lichenoid, seborrhæic or pityriasis rosea-like eruptions, granulomata, stomatitis and urethritis. Usually there is something atypical about the eruption that differentiates

it from the disease it mimics; but this is not always so, the lichenoid eruption due to mepacrine sometimes being identical to "idiopathic" lichen planus, possibly because it is, in fact, lichen planus, triggered off by the drug. Many toxic eruptions remain unexplained on a drug basis. Sometimes this is due to drug contamination of foods, for example, the use of phenolphthalein to tint icing pink; and the possibility of other food "processings" being the cause of toxic eruptions is a matter for speculation.

The more common manifestations and some of the drugs that may cause them include:

- Acneiform, pustular: bromides, corticotrophin, iodides, sometimes sulphonamides.
- Albuminuria: bismuth, calciferol, gold, mercury, sulphonamides, sera.
- Alopecia (cicatrical): gold, mepacrine.
- Bullous (pemphigoid): barbiturates, chloral, cinchophen; dapsone, halogens, phenazone, phenolphthalein, phenytoin, quinine, salicylates, streptomycin, sulphonamides.
- Coryza: arsenic, iodides, salicylates, sulphonamides.
- Cyanosis: phenacetin, sulphonamides.
- Eczematoid: antihistamines, arsenic, gold, halogens, mepacrine, mercury, penicillin, quinine, sulphonamides.
- Erythemata, morbilliform and scarlatiniform: most of the drugs mentioned elsewhere in this list; also atropine, belladonna, digitalis, ephedrine, insulin, ippecacuanha, phenylbutazone, procaine, rhubarb, santolin, turpentine.
- Erythema, multiforme-like: acetanilide, barbiturates, bismuth, dapsone, gold, quinine, sera, sulphonamides, thiouracil.
- Erythema, fixed (localised and recurrent): phenolphthalein most commonly; also reported from arsenic, amidopyrine, barbiturates, bismuth, bromides, cinchophen, gold, iodides, mercury, penicillin, phenazone, phenytoin, quinine, salicylates, sulphonamides.
- Erythema nodosum: iodides, salicylates, sulphonamides, thiouracil.
- Exfoliated dermatitis: arsenic (organic), barbiturates, bismuth, gold, mepacrine, mercury, phenolphthalein, phenytoin, streptomycin, sulphonamides.
- Fever: arsenic, barbiturates, sulphonamides.
- Genital lesions: phenazone, phenolphthalein, quinine.
- Gingivitis: bismuth, mercury, phenytoin (hypertrophy).
- Granulomatous, vegetating, ulcerative: halogens.
- Herpes simplex: arsenic.
- Infective (seborrhœic) dermatitis: arsenic, gold, mepacrine, mercury, penicillin, sulphonamides.
- Keratosis, carcinomata: arsenic (inorganic).
- Leucopenia: amidopyrine, arsenic, barbiturates, phenazone, sodium amino-salicylate, sulphonamides.
- Lichenoid: arsenic, bismuth, gold, mepacrine.
- Light sensitisation: arsenic, gold, mercury, quinine, sulphonamides.
- Lupus erythematosus: sulphonamides.
- Papulo-necrotic tuberculides: calciferol.
- Pigmentation: arsenic, barbiturates, bismuth, corticotrophin, gold, mepacrine, phenazone, phenolphthalein, quinine, silver.
- Pityriasis rosea-like: antihistamines, arsenic, gold, mepacrine.
- Pruritus, general: codeine, morphine, opium; also arsenic, bismuth, gold, mepacrine, penicillin, phenobarbitone, phenolphthalein, Pyramidon, sulphonamides.
- Pruritus, anogenital: chloramphenicol, chlortetracycline, codeine, phenolphthalein.

Psoriasiform : arsenic, gold, mepacrine.

Purpura : antihistamines, arsenic, aspirin, barbiturates, carbromal, chloral hydrate, halogens, mercury, penicillin, phenazone, phenytoin, Pyramidon, quinidine, quinine, salicylates, Sedormid, sera, sodium aminosalicylate, sulphonal, sulphonamides.

Stomatitis : antibiotics, arsenic, barbiturates, bismuth, gold, halogens, mercury, phenacetin, phenazone, phenobarbitone, phenolphthalein, quinine, salicylates, sulphonamides.

Tuberculides (exacerbation) : calciferol.

Urticaria : most of the drugs in this list ; arsenic, aspirin, barbiturates, bromides, cocaine derivatives, iodides, penicillin, phenacetin, phenolphthalein, quinine, sera and sulphonamides are common causes.

Vesiculation (varioliform) : halogens, sulphonamides.

Zoster : arsenic.

**Course and Prognosis.**—Many eruptions are transient, clearing rapidly after withdrawal of the drug ; but penicillin urticaria may persist for several weeks and halogen eruptions may continue to worsen after the drug has been withdrawn. Some injected drugs, for example gold, are cumulative in their effects and dermatoses caused by them often worsen steadily after the last injection. Inorganic arsenic has delayed effects, the first signs appearing some years after the drug is first taken, possibly even several years after its use has been abandoned.

The prognosis depends on the possibilities of bringing about elimination of the drug and on the presence or absence of toxic effects on the liver, kidneys and bone marrow.

**Diagnosis.**—The possibility of drug causation or aggravation has to be borne in mind in many dermatoses, particularly if there is something atypical in the eruption, and questioning has to be directed accordingly. Analgesics, aperients, hypnotics, sedatives and antibiotics are particularly suspect. Withdrawal of a suspected drug may be followed by immediate improvement. With nonspecific eruptions and when the patient has been taking more than one drug, a test dose is justifiable. This should only be given when the dermatosis has subsided and one-tenth of the previous therapeutic dosage should be given in the first instance because if the full dose is given an unnecessarily violent reaction may result.

**Prevention and Treatment.**—The history may indicate sensitivity to one or more drugs. Some drug eruptions result from neglecting to enquire into this possibility. Potent drugs are sometimes used without sufficient justification. In every case it is a useful self-discipline to ask oneself, "Do the advantages likely to be obtained by giving this drug outweigh its possible ill effects?" Whenever there is a choice, a drug of lesser toxicity and sensitising potential should be used. Especial care is necessary when there is albuminuria.

To make treatment easier, it is as well to tell the patient of possible side-effects of a drug. This encourages discontinuation of the drug immediately untoward symptoms develop and prevents further toxicity. For most drug eruptions, withdrawal of the drug is all the treatment that is necessary or, in fact, possible. An aperient or an enema is sometimes useful when there is reason to think that some of the drug remains in the bowel. Specific treatments are indicated in a few conditions. For halogen eruptions, sodium chloride or ammonium chloride may be given in a dose of 5 to 10 g. daily. In severe cases with toxæmia, intravenous normal saline infusions should be given daily, 100 ml. on each occasion, for a week.

Heavy metal intoxications (gold, bismuth, mercury) are treated with dimercaprol (B.A.L.) 2 ml. 4-hourly, gradually reduced to 2 ml. daily, in courses lasting a week, with a week of intramuscular crude liver extract interposed. The pigmentation of argyria is permanent. The effects of inorganic arsenic (raindrop pigmentation, keratoses, carcinomata, hepatitis) are irreversible. The keratoses are best treated with

carbon dioxide snow applications and the carcinomata by X-irradiation or carbon dioxide snow, depending on their size and situation. Toxic effects from organic arsenic need treatment with dimercaprol.

Rest in bed is advisable in the more severe eruptions. Plenty of fluids should be given. The urine should always be examined and treatment adjusted accordingly. A blood count is also advisable to detect hæmoglobin deficiency (as with dapsone) or leucopenia (as with sulphonamides, etc.). In purpuric eruptions the thrombocyte count should be estimated. If it is normal vitamin C should be given in large doses. If there is evidence of severe marrow depression, blood transfusions may tide the patient over the worst phase. In all forms of drug eruption, multiple vitamin supplements are a rational treatment and crude liver injections are often helpful. Anti-histamines are invaluable for controlling urticaria from penicillin, and once the optimum dosage has been found they are best given in gradually smaller doses until they can be abandoned. Local treatment is often unnecessary, or may consist of the application of a lead and calamine lotion.

### ERYTHRODERMA (EXFOLIATIVE DERMATITIS)

Erythroderma is a persistent redness of the skin, with exfoliation (as opposed to erythema, which is transitory).

**Ætiology and Pathology.**—There are numerous causes for this type of reaction. It may develop as a result of the over-treatment of eczema-dermatitis, infective dermatitis, or psoriasis. It may be a toxic phenomenon following the administration of organic arsenicals, mercurials, sulphonamides, gold, barbiturates, bismuth or mepacrine. It also occurs in an idiopathic form as lymphadenopathic erythroderma, a condition which is probably toxic and sometimes recurrent, with much pigmentation (lipomelanotic reticulosis).

Another form of erythroderma is associated with lymphoblastomatosis (*l'homme rouge*), sometimes preceding or following the clinical phenomenon of mycosis fungoides and ultimately being accompanied by an increase of circulating lymphocytes. An erythrodermatous form of sarcoidosis also occurs.

Histologically there is hyperkeratosis and parakeratosis, spongiosis with a variable degree of acanthosis and œdema, and an infiltrate of lymphocytes and histiocytes in the upper dermis and around the vessels and epidermal appendages. In the idiopathic form, there is much pigment in the melanophores of the dermis and the lymph nodes show little disorganisation but much melanin, hæmosiderin and lipid material in the reticulum cells. In the lymphoblastomatous form, there may be microabscesses in the prickle cell layer and either a basal infiltrate indistinguishable from the benign type already described or a massive infiltrate of lymphocytes or of lymphoblasts with eosinophils, neutrophils, histiocytes and reticulum cells, with many mitoses. This infiltrate is dense in the upper dermis and patchy in the deeper parts. The histological pattern of the lymph nodes is disorganised. It is sometimes difficult or impossible to differentiate, except by repeated sections at 3 to 6 months' interval, between the relatively benign lipomelanotic form and the malign reticulosis, but the clinical features are usually fairly distinctive, the former being characterised by much pigmentation and slight or moderate peeling, the latter by redness and marked peeling. The histology of the lymph nodes, the peripheral blood and bone marrow may all help to establish the diagnosis. Erythrodermatous sarcoidosis shows the histological features of sarcoidosis.

**Clinical Picture.**—In the over-treatment forms there is a history of a preceding more localised dermatosis and of its extension to the condition observed following the application of one or more known irritants or sensitisers. There is coarse peeling with moderate redness and sometimes a greasy texture to the scales particularly in

the flexural areas. In the toxic forms the exfoliation develops uniformly during or after a course of treatment with one of the drugs mentioned. In both these forms fissuring or secondary infection may develop and there may be considerable enlargement of the regional lymph nodes.

In the idiopathic lymphadenopathic erythroderma the skin is dark brown and shiny and the exfoliative element less marked. There is marked enlargement of the lymph nodes and those at the axillæ and groins may be observed bulging the skin. In the male, the breasts may become swollen and tender. The patient may have other, possibly toxic, manifestations, including psychosis, cardiac irregularities, etc. There may be a moderate intermittent fever.

In lymphoblastomatosis with erythroderma the skin is bright red and coarsely peeling. The lymph nodes may be moderately enlarged and the liver and spleen palpably enlarged.

In all forms of erythroderma, heat loss is excessive and care must be taken not to expose the patient unduly during examination; on the other hand, occlusive ointments may interfere with heat loss and cause pyrexia. There may be considerable loss of hair and thickening of the nails.

**Course and Prognosis.**—This depends on the cause. The form due to over-treatment of a dermatosis slowly resolves with suitable bland treatment. The toxic forms persist for some weeks or months, depending on the rapidity of elimination of the toxic substance. The severest examples may have a fatal outcome, from broncho-pneumonia, hepatitis or nephritis. The idiopathic form tends to clear after some months but may recur even after several years. The lymphoblastic form is steadily progressive to a fatal ending.

**Diagnosis.**—The recognition of erythroderma is a simple matter and the diagnosis of the different forms has been indicated above. But there are two conditions that can closely resemble erythroderma. The first is psoriasis universale, which can develop without any over-treatment. The history should help and the skin is bright red with mica-like scales. The nails may be abnormal in either condition, but more particularly in psoriasis. The blood count is normal in psoriasis but also in the earlier stages of lymphoblastic erythroderma. The histology of both conditions is distinctive.

The second condition which may be mistaken for erythroderma is pemphigus foliaceus (erythematodes). Here, the pathological process of poor cell cohesion is so superficial (in the granular layer) that any bullæ that form are quickly broken and a picture of exfoliation and infection results. Nikolsky's sign is positive and the histology characteristic, the granular layer being exposed to the surface.

In infants, extensive staphylococcal pemphigus may have erythrodermatous characteristics (Ritter's disease).

**Treatment.**—In all forms only bland applications should be used and they should not be occlusive. Oily calamine lotion, zinc cream or hydrous ointment are all useful. Care should be taken that the patient does not get chilled by exposure.

In the over-treatment form this soothing treatment, combined with such sedation as may be necessary, is all that is required, the patient being kept at rest in equable surroundings and the skin cleaned with a bland vegetable oil.

In the toxic form dimercaprol is valuable where arsenic, gold, mercury or bismuth is believed to be responsible. It is best given in a course of 6 days, 2 ml. 4-hourly on the first day, 2 ml. twice daily on the second, third and fourth, and 2 ml. daily on the fifth and sixth days. After this course, daily intramuscular injections of 4 ml. of crude liver extract may be given with advantage for a week, followed by a second course of dimercaprol. The patient should also receive vitamin supplements.

In toxic erythroderma due to non-metallic poisons, the courses of dimercaprol are omitted but the intramuscular injections of crude liver extract may be given with benefit, 4 ml. daily.

In the idiopathic form, corticotrophin is invaluable for bringing about a remission,

50 mg. 8-hourly being given and the dose gradually reduced as improvement results. The condition may remain clear after withdrawal of the drug, or it may recur, in which circumstances it is best to give cortisone in the smallest dose which gives relief and to withdraw it gradually as soon as possible.

In the lymphoblastomatous form corticotrophin may give symptomatic relief without objective improvement beyond a slight diminution of scaling. Radioactive phosphorus is worth a trial. Otherwise treatment is symptomatic and supportive.

## SQUAMOUS DERMATOSES

### PSORIASIS

Psoriasis is a common condition of sharply margined, reddened areas of skin with abnormal scaling. The malady is most variable in its intensity and course, remissions, recurrences and exacerbations being a characteristic feature.

**Ætiology and Pathology.**—The fundamental cause is an unknown biochemical fault in epidermal cell formation, resulting in abnormal horn cells. The fault is inherited and psoriasis occurs in 1 in 5, on the average, of children of a psoriatic parent. The first signs are usually noted in the second or third decades but it may first appear in children under 10 or in persons over 30 or even in old age. Histologically, there is parakeratosis (nucleated cells in the stratum corneum), some hyperkeratosis and irregular acanthosis (hyperplasia of the stratum mucosum) with such gross variability in the thickness of the epidermis that at one site there may be only a few cells between the dermis and the surface, while nearby there may be a large number. There is "clubbing" of the interpapillary rete ridges of the epidermis. In the dermis there is vascular dilatation, particularly in the upper part, and a patchy lymphocytic infiltrate around the vessels and the cutaneous appendages.

Precipitating factors are the hereditary predisposition, infections, unfavourable physical and emotional environments, emotional conflict and trauma to the skin.

**Clinical Picture.**—From the clinical standpoint, psoriasis is best divided into six types :

- (1) Guttate, post-infective psoriasis of children.
- (2) Localised, extensor psoriasis.
- (3) Flexural psoriasis.
- (4) Widespread psoriasis.
- (5) Pustular psoriasis of the palms and soles.
- (6) Psoriasis of the nails.

(1) **GUTTATE PSORIASIS IN CHILDREN** may have no obvious precipitant but often there is a history of an infection, particularly streptococcal throat infections, some 3 weeks before the onset of the rash. It may begin after scarlet fever or varicella, measles or mumps, suggesting that the malady is a type reaction of certain individuals to various infections.

The lesions are raindrop-sized, pink, flat-topped papules, with scaling which is at first inconspicuous. Itching is slight or absent. The scaling is made more obvious by scraping (grattage) a papule with a spatula (not a finger nail!). This makes visible the silvery mica-like delicate scales and pin-point bleeding indicates the presence of dermal papillæ very near the surface. The lesions are widespread, even generalised in distribution, but the face and hands tend to be less affected.

**Course and Prognosis.**—Provided the condition is not over-treated, this form of psoriasis often gradually clears in about 3 months. In others, it may persist, with enlargement of some of the lesions to coin-like (nummular) or discoid areas. At any time in life there may be recurrences or recrudescences of psoriasis, usually of the discoid type, the guttate form rarely returning.

**Diagnosis.**—Guttate psoriasis has to be differentiated from a secondary papulo-squamous syphilide on the basis of absence of lymph node enlargement or of mucosal involvement. The skin lesions are not infiltrated or ham-coloured in psoriasis and, although the scalp may be affected, there is no loss of hair.

**Infective (seborrhœic) dermatitis** presents with dirty grey scales of greasy texture beginning as follicular papules which affect by preference the face, sweat grooves and flexures; the scalp is involved, with loss of hair.

In pityriasis rosea the lesions are pink or fawn-coloured, with a centripetal free border to the collarette and the malady usually affects the trunk and proximal parts of the limbs.

Lichen planus presents with itchy, violaceous, polygonal papules with a waxy glaze, mostly on the flexor surfaces.

**Treatment.**—Calamine liniment makes the best local application. All measures directed towards improving the general well-being are likely to help, including a holiday, vitamin supplements and (if under skilled observation) ultra-violet irradiation with a suberythema exposure daily.

(2) **LOCALIZED EXTENSOR PSORIASIS** is another way in which the malady begins and it may persist, with fluctuations, for the remainder of the patient's life, without any obvious disturbance in the general health. This type may begin in childhood or in adult life and is most common at and just below the tip of the elbows and over the patella and patellar tendon. Other sites often affected include the lumbo-sacral region, the calves, the forearms and the scalp, or any of these areas may be affected alone. The lesions may be nummular, discoid, circinate, polycyclic or irregular in shape (psoriasis geographica). There is usually no itching.

**Diagnosis.**—Nummular eczema may resemble a nummular psoriasis but the lesions are papulo-vesicular, exuding or crusted. A single chronic patch of psoriasis has to be differentiated from lichen simplex, lupus vulgaris, tuberculoid leprosy, tertiary syphilis, Bowen's disease and superficial basal cell epithelioma (*q.v.*).

**Treatment.**—The patient is best advised that treatment is only necessary for the sake of appearance and that the condition in no way interferes with general health and is not contagious. At the same time, a pessimistic view that psoriasis is incurable and nothing can be done about it is not only unjustified but positively harmful. It is true that the fundamental cause of psoriasis is unknown and therefore cannot be removed; nevertheless, the precipitating factors causing recurrences and exacerbations are often discernible and it may be possible to adjust or remove them and so give relief to the skin condition. The importance of day-by-day traumata in this form must be remembered, particularly with regard to prognosis.

In the localised form, benefit is often derived from daily applications of a solution of coal tar to the lesions with a camel-hair brush, combined with soft paraffin ointment to any cracked or excessively dry areas, as required. Solution of coal tar may also be applied in a 6 to 12 per cent. concentration, with or without salicylic acid 2 to 4 per cent., in ointment of wool alcohols, simple ointment or soft paraffin ointment. Ointment of wool alcohols mixes most with skin fats and so brings the tar into more intimate contact with the skin. Simple ointment and, to a greater extent, soft paraffin ointment, mitigate the action of the tar and they are often more useful because of their soft paraffin content.

(3) **FLEXURAL PSORIASIS** is most commonly seen in the obese, and friction between opposing surfaces of skin plays an important part. The axilla, submammary folds, umbilicus, genito-crural folds and intergluteal cleft may be affected. Secondary infection may occur, particularly with monilia. Sometimes diabetes coexists. Psoriasis of the genito-crural region may be either the result or the cause of pruritus vulvæ. The lesions are sharply margined, smooth, shiny red areas.



**Diagnosis.**—The presence of psoriasis elsewhere usually helps in differentiation from infective dermatitis and from intertrigo.

**Treatment** depends on the cause. Obesity, diabetes, various causes of pruritus vulvæ (*q.v.*) need attention. Locally, magenta paint can be used to control any infective element. After this, a dusting powder may be helpful, or simple ointment with a 2 per cent. solution of coal tar. A 2 per cent. salicylic acid and sulphur ointment may prove useful.

(4) **WIDESPREAD PSORIASIS** may develop *de novo* or it may follow guttate psoriasis or localised psoriasis of the extensor or flexor surfaces. The reason for the extension may be some infection, over-treatment, intoxication, bad environmental conditions or emotional stress, due either to environmental or to personal difficulties. There may be no constitutional disturbance but mental depression is common. A persistent widespread rash may easily induce the leper complex and this accounts for the depression in some cases but, in others, the variation of mood is parallel with changes in the state of the skin, neither preceding nor following them, and suggests that fluctuations in intensity of the psoriasis and mood changes are often due to a common cause. The involvement may be widespread, subtotal or universal. The lesions may be nummular, discoid, figurate, polycyclic or annular. The Koebner phenomenon may be present, in which scratching the skin causes the development of psoriasis in the line of scratch. The skin in the centre of annular lesions does not show this reaction, having become refractory for a time to this stimulus. The sites commonly affected include the scalp (where the scales may be in several diminishing layers giving a limpet-like appearance—rupioid psoriasis), the trunk, particularly the lumbo-sacral region, the extensor surfaces of the limbs and the nails. Sometimes the flexures are also affected. The face and hands usually escape except in severe examples of the disease. Arthritis of the rheumatoid type is commonly associated with extensive psoriasis.

**Course and Prognosis.**—This severe form of psoriasis is of prolonged duration and uncertain, often unfavourable, prognosis, unless the causal factors can be controlled.

**Treatment.**—It is advisable to admit patients with extensive psoriasis to hospital for investigation and treatment. The investigations are directed to infective, metabolic and emotional disorders, and specific treatment is given accordingly. Nonspecific treatment for the psoriasis is best carried out by the Goeckerman régime, or some modification of it. In this, the patient's skin is cleaned of ointment with liquid paraffin each morning, then general ultra-violet irradiation is given, a first-degree exposure, with treatment of plaques of psoriasis with a second-degree exposure if this is practicable. The patient next takes a warm bath (to which may be added 2 to 4 oz. of solution of coal tar to 25 gallons of water if itching is severe). In the bath, the whole surface may be cleaned with a toilet soap, but forcible removal of scales with a coarse brush is inadvisable. After drying from the bath, the patient is treated by the inunction of 6 per cent. solution of coal tar in soft paraffin, excepting the flexural lesions, which are better dealt with more gently with Lassar's paste alone or with 2 per cent. of the solution of coal tar. The scalp needs special attention. Equal parts of Teepol and water with 1 per cent. of glycerin make an effective shampoo, followed by the inunction of up to 12½ per cent. of solution of coal tar in the ointment of wool alcohols or in emulsifying ointment. To this may be added 2 per cent. of salicylic acid and 2.5 per cent. of ammoniated mercury. (Soft paraffin is too sticky and messy in areas of coarse hair and Lassar's paste causes matting and is very difficult to remove.) Oil of cade 12½ per cent. may be used instead of the solution of coal tar, or 2 per cent. each of salicylic acid and of sublimated sulphur may be preferred in emulsifying ointment. The régime may include autohæmotherapy 10 ml. on four occasions every 5 days.

It is important in widespread psoriasis to do nothing that may cause an extension of the malady and possibly lead to its generalisation or to exfoliative dermatitis. For this reason alone its more rigorous treatment needs daily supervision by a trained observer. Dithranol has a justifiable reputation for relieving psoriasis but this treatment is best reserved for in-patients. Dithranol ointment (B.P.) (0.1 per cent.) is, in any case, too weak to be of value, while strong dithranol ointment (1 per cent.) is too strong for out-patient use and for the first trial of this substance. Its injudicious use can cause aggravation or even exfoliative dermatitis. It is best to start with 0.5 per cent. in soft paraffin and to raise this to 1 per cent., 1.5 per cent. or 2 per cent. in stages, as may be required. Dithranol causes an inflammatory reaction and stains the skin a violet-brown colour. Its daily application is continued until the lesions look paler than the surrounding skin. It is then withheld and soft paraffin ointment is substituted. Dithranol causes a severe conjunctivitis if it gets into the eyes.

In resistant psoriasis, T.A.B. injections are sometimes successful in intravenous doses of 25, 50 and 100 million organisms at 5 to 7 day intervals, the aim being on each occasion to attain a temperature peak of 103° F.

Sedation with bromides, promethazine hydrochloride or barbiturates may be necessary, and depressed patients may do well on amphetamine sulphate 5 mg. each morning. Dietetic and vitamin treatment is ineffective except in so far as conditions of obesity on the one hand or malnutrition on the other may require adjustment. X-ray irradiation (100 r three times at weekly intervals) is very effective in clearing individual patches but is only justifiable for special purposes, such as the clearance of a resistant patch on a site for operation.

Psoriasis does not respond to corticotrophin or cortisone.

Emotional factors may be dealt with, according to their relative importance, by reassurance, open discussion and moral support, by drug abreaction or even by psychoanalysis. Suggestion and hypnosis are undoubtedly helpful while they are used but are likely to cause an excessive rebound when the moral prop is withdrawn.

Complete clearance of all lesions is the aim, but the physician may well decide to be satisfied with some 80 to 90 per cent. of clearance, particularly if the psoriasis has appeared early in life and has been aggravated by relatively trivial stimuli. At this stage, the patient should be encouraged to live with the psoriasis and not to be forever trying to clear off the last traces by any new method recommended by all and sundry. It must be stressed that the treatment of psoriasis is the treatment of each individual according to the physical or psychological defects that are discovered: it is not a routine matter of one régime or another.

A holiday in congenial surroundings, with relaxation and isolation from the telephone, may be as effective as any of the above measures.

(5) PSORIASIS OF THE PALMS AND SOLES.—This condition is probably identical with "pustular bacteride" and one form of "acrodermatitis pustulosa continua".

**Clinical Picture.**—In pustular psoriasis, the lesions are golden yellow from the beginning and do not go through a vesicular stage. The pustules occur on palms or soles, less often on fingers or toes, amongst areas of red skin with dyskeratotic scaling. Psoriasis may also occur on the palms as patchy dyskeratotic areas with some adjoining erythema. On grattage, silvery scaling is apparent. Either form may occur with or without psoriatic lesions elsewhere.

**Course and Prognosis.**—Pustular psoriasis is extremely chronic and often fails to respond to remedies that are effective elsewhere, including X-rays. Its relief depends on the discovery and treatment of any infective focus (particularly streptococcal), the avoidance of local physical traumata and treatment of any metabolic or emotional factors that seem to be relevant.

Diagnosis is from pompholyx, in which the vesicles are skin-coloured and become yellow at a later stage.

**Treatment.**—Locally, soft paraffin ointment with 2 per cent. salicylic acid, is a useful application. Tonsillectomy has been followed by relief in some cases. X-rays in fractional (100 r) exposures up to four may help, but as often fail.

(6) **PSORIASIS OF THE NAILS** usually occurs with psoriasis elsewhere but occasionally it is the only evidence of the disease.

**Clinical Picture.**—The mildest form is a thimble-like pitting of the nail plates. This may vary in extent from a single pit on one nail to confluent affection of several nails, and is very characteristic of psoriasis, rarely being seen in other diseases affecting the nails.

In the next degree of severity, psoriasis causes brown or yellow discolouration affecting the sides or the distal parts or the whole surface of the nail plates. In this form, the nails are usually not thickened but, when psoriasis affects the nail beds and matrices, the nail plates become thickened, opaque, dull and friable. Paronychia involvement causes deformity with longitudinal or transverse ridging and grooving.

**Diagnosis.**—Psoriasis unguium has to be differentiated from tinea unguium, and eczema-dermatitis affecting the nail folds. Rarer possibilities include syphilis, lichen planus and idiopathic nail dystrophies.

Ringworm usually affects one or a few nails of the hands and feet in asymmetrical fashion and is often associated with ringworm elsewhere in toe clefts, on the feet or hands or in the groins. Microscopic examination of nail shavings removed with the edge of a glass microscope slide reveals fragments of mycelium. The nails in ringworm are usually a dirty grey colour, partly destroyed and deformed, with longitudinal or transverse ridging and a powdery friable surface.

Syphilis or lichen planus are recognised by evidence of the presence of these maladies elsewhere. Idiopathic nail dystrophy is a discoloured and deformed condition of the nails without evidence of psoriasis or of other skin disease elsewhere.

**Treatment.**—In the minor forms, treatment is not necessary unless the patient demands it. The results of treatment are always uncertain, but weekly applications of thorium-X, 1500 e.s.u. per ml. for about 3 months, often seem to give good results. This treatment is preferable to the use of X-rays or medication with liquor arsenicalis. Salicylic acid ointment makes a satisfactory local application. Trauma to the nail folds and excessive drying or degreasing must be avoided.

## PARAPSORIASIS

**PARAPSORIASIS** is a descriptive term for various forms of persistently abnormal scaling of the skin. They are rare and of unknown cause but are probably distinct conditions.

**PARAPSORIASIS GUTTATA** (pityriasis lichenoides chronica) occurs as guttate grey-brown scaly lesions, the scales often being concave and not having the mica-like appearance and pinhead bleeding points of psoriasis. They are distributed on the trunk and limbs. The lesions itch little, if at all, and there is very little redness of the skin around the abnormal scaling. The lesions persist, with slight fluctuations, for an indefinite period and there is no constitutional disturbance. It usually affects young or middle-aged adults.

**Pathology.**—There is parakeratosis and hyperkeratosis, slight atrophy of the stratum mucosum and a nonspecific infiltrate of slight degree around the vessels and appendages in the dermis.

**Diagnosis** is from secondary syphilis, lichen planus, drug eruptions and pityriasis rosea. After a time, the prolonged course rules out syphilis and pityriasis rosea. In syphilis, mucosal changes, condylomata, enlarged lymph nodes and evidence of a primary lesion may be found and the lesions are ham-coloured. In pityriasis rosea,

the herald patch, distribution of the eruption, cleavage line tendency and centripetal scaling are characteristic. Lichen planus is usually very itchy, the lesions give a "waxy glance", show pseudoscaling, have a characteristic distribution and often involve the oral mucosa and the external genitalia.

**Course and Prognosis.**—If untreated, the condition may persist indefinitely but it seems to have no effect on the general health.

**Treatment.**—The malady sometimes responds well to general ultra-violet irradiation or to calciferol by mouth in a dose of up to 150,000 units a day for up to 3 months, with fortnightly urine examinations and estimations of the blood urea to detect early signs of intoxication from the drug.

Locally, salicylic acid ointment is suitable.

**PARAPSORIASIS DISCOIDES** (parapsoriasis en plaque, xanthoerythroderma perstans) presents as yellowish-red discs and ovals, non-itchy, occurring on the trunk and limbs, usually in adults aged 30 or more, without constitutional disturbance.

**Histopathology** is not distinctive. There is focal parakeratosis and spongiosis and nonspecific infiltrate in the dermis, a picture resembling a low-grade dermatitis.

**Clinical Picture.**—Non-itchy, brown-pink plaques appear on the trunk and the limbs, with slight scaling and with no constitutional disturbance. There may be slight atrophy.

**Course and Prognosis** are both uncertain. Parapsoriasis en plaque may persist for months or years, and a proportion of the cases pass on to poikiloderma (telangiectasia, atrophy, pigmentation and depigmentation) or to reticulosis in one of its many guises (exfoliative dermatitis, mycosis fungoides, etc.). The prognosis must be non-committal and periodic physical examinations and, if necessary, biopsies should be made for early evidence of a reticulosis.

**Treatment** is most unsatisfactory, the malady resisting all efforts of the physician, including ultra-violet irradiation, calciferol and various nonspecific remedies.

**PARAPSORIASIS LICHENOIDES** (parakeratosis variegata) presents with reddish-brown scaly, flat-topped papules in reticular pattern chiefly on the extensor surfaces of the limbs, the neck and the trunk. The condition is slowly progressive but benign.

**Diagnosis** is from secondary syphilis and lichen planus (*q.v.*).

**Treatment** is symptomatic and supportive.

**PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA** is a fourth and uncommon form of parapsoriasis of more sudden exanthematous onset, with lichenoid and varioliform lesions, yellowish-brown and crusting. It resolves spontaneously after weeks or months, leaving depressed scars. The palms, soles and mucosæ escape but the lymph nodes may be enlarged.

**Diagnosis** is from varicella, secondary syphilis, drug eruptions, pityriasis rosea and lichen planus (*q.v.*).

**Treatment** is symptomatic and supportive.

## PITYRIASIS ROSEA

**PITYRIASIS ROSEA** is a scaly disease of limited duration, characterised by the appearance of a herald patch a few days before a generalised eruption.

**Ætiology and Pathology.**—The cause is unknown. It often follows an upper respiratory infection or slight fever and may be a viride. Second attacks are rare.

**The histopathology** is not distinctive. There is some parakeratosis and a non-specific cellular infiltrate in the dermis.

**Clinical Picture.**—Children and young adults are mostly affected. There is often a history of malaise, coryza and of sore throat a week or two

The first change in the skin is the herald patch, somewhere on the trunk, at the axilla or on a thigh, occasionally more distally on a limb. The lesion is an oval, rosy plaque becoming fawn-coloured, with scaling, the free edges of the scales being centripetal. Itching is slight or absent as a rule. The herald patch may be missed. The generalised eruption begins a week or two later and is usually confined to the trunk and proximal parts of the limbs. It often extends up the neck and down the arms and forearms, but the face, lower thighs and legs are seldom affected.

Two types of generalised eruption are seen, the more usual macular and plaque form and the follicular papular form, in which, however, a few plaques are always present as well. The plaques start as pink macules which extend to become oval "medallions" which, on the trunk, lie parallel to the ribs; they vary in size from 0.5 cm. to 2 cm. or more. Scaling is not apparent at first but, after a week or 10 days, the lesions become fawn-coloured and scaling begins from their centres, causing a centripetal arrangement of the free border of the scaling. In the early stage, when this feature is not apparent, it can be demonstrated by scraping a lesion so as to detach the looser scales. There are no mucosal changes and the lymph nodes are not enlarged.

The follicular papular variety is more difficult to recognise, but the manner of onset and the distribution should give rise to suspicion and the discovery of medallions makes the diagnosis clear.

**Course and Prognosis.**—The total course is usually about 6 weeks, but it may last only 4 weeks or continue for anything up to 10 weeks. Pityriasis rosea is modified in xerodermatous and seborrhœic subjects. Its course is prolonged if, owing to a misdiagnosis, treatment is given with fungicides. In these circumstances, it may become papular vesicular, eczematized and distressingly itchy.

**Diagnosis** is from secondary syphilis, drug eruptions, tinea circinata and infective dermatitis. In secondary syphilis, the examination of the genitalia, mucous surfaces and lymph nodes reveals other evidence of that disease. Pityriasis rosea-like drug eruptions are usually in some way atypical. Tinea circinata is usually more acute, with vesiculation as well as marginal peeling; the lesions are circular rather than oval; they are few in number and may appear on the face; the scalp, too, may be affected with scaling and short broken hairs. Microscopy reveals mycelia and spores. Infective dermatitis is recognised by its grey greasy scales and sweat area distribution.

**Treatment.**—Reassurance, explanation and calamine lotion are usually all that are required. The patient need not be isolated. Warm but not hot baths may be taken. If any doubt exists, the Wassermann reaction should be tested. Over-treatment must be avoided. To hasten peeling, general ultra-violet irradiation is sometimes given and the course may be shortened by about a week in this way, but there is rarely any justification for this procedure.

## PITYRIASIS RUBRA PILARIS

This is a rare chronic skin disorder characterised by red follicular papules with horny spines, keratoderma of the palms and soles and psoriasis-like plaques of a bright pink colour.

**Ætiology and Pathology.**—The cause is unknown. A defect of vitamin A metabolism is suspected. It may be a follicular variant of psoriasis.

Histologically there is follicular keratosis and plugging, with an infiltrate around. The psoriasis-like plaques show parakeratosis and a nonspecific infiltrate.

**Clinical Picture.**—There are widespread groups of pink or red follicular papules, with keratotic tips, on the body and limbs. The hairy backs of the proximal phalanges show follicular keratoses. There is marked thickening and dirty discolouration, with fissuring, of the horn on the palms and soles, and the nails become deformed and

brittle. The plaques are pink or red scaly areas, having a resemblance to psoriasis, on the one hand, and lichen simplex, on the other, but they differ from both these conditions in that central circles or polycyclic areas of normal skin are present. Ectropion may occur. The mucous membranes are not affected. There is no obvious constitutional disturbance.

**Course and Prognosis.**—The malady comes on insidiously and continues indefinitely in spite of treatment. A spontaneous remission may occur after several months.

**Treatment.**—There is no evidence that the administration of vitamin A shortens the duration. Estrogens may seem to bring about a remission but their evaluation is difficult. Treatment is symptomatic, with applications of salicylic acid ointment or a mixture of this with an equal part of glycerin of starch.

## DYSKERATOSIS FOLLICULARIS

Dyskeratosis follicularis, or Darier's disease, is a rare condition due to an inherited abnormality of horn formation.

**Ætiology and Pathology.**—The cause is unknown but an abnormality of vitamin A metabolism is suspected.

The highly characteristic histology consists of hyperkeratosis and papillomatosis, with keratotic plugging and dyskeratotic "corps ronds" and "grains" in the upper epidermis, with lacunæ at the epidermo-dermal junction, which results in the formation of vegetations.

**Clinical Picture.**—Early in life, the child is noted to have dirty grey keratotic plugs on the skin. The flexures and the hair-bearing areas are affected most. Secondary infection may lead to moist warty nodulation and an offensive odour. The finger-tips show pinhead and smaller depressions on the epidermal ridges. They are peculiar to this malady.

**Course and Prognosis.**—The course is prolonged but the malady does not disturb the general health except from the effects of secondary infection. Some degree of mental retardation is not uncommon.

**Diagnosis** is from acanthosis nigricans, in which there are velvety, pigmented folds and wartiness, and from pemphigus vegetans and dermatitis vegetans (*q.v.*).

**Treatment** is symptomatic. Ten per cent. salicylic acid ointment is a useful application. Vitamin A is ineffective.

## LICHENOID DERMATOSES

These eruptions are of widely differing ætiology and pathology but they have in common some degree of similarity in their physical signs.

### LICHEN SIMPLEX CHRONICUS

This is a common condition in which oval areas of pinkish-brown, thickened skin develop at sites of repeated friction (see *Sensory Disorders*).

### LICHEN PLANUS

This is a disorder of uncertain duration in which itchy flat-topped, shiny, violaceous papules appear on various parts of the body.

**Ætiology and Pathology.**—The cause is unknown. It is suspected to be of virus origin and set off by varied noxæ, including drugs, physical agents, nutritional deficiencies and emotional stresses.

Histologically the picture is characteristic; but it is modified by the amount of

atrophy or hypertrophy present and by the extent of involvement of hair follicles. Hence, terms such as lichen planus atrophicus, lichen planus hypertrophicus (lichen planus verrucosus) and lichen plano-pilaris (lichen planus follicularis). Lichen spinulosus et folliculitis decalvans of Graham-Little is a variety of lichen plano-pilaris affecting the scalp.

There is hyperkeratosis, thickening of the stratum granulosum, either atrophy of the stratum mucosum or an irregular acanthosis and, depending on the intensity of the dermal infiltrate, a variable degree of liquefactive degeneration of the stratum germinativum, which in extreme cases may result in histological or even clinical evidence of bulla formation (lichen planus bullosus). The rete ridges may be of "saw tooth" type or, in atrophic areas, absent; in hypertrophic cases there is papillomatosis. In the upper dermis, immediately subjacent to the epidermis, is a heavy infiltrate almost entirely composed of lymphocytes with a few histiocytes.

In lichen plano-pilaris the same histological features are observed at and around the hair follicles.

**Clinical Picture.**—Lichen planus most characteristically affects the buccal mucosæ, the fronts of the wrists, the lumbosacral region, the external genitalia, the medial aspects of the thighs, the shins, calves and ankles: it may appear on the palms or soles and anywhere on the body, though rarely, if ever, on the face. Scratching sometimes causes linear lesions (Koebner's phenomenon) or exposure to sunlight may localise the rash. Involvement of the scalp with lichen plano-pilaris may end in the picture of pseudopelade (*q.v.*) and rarely the nail matrices are affected and the nails dystrophic and deformed as a result.

The elementary lesion of lichen planus as seen on the skin is a violaceous, polygonal, flat-topped, shiny papule. Sometimes the papules are only a shade darker than the surrounding skin. Often Wickham's striae and spots can be seen upon them—grey streaks and spots of pseudo-scaling, thought to be colour changes caused by the thickened stratum granulosum. The individual papules often enlarge or run together to form extensive plaques.

Central healing, often somewhat atrophic, is common, resulting in lichen planus annulare. On the penis this is most characteristic and the lesions here are often non-itchy. Resolution of lichen planus is nearly always accompanied by a great deal of pigmentation. It is not unusual for all the lesions to clear except those on the legs which may, on the contrary, become verrucose and persist indefinitely.

Lichen plano-pilaris presents as shiny follicular papules with a violaceous rim, the papules often being grouped. The process ends in atrophic scarring, at first violaceous, later white and in patchy baldness.

Lichen planus of the mouth gives rise to white, slightly raised polygonal spots and white streaks and delicate feathery patterns. Ulceration or redness are unusual and the lesions are either symptomless or give rise to a sensation of slight roughness.

Lichen planus of the nails is very rare. Involvement of the nail matrices may cause grey, rough, dystrophic nails.

**Course and Prognosis.**—Lichen planus is extremely variable and unpredictable in its course, no doubt depending on the possibilities of controlling the causal factors. The subacute form may, in fact, persist for months, new lesions appearing while others become inactive and are converted into pigmented macular remnants. The chronic form may persist indefinitely or clear at some sites but not at others. The legs are particularly likely to be affected by chronic and often hypertrophic lichen planus. Even after complete disappearance of all lesions, fresh outbreaks may occur some months or years later.

The development of carcinoma on lichen planus in the mouth has been described in a very few cases: lesions on the vulva, because of the irritation they cause, may result in leucoplakic changes and carcinoma.

**Diagnosis** is from psoriasis, parapsoriasis guttata, syphilis, warts, lichen simplex,

lichen nitidus, lichen sclerosus et atrophicus and lichen amyloidosis (*q.v.*). The diagnosis depends on a careful consideration of the elementary lesions, their "waxy glance", their distribution, and the presence of orogenital lesions. Lichen planus may be non-itchy and in the early stage of evolution the lesions may be atypical. Hence it is sometimes necessary to reinspect a patient after a week's interval, with a view to coming to a firm diagnosis. It may also be necessary to perform biopsy, a very useful procedure because of the highly characteristic histology in lichen planus.

**Treatment.**—There is no specific treatment for lichen planus and each patient must be dealt with according to the relative significance of emotional, drug, physical or other factors that become evident when taking the history.

Sedation is usually necessary, either by an evening dose of a barbiturate such as butobarbitone gr. 3, or with gr.  $\frac{1}{2}$  doses of phenobarbitone two or three times a day in addition.

The withdrawal of any drugs the patient may have been taking is advisable if they are suspected as causal, for example, gold or mepacrine. Appropriate detoxicating remedies such as dimercaprol should be given when indicated, and more specific "supporting" treatments such as crude liver injections and vitamin supplements are justifiable.

Bed rest is a valuable prescription for subacute, widespread lichen planus, or when the history suggests that fatigue may be an important factor. Such adjustments to the patient's mode of living that may seem necessary play an important part in treatment and unless these psycho-physical factors are dealt with the malady may prove intractable.

Certain drugs have a reputation for relieving resistant lichen planus. They include mercury and potassium iodide mixture, intramuscular injections of bismuth (0.2 g. in 1 ml.), or of mercury salicylic arsonate (0.06 g. in 2 ml.) or a short course of Fowler's solution. A short course of corticotrophin may bring about a remission.

Fractional X-ray exposures (75 r up to four weekly treatments) to confluent patches, or fortnightly applications of thorium-X (1,500 c.s.u. per ml.) often help to tilt the balance in the patient's favour.

Other local applications are not of great value. Phenol 1 per cent. in zinc cream or calamine lotion may be used as an antipruritic.

### LICHEN NITIDUS

This is a rare eruption of uncertain aetiology, consisting of lichenoid papules in which there are focal areas of tuberculoid histology enclosed as it were between claws of epithelium. The overlying epidermis is atrophic. The collagen and elastin are degenerate. A tuberculous cause has not been established and the condition may in fact be a variant of lichen planus.

**Clinical Picture.**—Non-itchy, skin-coloured or pink, shiny, flat-topped papules occur in close-set groups, particularly on the penis, the flexor surfaces of the forearms or on the abdomen.

**Course and Prognosis.**—The lesions persist indefinitely but may finally fade away without residual pigmentation.

**Diagnosis** is made from lichen planus by the absence of itching and pigmentation and the characteristic histology.

**Treatment** is ineffective. Success has been claimed for iodine taken by mouth in the form of Lugol's solution. The patient should be examined for any possible tuberculous focus.

### LICHEN SCLEROSUS ET ATROPHICUS

A condition of lichenoid papules, ending in atrophy and sclerosis, affecting both sexes; commoner after 30 years of age; rare in children.



**Ætiology and Pathology.**—The ætiology is unknown.

The histopathology is characteristic and includes hyperkeratosis and acneiform follicular keratotic plugging, atrophy of the stratum mucosum, œdema of the upper dermis with homogenisation of the collagen and an inflammatory infiltrate in the deeper parts of the dermis, without obliterative vascular changes as seen in scleroderma.

**Clinical Picture.**—The malady presents with genital and extragenital lesions. In both sexes the latter consist of roughly circular pinkish-grey atrophic parchment-like patches with a few comedones. At flexural sites there may also be white lichenoid papules and scleroderma-like plaques without comedones.

In the male the genital lesions may be similar to those already described if they are on the shaft of the penis. There may be a fibrous constriction of the prepuce causing phimosis. On the inner surface of the prepuce, at the coronal sulcus, and on the corona and glans, there is a variable degree of atrophy and sclerosis. Atrophy may be confined to the penile meatus and this may later cause some urethral stenosis; or the whole surface of the glans may be irregularly thickened, dry, white and hard, a condition known as balanitis xerotica obliterans. In the female the atrophic and sclerotic changes may affect the labia minora or majora and the adjoining skin of the perineum and perianal region. Itching is variable but may be intense. The severest cases may have bullous lesions owing to interference with lymph drainage.

**Course and Prognosis.**—Lichen sclerosus et atrophicus continues indefinitely but may undergo considerable spontaneous improvement. There are no serious complications on the extragenital skin but on the penis urethral stenosis may occur and on the vulva intense itching and scratching may lead to leucoplakic and carcinomatous changes.

**Diagnosis** is from the localised form of scleroderma (morphœa), macular atrophy, leucoplakia and atrophic vaginitis with kraurosis.

Morphœa presents as an oval, firm, white or pink, shiny plaque with a lilac halo. Atrophy is not marked except sometimes in the later stages. There are no comedones. The histology is different from that of lichen sclerosus et atrophicus. In macular atrophy there are soft bulgings, giving a hernia-like feeling on pressure. Leucoplakia only affects mucous surfaces. Lichen sclerosus et atrophicus of the vulva may be complicated by leucoplakia. Atrophic vaginitis presents as shrinkage of the vaginal orifice (kraurosis vulvæ) with patchy pigmentation, depigmentation, atrophy and telangiectasia of the mucosa of the vulva. The labia minora are often atrophic or absent.

**Treatment.**—There is no specific treatment. It has been claimed that vitamin E by mouth is of value. The ointment of wool alcohols or hydrous ointment make useful local applications. Meatal stenosis may need suitable attention. If leucoplakia or carcinoma supervene on the vulva, excision is called for, but excision of the perineal and perianal skin is unnecessary because carcinoma does not develop on extragenital lesions of lichen sclerosus.

#### LICHEN STRIATUS

This is a rare malady occurring usually in children. A band of lichenoid papules erupts usually in the long axis of a limb and after a few weeks or months involutes spontaneously. Itching is slight or absent.

The histology is that of chronic dermatitis.

**Diagnosis** is from lichen planus linearis.

**Treatment** is symptomatic and supportive.

#### LICHEN SPINULOSUS (KERATOSIS FOLLICULARIS)

This is a condition of widespread or grouped horny, follicular papules. The widespread form involves in particular the extensor surfaces of the limbs and trunk

(phrynoderma). The cause is believed to be a deficiency of vitamins A and C and the malady is mostly seen in children.

A somewhat similar picture may occur in the follicular variety of xeroderma (keratosis suprafollicularis).

An eruption of oval areas of lichen spinulosus on the trunk and limbs may occur with fungous infections of the feet (lichen trichophytide).

**Pathology.**—In xeroderma the stratum granulosum is deficient. In avitaminosis A and C there may be perifollicular hæmorrhages.

**Diagnosis** is from lichen plano-pilaris in which the papules have violaceous rims and on the scalp cause a variety of folliculitis decalvans.

**Treatment.**—Depending on the cause, treatment consists of vitamin supplements, elimination of a fungous infection or attention to xeroderma or lichen planus. Salicylic acid ointment may be applied.

### LICHEN SCROFULOSORUM

This is an eruption of skin-coloured or pink, lichenoid papules, usually occurring on the trunk in childhood. There is often also tuberculosis of lymph nodes, bones or joints, etc., a strongly positive Mantoux reaction and a tuberculoid histology (see Tuberculides).

### LICHEN AMYLOIDOSIS

This is a localised cutaneous form of amyloidosis presenting as itchy, elevated, nodular plaques on the shins, resembling hypertrophic lichen planus. The diagnosis is confirmed by staining for amyloid (see Amyloidosis).

### LICHEN URTICATUS

This is a papular urticaria of childhood. The lesions resemble varicella more than lichen (see Urticaria).

### PITYRIASIS LICHENOIDES CHRONICA

#### PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA

(See Parapsoriasis)

#### PARAPSORIASIS LICHENOIDES

(See Parapsoriasis)

### LICHENOID ERUPTION OF AXILLÆ (FOX FORDYCE DISEASE)

This malady occurs mostly in women as pink or brown dome-shaped, grouped papules in the axillæ, also sometimes at other apocrine sites, the areolæ of the nipples, the umbilicus, pubic region and the perineum. Itching is severe.

**Ætiology and Pathology.**—The cause is unknown.

There is follicular hyperkeratosis and plugging, acanthosis and a chronic inflammatory infiltrate around the apocrine glands.

**Treatment** consists of œstrogens by mouth and salicylic acid 2 per cent. in hygroscopic ointment locally. Fractional X-ray exposures 100 to 150 r weekly up to a total of 600 r may prove helpful.

## ACNEIFORM DERMATOSES

These are eruptions in which acuminate papules provide the most characteristic feature.

## ACNE VULGARIS

A papular condition due to hyperkeratotic plugging of the pilosebaceous follicles combined with hyperplasia of the sebaceous glands.

**Ætiology and Pathology.**—Acne is brought about by an imbalance between androgenic and æstrogenic hormones. In the male, an excess of testosterone is responsible; in the female, an excess of progesterone is believed to be the cause. In either case there is a resultant sebaceous hyperplasia and a diffuse hyperkeratosis which, at the pilosebaceous orifices, particularly at the openings of glabrous hairs, causes obstruction to the flow of sebum. A blackhead (comedo) is an hyperkeratotic follicular plug. This follicular obstruction leads to inflammatory changes (papular acne), the keratin and sebum having a foreign body effect. This inflammation may end in resolution or in suppuration (pustular acne): in either case the end result is some degree of fibrosis. The pus is usually sterile and, if the suppuration is deep it may form cystic swellings in the hypoderm (acne conglobata). Burrowing tracks may form, lined with epidermis, and there may be small epidermal bridges and tunnels with several openings.

Severe acne tends to end in keloid formation, particularly at the nucha, over the sternum and, with smaller lesions, on the face and neck (acne keloid).

In addition to the cystic swellings already mentioned, epidermal cysts of pinhead size may be interspersed amongst the acne lesions ("white" acne).

There is no evidence that the acne bacillus is the cause of acne. This organism is, like the pityrosporon of Malassez and the *Staphylococcus saprophyticus*, a secondary invader of the truly seborrhœic skin. Some comedones contain an acarus, the demodex folliculorum. Most acne lesions are sterile but sometimes there is a heavy secondary infection with staphylococci (acne sycosis); in these circumstances the pustules are notably more superficial and contain liquid pus as opposed to the cheesy contents of many acne pustules.

**Clinical Picture.**—Slight degrees of acne at puberty are so common as to be regarded as physiological. It usually begins at about 12 to 14 years of age and diminishes in severity at 18 to 20. In girls it often coincides with the menarche. Occasionally acne persists into adult life and may even last throughout life. As a rule, males are more severely affected than females.

Acne affects the face and neck, the upper trunk and, to a lesser degree, the lumbar region, buttocks and limbs.

A comedo (blackhead) (acne punctata) is a black or dirty grey, pinhead sized, hard speck at a pilosebaceous orifice. In an uncomplicated comedo there is no redness or swelling but when this occurs an acne papule results, acuminate, firm and comedo-topped; liquefactive changes lead to a deep-seated pustule. This may resorb or break spontaneously or be broken by the patient's manipulations, and a funnel-like, depressed scar results. Lesions of acne conglobata are obtuse, dome-shaped, bluish-grey nodules. It is not unusual to see comedones, papules, pustules, small epidermal cysts, cystic swellings and scars, often keloidal, in the same patient.

The complexion in acne is greasy and muddy, the thickened epidermis diminishing transmission of colour from blood flowing in the superficial vessels of the dermis. Visibly enlarged patulous follicles are present and excessive sebum formation may be visible especially at the alæ nasi. There may be an increase of dandruff but this is by no means the rule. The acne patient of either sex is usually somewhat hirsute and in females the pubic hair often has a masculine distribution. There may also be hyperidrosis.

**Course and Prognosis.**—Acne vulgaris usually clears up or improves considerably after the teens. If it does not, some cause can usually be found (see below). A variable amount of scarring is inevitable, except in the milder forms.

**Diagnosis** is from sycosis, acneiform tuberculides, syphilides, drug eruptions and rosacea.

In sycosis, involvement is of coarse hair-bearing areas, whereas acne involves areas of glabrous skin and the borderline between coarse hair-bearing areas and glabrous skin. The two conditions may coexist.

Acne agminata presents as grouped translucent papules, particularly on the eyelids, nose and penis.

Acneiform syphilides are papulo-pustular but without comedones; but syphilis may also aggravate a pre-existing acne vulgaris.

Halogens, too, particularly iodides, may cause acneiform eruptions without comedones, or aggravate pre-existing acne vulgaris. Halogen acne is usually more exuberant than acne vulgaris. Occupational acne often affects the forearms and thighs as much as the face.

Rosacea usually occurs in an older age group than acne vulgaris but occasionally starts in the teens. The lesions involve an oval area of the centre of the face. They are erythematous-papular and pustular but there are no comedones, though scars of previous acne may remain. There is marked vasolability and the face is bright red, not the muddy colour of acne vulgaris.

Treatment depends on control of the primary cause and of the aggravating factors. The primary cause is a relative excess of androgens in relation to oestrogens. The aggravating factors are numerous. They include a familial predisposition, dietetic errors, certain drugs, contact irritants, imperfect hygiene and insufficient weathering and emotional tension related in particular to conflicts with parental authority and difficulty in psychosexual adjustment to adult life, the acne sufferer often being somewhat retarded in this respect while intellectually adequate and physically mature.

Treatment aims at correcting the endocrine imbalance so as to diminish sebaceous over-activity; and attaining and retaining patency of the pilosebaceous follicles.

It is inadvisable to use oestrogens in the male: in the dosage necessary to give a good result the emasculating effects that also result are undesirable. Emotional changes and gynecomastia may result. In females oestrogens may justifiably be given if there is oligomenorrhœa, irregular menstruation, male type hirsutism or marked aggravation of the acne before the menses, but it is inadvisable to use them even in these circumstances for the first few years after the menarche; it is better to allow time for menstruation to acquire a regular rhythm.

When prescribing oestrogens for acne, the patient should be asked to estimate the expected first day of the next menstrual period and to begin the treatment 10 days before this date and continue until menstruation begins. In this way there is no interference with ovulation. If menstruation is markedly irregular, it is not possible to adopt this procedure and the patient is instructed to start treatment a fortnight after the last day of the previous menstrual flow and continue for a fortnight or until the next period begins, whichever is the shorter. This treatment is continued for 3 to 6 months.

The diet should be high in protein and vitamin content. Excess of fats and carbohydrates must be avoided. In particular, chocolate, cocoa, cream pastries and cheeses are liable to aggravate acne.

Bromides and iodides have in the past been responsible for much aggravation of acne but they are in less common use to-day. Other drugs, for example aspirin, occasionally aggravate acne.

The skin should be washed at least twice a day with a good toilet soap. Medicated soaps are best avoided. If cosmetics are used they should be of the lotion type, not creams. The patient should be discouraged from experimenting with local applications. Irritant or sensitising substances incorporated in a base capable of mixing well with fat and water may cause a severe chemical folliculitis. Similarly, exposure

to brine, pitch, tar, organic chlorine compounds, paraffin or petroleum oils (cutting oils, greases, waxes) may cause or aggravate acne.

Woollen underclothing should not be worn next to the skin.

The acne patient should be encouraged to take outdoor exercise in all weathers. The fine exfoliation that follows sun-bathing is beneficial, as is the flush that follows exposure to wind and rain.

Infected acne may be improved with appropriate topical antibiotics and by staphylococcal toxoid injections.

In those cases of acne in which emotional factors are relevant the control is difficult and psychiatric assistance is sometimes necessary. The acne patient should be encouraged to mix with other young people and to have wide social activities.

*Local treatment.*—This mainly aims at bringing about a fine peeling of the skin. For this purpose a weekly second-degree exposure to ultra-violet irradiation (enough to cause a branny peeling) is most helpful. The carbon arc lamp is most efficacious but, if not available, good results can usually be obtained with the mercury vapour lamp. Before giving either of these treatments to acne involving the trunk, it is advisable to make a radiographic examination of the chest in order to exclude the presence of an asymptomatic focus of tuberculosis which might be activated by this treatment. For more severe acne induratum, a third-degree exposure (to cause coarse peeling) may be necessary.

Medicaments for local application in acne should either be lotions or pastes. Creams and ointments are likely to prove harmful. Zinc sulphate lotion, compound sulphur lotion and calamine lotion with 2 per cent. of sulphur are all useful. A flesh-tinted paste will serve the double purpose of treatment and camouflage. Resorcin and sulphur paste (tinted) is of reasonable cosmetic quality.

The liberal use of soap and water and the avoidance of cream cosmetics should go hand in hand with the above treatment. Many patients with acne vulgaris manipulate the lesions by squeezing, in the hope that contents will be expressed and resolution hastened. This undesirable habit is the cause of much funnel-like scarring of the follicular orifices. Manipulation should be limited to brisk friction with a face flannel or a soft nail brush.

Carbon dioxide snow applications (1 to 3 seconds) to larger nodules are useful by bringing about a coarse peeling.

Cystic swellings need puncture before giving this treatment.

X-rays can be used with a view to bringing about some involution of the sebaceous glands in severe and resistant acne, particularly if it is localised. An exposure of 100 to 150 r repeated weekly up to a total of 600 r is a reasonable dosage. Any cystic swellings should be punctured before this treatment is given. On no account should more than two of such courses be given (total 1200 r) because above this level post-irradiation atrophic changes are likely to occur.

### ACNE EXCORIÉE DES JEUNES FILLES

In this condition excoriations dominate the picture. Comedones are usually but not always present and numerous excoriated papules and scars, particularly at the forehead, temples, cheeks and chin.

Acne excoriée indicates the presence of an emotional conflict and calls for psychological investigation and treatment. Local treatment is ineffective unless the urge to pick the spots has been removed. The best application is a flesh-tinted paste, for example, titanium dioxide paste.

### ACNE IN INFANCY

This is rare, but may occur in the following ways :

(1) Newborn babies often have numerous small papulo-pustules on the face for

the first few days after birth. It has been suggested that these are due to androgenic hormonal influences (progesterone) from the mother.

(2) The use of camphorated oil, olive oil or tallow as an embrocation may cause an acneiform eruption on the face or chest (grouped comedones).

(3) Excessive and occlusive wrapping up of the child's body may, by increasing sweating on the face, cause some inflamed follicular papules.

(4) Occasionally cod liver oil given by mouth causes acneiform papules.

(5) Unilateral naevi consisting of grouped comedones occur.

(6) Adrenocortical neoplasms are accompanied by acne as is the administration of corticotrophin or cortisone.

## ROSACEA (ACNE ROSACEA) (see p. 1207)

### ACNE NECROTICA (ACNE VARIOLIFORMIS)

This is a relatively rare inflammatory condition of the follicles with discrete papulo-pustulation on the forehead, scalp and temples, going on to necrosis and scarring.

**Ætiology and Pathology.**—The condition is a folliculitis due to coagulase-positive staphylococci. *Histological changes of acne vulgaris* are present with the addition of œdema and an inflammatory infiltrate leading to superficial follicular necrosis.

**Clinical Picture.**—The patients are usually middle-aged men but women may also be affected. Near the hair margin across the forehead, at the temples and on the neck are discrete, brownish papules, pustules and scabs, with depressed scars. It may also appear on the face, limbs and trunk. There may be much itching and picking of the lesions, which are present in all stages at the same time. Affected individuals usually show evidence of the "seborrhœic" state.

**Course and Prognosis.**—The condition tends to persist indefinitely and to relapse after treatment is stopped.

**Diagnosis** is from seborrhœic folliculitis, acne vulgaris, syphilis and variola. The duration, distribution, itching and polymorphic lesions suggest the correct diagnosis. Seborrhœic folliculitis leaves little or no scarring.

**Treatment**, which is usually effective, consists of the application of the appropriate antibiotic, depending on sensitivity tests. The associated seborrhœic state must receive attention. Other remedies sometimes used include zinc and copper lotion, potassium sulphate lotion, Vioform cream or Quinolol ointment.

### ACNE URTICATA

This is an eruption of small wheals on the scalp, face or elsewhere. Excoriations often result (see Urticaria).

### ACNE SCROFULOSORUM (see Cutaneous Tuberculosis)

### ACNE AGMINATA (ACNITIS; LUPOID PAPULAR TUBERCULIDE)

**Clinical Picture.**—This is a papular eruption affecting the forehead, eyelids, nose and cheeks and sometimes the penis. The papules are yellow and translucent, giving a lupoid apple-jelly appearance on diascopy. The lesions are all at the same stage of development. Necrosis subsequently occurs, and when the scabs separate depressed scars are left.

**Ætiology and Pathology.**—The condition has been thought to be a tuberculide but the Mantoux reaction may show normergy or hypoergy to tuberculin and it has been suggested that the condition is a viride.

Histologically there is a tuberculoid pattern with central caseation and a surrounding inflammatory infiltrate.

**Course and Prognosis.**—The lesions are resistant to treatment by antituberculous drugs but tend to undergo spontaneous resolution after several months, leaving scars.

**Treatment** is supportive and nonspecific.

## CHRONIC BULLOUS ERUPTIONS

The chronic bullous eruptions are a group of reactions of unknown cause, the recognition of which is nevertheless most important because of their differing prognoses and treatments. In their differentiation reliance has to be placed on the history and physical signs, and in particular on the presence or absence of Nikolsky's sign. The Tzanck test also is a simple and useful diagnostic procedure.

Nikolsky's sign can be demonstrated in two ways. If there is an intact bulla an attempt is made to push this along in the skin with one thumb, while anchoring the adjacent skin with the other hand. Nikolsky's sign is positive if the bulla can be moved along in the skin. The other method is to apply tangential stress to the apparently normal skin. The skin over the collarbone or tibia is anchored with the left thumb and forcible lateral pressure is applied with the right thumb. The sliding off of the superficial layers indicates a positive Nikolsky's sign. The sign is positive in pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematoses, pemphigoid, benign familial pemphigus and epidermolysis bullosa. It is negative in dermatitis herpetiformis and in erythema multiforme.

The Tzanck test is performed by removing the roof and scraping the floor of a bulla. The material thus obtained is spread on a slide, stained and examined under the microscope for acantholytic cells (epidermal cells which have lost their prickles). Alternatively, lateral stress may be applied to a portion of skin and biopsy subsequently performed. The Tzanck test is positive if slit-like clefts are apparent within the epidermis and if within them single acantholytic cells or groups of them are seen.

## DERMATITIS HERPETIFORMIS (DUHRING'S DISEASE)

Dermatitis herpetiformis is a disorder in which grouped, itchy vesicles and small bullae arise on normal or reddened skin.

**Ætiology and Pathology.**—The cause is unknown: a virus cause is suspected. It is most common between the ages of 30 and 50 and is rare in early adult life and in childhood. There is an excessive susceptibility to the blister-producing influences of potassium iodide both by its ingestion and by its topical application.

Histologically the bullae are at the epidermo-dermal junction; they tend to be oval in shape when seen in sections; they contain blood cells with many eosinophils but no abnormal epidermal cells. There is an infiltrate of inflammatory cells around the bullae. The overlying epidermis shows evidence of scratching, with loss of tissue, a nonspecific infiltrate including some eosinophils and perhaps some patchy spongiosis, and irregular excesses of melanin pigmentation.

**Clinical Picture.**—The patient complains of an intensely itchy eruption which, though often widespread, shows a marked tendency to grouping. The sites most commonly affected are the shoulder blades, the elbows, the buttocks and genitalia, and the knees, but no area is immune, and the face may be involved. The eruption is polymorphic. The individual lesions are flaccid or tense, millet seed sized vesicles arising from skin which may be apparently normal or reddened. Owing to the severe itching it is rare to see many intact vesicles and the physical signs usually consist more of excoriated and scabbed erythematous papules, erosions, scars and patchy pig-

mentation. The mouth is not affected. Nikolsky's sign is negative and the Tzanck test shows blood cells, particularly eosinophils, but no acantholytic epidermal cells. The administration of potassium iodide by mouth or a patch test with potassium iodide causes an increased vesiculation. There is usually eosinophilia. The general health suffers little, if at all, apart from the disturbing effects of the intense itching.

**Course and Prognosis.**—Dermatitis herpetiformis may persist for several years, with fluctuations, after which it sometimes gets gradually milder and finally disappears. Its onset and course is controlled to some extent by any emotional stresses to which the sufferer may be exposed. The prognosis as regards life is good.

**Diagnosis** is from other bullous eruptions, erythema multiforme, urticaria, prurigo, general pruritus and infestations. The other bullous eruptions are in no way so itchy as dermatitis herpetiformis. Pemphigus often affects the mouth and leaves extensive raw areas, the patient being gravely ill. In erythema multiforme bullosum itching is less, the blisters are always within erythematous areas and excoriations are absent. Urticaria is evanescent, though possibly recurrent. In prurigo lichenification and excoriation are the predominant features and vesicles are never seen. In pruritus there may be scratch marks and excoriations but no vesicles. In infestations there are scratch marks on the shoulders and around the waist and an examination of the scalp and underclothes should disclose the cause.

**Treatment.**—Sulphapyridine (but no other sulphonamide) acts as a specific in dermatitis herpetiformis, with very few exceptions. A dose of 1 g. three times a day controls the itching and the development of vesicles within 24 to 36 hours. After this, the dose is reduced until the optimal level is found at which the symptoms are just controlled. The addition of nicotinic acid 50 mg. up to three times a day may enable a smaller dosage of sulphapyridine to be used. Periodic total and differential white cell counts should be performed to detect drug leucopenia. If the white cell count remains around 6000 per c.mm. the drug may be continued indefinitely without harm. If the white cell count drops to 4000 per c.mm. or lower it is advisable to suspend the sulphapyridine for a time and to replace it by some other form of treatment. Dapsone 50 mg. daily is often as effective as sulphapyridine. When taking this drug, the patient should also be given ferrous sulphate tablets and vitamin B. Fowler's solution in a dosage of 3 to 5 minims three times a day is often effective, but it is best to revert to sulphapyridine or to dapsone as soon as the white cell count permits because of the long-term toxic effects that may result from the use of Fowler's solution.

Antibiotics sometimes help and sometimes aggravate dermatitis herpetiformis and their trial is only justified when other means fail. When they are used, the patient should be kept under close observation so that treatment can be suspended at once if untoward symptoms develop.

General ultra-violet irradiation sometimes seems to relieve the itching. Phenobarbitone is also useful in the interim between courses of sulphapyridine or dapsone but bromides are contraindicated because, like iodides, they may aggravate the condition.

Local applications that may help include 1 per cent. of phenol in calamine lotion and 2 per cent. of solution of coal tar in Lassar's paste. Sodium bicarbonate baths (4 oz. in 25 gallons) may prove soothing.

### HERPES GESTATIONIS

This is a form of dermatitis herpetiformis affecting pregnant women, usually in the third trimester. It may recur in subsequent pregnancies. Relief usually, but not always, occurs after delivery.

**Treatment** is complicated in that both sulphapyridine and Fowler's solution are undesirable because of the pregnancy. Dapsone may be used or recourse had to



symptomatic relief with phenobarbitone or promethazine hydrochloride until the time of delivery.

### PEMPHIGUS VULGARIS

A bullous disorder with an irregular course, often ending fatally. In the flexures it forms vegetations (pemphigus vegetans).

**Ætiology and Pathology.**—The cause is unknown: essentially there is a lack of cohesion between the epidermal prickle cells. The malady usually occurs after the age of 40 and Jews are especially liable to be affected.

Histologically there are slit-like clefts within the stratum mucosum just above the stratum germinatum and acantholytic cells are seen within the clefts. In section, the extremities of the clefts are acute as opposed to the obtuse clefts seen in dermatitis herpetiformis.

**Clinical Picture.**—Large and small flaccid bullæ are present on seemingly normal areas of skin. Many ruptured bullæ are seen with extensive red, raw areas from which considerable loss of serum occurs. These raw areas tend to spread peripherally and show no tendency to heal spontaneously. Itching is slight or absent. The general health steadily deteriorates. Secondary infection is common particularly in the flexures where malodorous soft, moist, warty elevations or vegetations develop. The malady may at first be localised but ultimately the whole surface may be patchily affected. At pressure sites such as the elbows, scapulæ, sacrum, buttocks and heels, deep sores are liable to form. The mucous membranes of the mouth, vulva and penis are usually affected, with considerable distress to the patient. The vermillion surface of the lips and the mucous surfaces of the tongue, cheeks and roof and floor of the mouth are extensively denuded, giving an appearance of rawness covered by a white exudate and with loose tags of epidermis at the edges. Nikolsky's sign and the Tzanck test are positive. The serum proteins are often markedly diminished (particularly the albumin) owing to loss of body fluids from the extensive oozing, raw areas. There is severe hypochromic anemia and salt depletion. Sodium, chloride and calcium depletion also occur but the serum potassium may be raised. Ulceration of the mouth interferes with swallowing and may further weaken the patient from nutritional deficiency.

**Course and Prognosis.**—The natural course is one of worsening with occasional spontaneous remissions, usually followed by fresh outbreaks of increased severity, ultimately leading to death from general infection and pneumonia, complicated by protein and electrolytic deficiencies. This gloomy picture has been greatly improved since the introduction of corticotrophin and cortisone.

Diagnosis from other bullous eruptions is made with certainty from a consideration of the physical signs and the results of the Tzanck test.

**Treatment.**—The first essential is nursing care of the highest standard. Corticotrophin intramuscularly in a dose of up to 50 mg. every 6 hours usually leads to a remission. The dose is then reduced to the minimal maintenance level. The mucous lesions do not respond so well as the skin lesions. The latter heal well, with deep pigmentation. When the patient becomes ambulant, cortisone orally is more convenient in the smallest dose consistent with relief. This treatment may have to be combined with an antibiotic to combat any infection that is present.

Whole blood or plasma transfusions are useful but they cannot in themselves replace the deficiency of albumin and an adequate diet, high in protein content, must be given. Nasal feeding may be necessary. The mouth must be kept as clean as possible with normal saline or glycerin and thymol.

For the infected skin, chlortetracycline ointment is useful and when the lesions are clean tulle-gras applications are comforting. Some prefer a powder bed, the patient lying in sheets heavily sprinkled with boric talc powder.

## PEMPHIGUS FOLIACEUS AND PEMPHIGUS ERYTHEMATODES

These are forms of pemphigus in which exfoliation is the most prominent feature, bullæ rarely being seen because they are superficial and easily ruptured. The course is irregular but usually somewhat more benign than pemphigus vulgaris. Remissions and relapses occur. It is uncertain whether the condition can develop into pemphigus vulgaris.

**Pathology.**—The cellular disruption is at the granular cell layer. The overlying cells become detached with the result that on section blisters are not seen but the granular layer is either exposed to the surface or covered by loosely attached groups of horny cells.

**Clinical Picture and Differential Diagnosis.**—In pemphigus foliaceus the picture resembles erythroderma, perhaps with some secondary infection, but Nikolsky's sign is positive in pemphigus foliaceus and negative in erythroderma. There is crusting and a tendency to wartiness, with pigmentation. In pemphigus erythematodes (Sencar-Usher syndrome) the condition resembles infective dermatitis because the superficial lesions become secondarily infected; or with single or few lesions on the face there may be a resemblance to lupus erythematosus but the moistness of the lesions and the looseness of the overlying skin cast doubt on the diagnosis of lupus erythematosus.

Nikolsky's sign is positive. There is a variable degree of general disability.

**Course and Prognosis.**—The natural course is a slow worsening with remissions and recrudescences and a fatal outcome, usually from some infective complication.

**Treatment** is as for pemphigus vulgaris (*q.v.*) with corticotrophin or cortisone and antibiotics. Blood or plasma transfusions are usually unnecessary because the loss of body fluid is much less than in pemphigus vulgaris. When the secondary infection is under control, calamine liniment may be applied.

## SENILE DERMATITIS HERPETIFORMIS OR PEMPHIGOID

An eruption of tense bullæ, often with considerable erythema around, with much itching, occurring in the seventh or eighth decades and sometimes ending fatally.

**Ætiology and Pathology.**—The cause is unknown.

The bullæ are at the epidermo-dermal junction and contain blood cells including many eosinophils. They are oval when seen in sectional view.

**Clinical Picture.**—Large tense bullæ, some containing straw-coloured fluid, others containing blood or even pus, are present in the skin, particularly on the limbs. The mucous membranes of the mouth are sometimes affected with blisters and raw areas but the vermilion surfaces of the lips escape. There is intense itching but less constitutional upset than in pemphigus vulgaris. Nikolsky's sign is positive but the Tzanck test shows eosinophil and other blood cells but no acantholytic cells. The bullæ do not rupture easily and if they are broken they tend to heal and do not spread spontaneously as in pemphigus vulgaris. Small white cysts (milia) may form in the process of healing. Serum protein and electrolytic changes are minimal.

**Course and Prognosis.**—The natural course is chronicity with occasional remissions. The prolonged course, with loss of sleep from itching and secondary infection, may lead to death.

**Diagnosis** from erythema multiforme may be difficult. In erythema multiforme Nikolsky's sign is negative and spontaneous resolution occurs in a few days or weeks.

Pemphigus vulgaris differs from pemphigoid by its more flaccid and easily ruptured blisters with severe involvement of the mouth and lips and a heavy loss of electrolytes and protein. Senile dermatitis herpetiformis differs from dermatitis herpetiformis in its larger tense bullæ, positive Nikolsky's sign, mucosal involvement and more serious course.

**Treatment** is as for pemphigus (*q.v.*) with corticotrophin or cortisone. After

obtaining a remission with intramuscular corticotrophin the ambulant patient can be treated with gradually reduced doses of cortisone until in some cases the drug can be withdrawn and recurrence does not occur. In others, mild or severe recrudescences necessitate further treatment with corticotrophin. Local treatment consists of aseptic puncture and collapse of the large tense bullæ and suitable antibiotic or emollient dressings.

### BENIGN PEMPHIGUS OF THE MUCOUS MEMBRANES (OCULAR PEMPHIGUS)

A bullous eruption in which the eyes and mouth are mostly affected and the skin slightly or not at all.

**Pathology.**—The blisters are at the epidermo-dermal junction; there is no acanthosis but a heavy inflammatory infiltrate and later fibrosis.

**Clinical Picture.**—The conjunctivæ become inflamed and fibrous adhesions form between the palpebral and ocular surfaces or between the upper and lower palpebral surfaces. The conjunctival sacs become shallow and the palpebral fissures narrow and the eyeballs limited in their range of movement. The cornea may be damaged by entropion, xerosis or pannus, with loss of vision. Vesicles form in the mouth and by coalescence form large red, denuded areas. The vermilion surface of the lips escapes but the mouth may be narrowed by adhesions. Lesions may form anywhere in the mouth, nose or throat; in the œsophagus, causing dysphagia; on the glans penis or prepuce, causing phimosis; or on the vulva or vagina, causing narrowing. The skin of the scalp or face is affected in about half the patients with erythema, flaccid bullæ and erosions, going on to scarring.

**Course and Prognosis.**—The malady is slowly progressive, with remissions and recurrences.

**Diagnosis** is from pemphigus vulgaris, pemphigoid, severe erythema multiforme and aphthosis, including Behcet's syndrome.

In pemphigus the lesions are in the epidermis and the vermilion surfaces of the lips are often affected. In pemphigoid the eyes usually escape and the skin lesions, which predominate, consist of large tense bullæ. In severe erythema multiforme the onset is abrupt, the patient is a child or young adult and the skin involvement is extensive. In Behcet's disease there are erosions and ulceration of the eyes, mouth and genitalia, often with some destruction of tissue.

**Treatment.**—Cortisone eye drops are invaluable and corticotrophin or cortisone may help to alleviate the other manifestations. For the mouth a bland mouth wash should be prescribed.

### BENIGN FAMILIAL PEMPHIGUS (OF GOUGEROT AND HAILEY-HAILEY)

This is a chronic erosive condition of friction sites occurring in many members of the same family, benign in its course and with a tendency to spontaneous remissions.

**Ætiology and Pathology.**—This inherited malady is possibly a bullous variant of dyskeratosis follicularis.

Histologically there is acantholysis, the detachment occurring in the stratum mucosum.

**Clinical Picture.**—Benign pemphigus resembles a very resistant infective dermatitis. The lesions are flexural or at sites of friction such as the collar line, axillary folds and groins; and they consist of erosions covered by greasy scaling. The patient complains of a tendency to chafing of the skin at sites of pressure from clothes and there is a history of a similar condition in other members of the family.

**Course and Prognosis.**—The course is chronic, with occasional remissions which

bear no relation to treatment, seasons or any other known cause. Regarding length of life the prognosis is good.

**Diagnosis.**—From infective dermatitis the condition is recognised by its chronicity and by the characteristic histology.

**Treatment.**—There is no effective treatment. The lesions should be covered with calamine liniment to which may be added 1 per cent. of ichthammol or 0.1 per cent. of pyrogallol. Antibiotics may be used for any serious degree of secondary infection. Clothing should be soft and smooth and loosely fitting. A dusting powder containing zinc oxide and zinc stearate may, by giving "slip", help to prevent the development of lesions.

### EPIDERMOLYSIS BULLOSA

This inherited malady occurs in two forms, the simple and the dystrophic. The skin is vulnerable to minor traumata and to sunlight.

**Ætiology and Pathology.**—The cause is a genetic fault.

The histology differs in the two forms. In the simple form, clefts occur in the epidermis but in the dystrophic form they are in the dermis and scarring and loss of tissue often result, with the formation of epidermal cysts.

**Clinical Picture.**—In the simple form the infant is noticed to blister easily at sites of trauma, especially the hands and feet, elbows and knees, shoulder and buttocks. In milder forms this phenomenon may not be apparent until later in life, and serious blistering may only be noticed when the individual starts soldiering.

In the dystrophic form the disruption of the dermis is so severe that scarring and deformity often result. In particular the nails are likely to be shed, and the new nails are dystrophic and irregular. Ectodermal defects of the hair and teeth may also be present and erosions occur on mucous surfaces as well as on the skin.

**Course and Prognosis.**—The course is uninterrupted and there are no remissions. The condition interferes considerably with the patient's activities.

**Treatment.**—There is no effective treatment. The aim should be the avoidance of traumata likely to cause blistering. Special care is necessary in the choice of clothing, particularly shoes, and the sufferer cannot join in many of the activities usually indulged in by the young. Blisters should be dealt with by careful puncture and antibiotics applied if infection occurs.

## SCLERODERMA AND ALLIED CONDITIONS

Sclerosis is a condition in which collagen undergoes inflammatory fibrotic changes proceeding to a terminal atrophic phase. If the skin seems to be the only organ affected the term scleroderma is appropriate; but when one or more internal organs are affected the term systemic sclerosis is more suitable.

### CIRCUMSCRIBED SCLERODERMA

**Clinical Picture.**—Circumscribed scleroderma (morphœa) presents as an itchy, round, oval or irregular, firm, pale or skin-coloured, smooth candle-wax-like plaque with a lilac halo. There may be one or several of such lesions and, when numerous, there is a marked tendency to symmetry. A variant is morphœa guttata.

**Ætiology and Pathology.**—The cause is unknown. Adults are affected more than children, and women more than men.

**Histologically,** there is an early inflammatory stage in which the collagen bundles are swollen, homogeneous and separated by œdema, the fat and elastic tissue degenerate or destroyed. There is a lymphocytic infiltrate. Later, the infiltrate diminishes and the collagen of the dermis is seen to be thickened and condensed. The blood

vessels of the dermis and hypoderm show similar changes. The pilosebaceous follicles disappear but the sweat glands usually persist.

**Course and Prognosis.**—Clinically, the lesions may cease to itch and end in moderately atrophic plaques. This form, whether solitary or multiple, seems to be unrelated to systemic sclerosis. In the severest forms bullæ may develop owing to lymph stasis.

**Diagnosis** is from lichen sclerosus et atrophicus, vitiligo, paraffinoma, leprosy (*q.v.*).

**Treatment.**—There is no specific treatment. A bland application such as unguentum aquosum to make up for the secondary sebaceous deficiency is often comforting. Sedatives may be required for severe itching.

### SYSTEMIC SCLEROSIS

**Ætiology.**—The cause is unknown. The disease occurs almost exclusively in women, and usually starts before the age of 40.

**Pathology.**—The changes in the skin are similar to those in circumscribed scleroderma. In the gut there are areas where the muscularis is replaced by fibrous tissue. There may be invasion of the myocardium and skeletal muscles by connective tissue with atrophy of muscle fibres. The alveolar walls in the lungs may be infiltrated by fibrous tissue, and the capillary loops of the kidney often show fibrinoid degeneration.

**Clinical Picture.**—This is usually a very slowly progressive disease in which the early manifestations are due to involvement of the skin and subcutaneous tissue; later there is often evidence of visceral involvement. The earliest changes in the skin are thickening and non-pitting œdema, but this stage may be absent. Later there is induration so that the skin cannot be pinched up, and finally there is atrophy involving also the subcutaneous tissue, when the skin is bound down to the deeper structures.

The onset is usually insidious, starting in the hands with Raynaud's phenomenon or aching, stiffness and swelling of the fingers. If Raynaud's phenomenon is the first symptom it is usually followed in a few weeks by swelling and limitation of movement, but occasionally there is an interval of many years. There is a gradual extension over several years to the forearms, face and chest. Later the feet and legs may be affected, and rarely the whole body. The onset is sometimes more rapid, the evolution taking about a year. Rarely the disease may start in the face and trunk, sparing the hands.

The fingers are pointed, with wasting of the pulps of the terminal phalanges, the nails curved, the skin is shiny, thin and tightly bound to the deep fascia causing limitation of movement; there may be painful fissures and ulcers, and areas of superficial gangrene. The face is expressionless, with loss of the natural creases; the nose is pointed, the mouth pinched and the lips thin and puckered. The skin of the limbs and trunk is thickened and difficult to pinch up. There is limitation of movement of the joints within the affected area. There is often diffuse dark brown pigmentation of the skin, and sometimes telangiectasia. Subcutaneous nodules of calcinosis may be found, especially in the fingers and near the elbow joints. The skeletal muscles may be weak and wasted.

Visceral involvement is often discovered by special investigation in the early stages, and as the disease progresses symptoms may be produced, cough and dyspnoea from pulmonary lesions and dysphagia and constipation from alimentary lesions are common. Heart failure may be caused by myocardial lesions or by the pulmonary fibrosis. The spleen and lymph glands may be enlarged. Albuminuria may be found, but renal failure is rare.

**Special investigations.**—Radiography of the hands almost invariably shows re-

sorption of the tufts of the terminal phalanges and there may be subcutaneous deposits of calcium. Radiography of the chest may show reticulation due to pulmonary fibrosis, or areas of pneumonia due to aspiration from the œsophagus; there may be hypertrophy of the right side of the heart and the electrocardiogram may be abnormal. Radiological investigation of the gastro-intestinal tract is often abnormal; in the œsophagus fibrous stricture, dilatation, absence of peristalsis and hiatus hernia have been described; diminished peristalsis, dilatation and diverticula have been seen in the small and large intestine.

**Course and Prognosis.**—Rarely there is rapid evolution of the disease with death in a few months. More usually the disease is slowly progressive without remissions, with increasing disability from Raynaud's phenomenon, painful, indolent fissures of the fingers, limitation of movement of the fingers, wrists, elbows and shoulders, increasing dyspnoea and perhaps dysphagia. Death occurs in 5 to 10 years from inhalation broncho-pneumonia, heart failure or renal failure. The disease may become arrested, leaving the patient with residual deformities due to fibrosis.

**Diagnosis.**—In the early stages the aching and swelling of the fingers may suggest rheumatoid arthritis, and Raynaud's phenomenon has to be distinguished from Raynaud's disease.

Pulmonary involvement may be confused with bronchiectasis, pigmentation with Addison's disease and œsophageal involvement with cardiospasm.

**Treatment.**—Local applications such as compound tincture of benzoin in lanoli may be necessary for the painful fissures of the fingers. Raynaud's phenomenon should be treated in the same way as Raynaud's disease; if it is severe, cervical sympathectomy is justifiable, although it has no influence on the course of the disease.

Corticotrophin and cortisone may produce a temporary improvement in the œdematous stage, but has no effect on the fibrotic lesions, and it does not appear to have any effect on the ultimate prognosis.

### DERMATOMYOSITIS

**Ætiology.**—The cause is unknown. Males and females are equally affected; the disease usually starts between the ages of 20 and 40. Some cases have been associated with carcinoma of the lung and other organs.

**Pathology.**—In the skeletal muscles there is parenchymal degeneration with an interstitial inflammatory reaction; there is proliferation of nuclei of the muscle fibres and loss of the normal cross-striations; in the interstitial tissue there is a variable infiltration with lymphocytes, histiocytes, plasma cells and fibroblasts. Later there is replacement fibrosis of the muscles. Similar changes may be found in the myocardium. In the dermis the collagen fibres may be swollen and homogeneous, and there is a perivascular infiltration with lymphocytes and other cells.

**Clinical Picture.**—The onset is usually insidious but may be acute. The early symptoms are muscular pain and weakness, or subcutaneous œdema and erythema. Occasionally Raynaud's phenomenon is the first symptom. There may be generalised involvement of skeletal muscles from the start, or the disease may begin in the limbs and spread to the trunk. The neck, shoulder and pelvic girdle muscles are most affected. The muscles are painful, tender and weak; they feel indurated and later hard and fibrous.

There is limitation of movement because of inability of the muscles to stretch. The tendon jerks are diminished or absent. Dysphagia, dysphonia and dyspnoea are common from involvement of the pharynx, larynx, intercostal muscles and diaphragm. Facial weakness and diplopia may be found.

Skin changes are rarely absent, and may be persistent or transient. The commonest change is a firm subcutaneous œdema, which may be generalised but is usually confined to the face and limbs. There may be a diffuse, mottled, purple

erythema, not necessarily coextensive with the œdema or the muscles involved, which is usually confined to the face and limbs. Later there may be areas of pigmentation and atrophy of the skin, usually on the backs of the hands, elbows, knees or face. Stomatitis with œdema, redness and crusted erosions, alopecia and subcutaneous calcinosis may be found. Less common features are Raynaud's phenomenon, paræsthesiæ of the fingers and enlargement of the spleen, liver and lymph glands. The temperature is usually normal or only slightly raised.

*Special investigations.*—Creatinuria is constantly found. The radiograph of the chest may show enlargement of the heart and the electrocardiogram is occasionally abnormal. Albuminuria is found in about half the cases.

*Course and Prognosis.*—The course is often indicated by the onset; when the onset is acute the course is likely to be rapidly fatal; when the onset is insidious complete or partial remission is probable. The muscular weakness progresses, steadily or with remissions, in extent and degree. About half the patients die in a few months to 5 years of broncho-pneumonia or respiratory paralysis. Occasionally death is due to heart failure. At any stage the disease may become arrested or regress, leaving permanent incapacity from limitation of movement, and residual changes in the skin of sclerodermatous thickening. A few patients recover completely.

*Diagnosis.*—The skin lesions have to be distinguished from scleroderma, disseminated lupus erythematosus, and poikiloderma atrophicum vasculare. Oedema of the face with muscle pain may mimic trichiniasis. If weakness is the outstanding feature, polyneuritis and myasthenia gravis have to be excluded.

*Treatment.*—Dysphagia and respiratory paralysis are the chief causes of death; they may require treatment by gastric intubation, pharyngeal suction and artificial respiration as in acute anterior poliomyelitis.

Physiotherapy is necessary to prevent and correct deformities. Corticotrophin or cortisone may arrest the progression of the disease and produce a complete remission.

### SCLERØDEMA ADULTORUM (BUSCHKE)

This is a condition in which œdema and induration develop in the skin and hypoderm, usually after a period of fever. It starts on the head and spreads over the neck and trunk. Serous effusion into the pericardium, pleura and joints may occur but the disorder is self-limited, clearing up after a few months to a year.

*Ætiology and Pathology.*—The cause is unknown.

Histologically, there is swelling of the collagen with interstitial œdema and a slight perivascular inflammatory infiltrate.

*Treatment* is symptomatic and supportive.

### SCLEREMA

Two types of this malady occur.

In the *generalised form* (sclerema neonatorum) the skin all over the body is waxy, hard, cold and pale or livid. The temperature is subnormal. Death may occur within the first week or two after birth but milder forms occur from which the infant may recover.

*Ætiology and Pathology.*—The olein content of the fat is diminished, giving the body fat a higher melting point, with the result that solidification occurs at ordinary temperatures.

Histologically there is crystallisation of the hypodermal fat, with an inflammatory infiltrate of foreign body giant cell type, ending in fibrosis.

In the *nodular form* (lipophagic granuloma) the histological features are the same but the process is localised and self-limited, the hard areas disappearing in a few months. This form may affect adults and clinically resembles morphaea or paraffinoma (q.v.).

*Diagnosis is usually made on histological grounds.*

*Treatment.*—There is no effective treatment.

## ATROPHY OF THE SKIN

This occurs in the ageing skin but, to a greater extent in areas exposed to light than in those not so exposed. In its simplest form, in covered areas, there is thinning and loss of elasticity, giving a yellowish, wrinkled and tissue-papery appearance and texture. Histologically there is thinning of the epidermis with a flattened epidermo-dermal junction. The dermis is also thin and shows collagenous atrophy; the hypodermic fat is also less marked. At sites exposed to light, degeneration of the collagen and of the elastin are more marked, both becoming basophilic and the latter being fragmented and forming irregular clumps.

*Senile elastosis* ("peasants' skin") is a leathery thickening with marked furrowing, occurring especially on the back of the neck (*cutis rhomboidalis nuchæ*). Histologically there is an apparent increase of elastic tissue with degenerative clumping, swelling and fragmentation of its fibres.

"*Glossy skin*" (*atrophyderma neuriticum*) occurs in conditions such as leprosy where there may be interference with the nerve supply to a part.

*Pressure atrophy* occurs at sites of continuous pressure, for example under the pads of trusses.

*Vulvar atrophy* (senile atrophic vulvitis) may cause stenosis of the vaginal orifice (*kraurosis vulvæ*). The mucosa is dry, shiny, smooth and pale, or there may be patchy telangiectasia and pigmentation. Leucoplakia (mucosal hyperkeratosis) and even squamous carcinoma may be the final outcome. Histologically the epidermis is thinned, the collagen and elastin degenerated, the blood vessels sclerosed and there may be lymphœdema of the upper dermis, even going on to bulla formation.

*Macular atrophy* (round and oval atrophic patches, particularly on the trunk) may be an idiopathic condition or a manifestation of past secondary syphilis. It may also occur in leprosy, lupus erythematosus, as a later stage of morphea, or as a part of the condition known as *acdermatitis chronica atrophicans*. The idiopathic form has two varieties, one preceded by inflammation (*Jadassohn*), the other (*Schweninger-Buzzi*) having no earlier inflammatory stage. Diagnosis is from von Recklinghausen's disease. In both conditions there are hernia-like orifices and grape-like swellings in the skin but in macular atrophy the other features of von Recklinghausen's disease (*q.v.*) are absent.

*Macular and striate atrophy* is seen in the condition sometimes called "*striæ cutis distensæ*", or "*striæ gravidarum*". This linear form of atrophy chiefly affects the breasts, abdomen and thighs of pregnant women but is also seen in Cushing's syndrome and in some fat young people of either sex. It is believed that in all cases an endocrine factor is responsible, distension by itself not causing this condition, as is clear from observation of fat persons. The atrophic areas may be pink or purple when fresh; skin-coloured and more fibrotic when older.

*Atrophyderma reticulatum* is a condition of pinhead-sized atrophic ridges separated by narrow ridges of normal skin. It occurs on the cheeks, is of unknown cause and is untreatable except by cosmetic camouflage.

*Acrodermatitis chronica atrophicans* is a disease which is rare in the British Isles and much more common on the Continent of Europe. As the name implies, it affects mainly the extremities where the skin is brownish-red and swollen, later becoming atrophic and wrinkled, with subcutaneous veins clearly visible. One or more limbs may be affected. Usually fibrotic nodules and bands are present over the subcutaneous surface of the ulna or of the tibia. Histologically there is hyperkeratosis, thinning of the rest of the epidermis, and œdema and degeneration of the collagen, with a



band-like infiltrate of lymphocytes under the epidermis but separated from it by a thin band of relatively normal collagen. There is also a perivascular infiltrate. The hair papillae and sebaceous glands are atrophic but the sweat glands survive under the thinned dermis. The hypodermic fat is atrophic. The cause of the malady is unknown. It goes on from an early inflammatory and swollen stage to a later atrophic stage but it has no effect on length of life. Diagnosis is from the "main succulente" of syringomyelia (by the absence of neurological signs); from erythromelalgia (by the absence of pain and warmth). Treatment is empirical. Systemic penicillin has a reputation for bringing about an early remission.

*Poikiloderma*.—This is a condition of the skin in which telangiectasia, pigmentation, depigmentation and atrophy are intermingled. It is an atrophic precancerous process.

**Ætiology and Pathology.**—*Poikiloderma* occurs after excessive solar or X-irradiation. It also occurs in an idiopathic form (*poikiloderma vasculare atrophicans* of Jacobi-Lane) which may terminate in cutaneous reticulosis with tumour formation. *Poikilodermato-mycosis* is an atrophic end stage of certain cases of *dermatomyositis*.

The epidermis is atrophic, and statically dilated blood vessels are present in the atrophic dermis.

**Course and Prognosis.**—All cases have to be watched for the development of keratoses or squamous carcinomata, or in the idiopathic form for reticulosis or *mycosis fungoides*.

**Diagnosis.**—The irradiation forms are usually easy to recognise from the history and situation. The idiopathic form may occur with lichenoid papules on the trunk and with parapsoriasis-like patches in addition to the *poikiloderma*.

**Treatment** is by bland local applications, for example, hydrous ointment, and by appropriate action if malignancy occurs. For cosmetic purposes the telangiectasia may be lessened by a touch with the galvano-cautery or a suitable cover cream may be applied to mask the lesion.

*Poikiloderma atrophicans vasculare* (Jacobi-Lane).—This is a rare disorder of lichenoid papules, with *poikiloderma* (pigmentation, depigmentation, telangiectasia and atrophy). The skin is dry and itchy. The disorder is slowly progressive and may end in cutaneous reticulosis with tumour formation.

Diagnosis is from radiodermatitis, systematised lupus erythematosus and *dermatomyositis*. In radiodermatitis there is a history of irradiation; in lupus erythematosus (*q.v.*) there are cytological and serological changes; and in *dermatomyositis* there are muscle pains and creatinuria.

*Lichen sclerosus et atrophicus* (see p. 1279).

*Pseudo-xanthoma elasticum*.—This is a congenital abnormality consisting of a defect of the elastic tissue in the skin, of the elastic membrane of the retina and of the elastic tissue of the arteries. The eye changes cause angioid streaks due to defects in Bruch's membrane. The skin lesions consist of yellow papules and plaques, particularly around the neck, tending to have a linear arrangement. Histologically there is a patchy increase of elastic tissue, with fragmentation and clumping in the deeper parts of the dermis. This degenerate elastin stains with basophilic dyes. The collagen is normal. The histological picture resembles senile elastosis but the latter is more diffuse and the collagen is also degenerate. On clinical grounds the conditions are not likely to be confused.

*Cutis hyperelastica* (Ehlers-Danlos syndrome).—This is a congenital abnormality in which there are hyperelasticity of the skin, hyperflexibility of the joints, scarring over the elbows and knees, and soft polypi which result from injury and hæmorrhage into the over-stretchable skin. Histologically the elastic tissue is increased in amount and the fibres are coarse. The collagen is atrophic and disrupted. The polypi consist of collagen fibres with a foreign body giant cell reaction. The patient shows double-jointedness, and is able to stretch the skin excessively. Grape-like swellings

are present and there is extensive atrophic and pigmented scarring over the elbows and knees. Treatment is protective only.

## HYPERTROPHY OF THE SKIN

A *corn* (clavus) is a localised reactive hypertrophy, the result of intermittent pressure and friction. Histologically there is a dense hyperkeratosis with an acuminate downgrowth which presses the stratum mucosum down towards the dermis. The stratum mucosum becomes thinned and atrophic. Under the dermis there is often a bursa—a lymph space containing serous fluid. Abacterial or bacterial inflammation may occur, the latter sometimes with suppuration. Corns most commonly occur on the upper surfaces of the toes, particularly the small toes. Sometimes they occur between the toes and owing to maceration are known as "soft" corns. In this situation, exostosis and fungous infection should be excluded as the cause. Diagnosis is from warts by the fact that the latter either have a papillated surface or at least show a break in continuity of the epidermal lines of the skin. Plantar warts may become buried under an hyperkeratotic cap. Prevention is the ideal, by suitable footwear. Treatment consists of well-fitting shoes and hose, and paring of the excessive horny matter. A salicylic acid plaster previously applied renders this procedure easier. Recurrence is likely unless further pressure or friction is avoided.

*Callosities* are diffuse thickenings of the horny layer without downgrowths such as occur with corns. Callosities are due to excessive weight-bearing, as in obesity or from unnatural stresses as in pes planus. They may also arise from roughened shoe linings, and at innumerable sites in different occupations from intermittent friction and pressure (for example, in gardeners, boatmen, housewives, cobblers, etc. etc., as occupational stigmata). *Bursæ* may form beneath the thickened, firm, inelastic skin which has a yellowish, dirty appearance with a shelving edge, and is painless. Callosities are liable to undergo fissuring from which infection may result.

*Tylosis* is a congenital hyperkeratosis of the palms and soles, dominant in its inheritance. The hard, thickened skin cracks easily in the winter and becomes macerated and offensive in the summer. The condition can be alleviated by 5 per cent. salicylic acid ointment.

*Keratoderma climacterium* affects the palms, soles and heels, and sometimes the knees of menopausal women, usually obese. There is much horny thickening at these sites and painful fissures tend to form around the heels. Treatment is by œstrogens by mouth and salicylic acid ointment 2 to 5 per cent. locally. It is advisable to reduce the patient in weight by a stone or two in the course of a few months, if possible.

*Keratoderma punctatum* occurs in two forms, one hereditary but occurring in early adult life, the other apparently acquired and related to keratin stimulants operating around the sweat ducts. On the palms (and sometimes on the soles) are discrete conical or rounded excrescences of dense keratin with central puncta. The condition is resistant to treatment but a 5 per cent. salicylic acid ointment may help to soften the lesions.

*Arsenical keratosis* (due to the ingestion of Fowler's solution) affects the palms with pinhead lesions although the soles may show larger excrescences. Dirty grey keratoses and basal cell carcinomata may be present on the trunk and there may be raindrop depigmentation and pigmentation.

*Keratoderma blenorrhagica* is an hyperkeratotic condition of the palms and soles and of the skin around and beneath the nails in which thick, limpet-like scaling and crusting occurs. The condition is accompanied by urethritis, polyarthritis and conjunctivitis. The urethritis may be gonococcal or nonspecific. Local treatment is with keratolytics.

*Porokeratosis of Mibelli* is a congenital hyperkeratosis affecting in particular the

sweat duct ostia. The lesions are grey or brown, warty elevations which spread peripherally, leaving a depressed, scaly, atrophic centre. Treatment is by cautery destruction.

*Warty hard or epidermal naevi* usually present as linear bands of itchy, brown, warty, cracked and bleeding skin. The condition is unilateral, affecting the whole or part of a limb, one side of the vulva, or the side of the neck or trunk (ichthyosis hystrix, *nævus unius lateralis*, linear *nævus*). Histologically there is hyperkeratosis and papillomatosis but *nævus* cells are not present in the dermis. Warty *nævi* are present at birth or develop at any time up to puberty and persist indefinitely. Epithelioma may become superimposed. Treatment is by protective dressings but if the lesion itches badly and tends to become excoriated and infected it is best excised and the area grafted.

*Lichenification* is hypertrophy of the stratum mucosum (see Lichen Simplex).

*Cutis laxa* is an hypertrophy of the skin and subcutaneous tissue with lax attachment to the deeper structures, with the result that the skin hangs in folds. One variety is *cutis verticis gyrata*, a cerebriform folding of the scalp, sometimes congenital, sometimes seen in acromegaly.

## DEGENERATIVE CONDITIONS

### XANTHOMATOSES

*Xanthoma tuberosum*.—This is a familial hypercholesteræmic xanthomatosis in which yellow nodules develop on the extensor surfaces of the elbows and knees, the buttocks and elsewhere. In the folds of the palms and soles there may be yellow streaks (*xanthoma planum*). Internal organs are also affected, particularly mucous surfaces, the tendons, the endocardium and the intima of blood vessels. Numerous *xanthoma* (foam) cells are seen in the dermis. These are phagocytes containing lipid material. The cutaneous lesions are of no importance in themselves but the associated vascular lesions may cause death through coronary occlusion.

The patient should be put on a diet with a small fat, vitamins A and D content. By this means, after several months, the skin lesions may become smaller. The aim of the treatment is to bring about a similar regression in the vascular lesions. Lesions identical to those of *xanthoma tuberosum* also occur with biliary cirrhosis, but in this condition the lesions are preceded by jaundice for months or years.

*Secondary xanthomatosis* consists of yellowish-red transitory, itchy papules, which consist of foam cells with an inflammatory reaction. The condition is brought about by hypercholesteræmia and occurs in primary xanthomatosis, diabetes mellitus (*xanthoma diabetorum*) and biliary cirrhosis; also in hypercholesteræmia sine *xanthoma tuberosum*. Treatment is of the primary condition.

*Cholesterol histiocytoses* are normocholesteræmic conditions; reticuloses with secondary cholesterol depositions. Letterer-Siwe's disease is the infantile form, in which petechiæ, papules and pustules are observed and in which fever, anæmia, liver, spleen and lymph node enlargement occur with multiple bony defects. The condition is fatal before lipid deposits develop in the skin.

In the Hand-Schüller-Christian disease there may be diabetes insipidus, exophthalmos, dwarfism, enlargement of liver, spleen and lymph nodes and bony defects. The skin condition consists of yellowish macules and nodules with greasy, overlying scales, giving a resemblance to a mild infective dermatitis. It tends to affect the scalp, face and the flexures. Petechiæ may also be present. Histologically there are numerous histiocytes and some foam cells.

*Eosinophilic granuloma*.—This is a localised form of the same syndrome, affecting chiefly the bones. Sometimes the skin is affected with *granulomata* which tend to

ulcerate. Histologically there are many histiocytes and an infiltrate in which eosinophil cells preponderate.

*Xanthelasma palpebrarum*.—In this condition there are flat or slightly raised depositions of cholesterol in the skin of the eyelids, secondary to degenerative changes in the tissues. The blood cholesterol may be normal or raised. Sometimes there is diabetes but more often this is not so. Under local anaesthesia the lesions can be destroyed with the cautery or the skin can be excised and left to heal without stitching.

*Juvenile xanthoma* (naevo-xantho-endothelioma) presents as one or several yellowish, obtuse nodules on the limbs or on the neck and trunk of infants in the first year or two after birth. The lesions regress spontaneously after a few years. Histologically histiocytes containing fat (foam cells) are numerous with foreign body giant cells; and there is proliferation of the vascular endothelium. The blood cholesterol is normal.

### GRANULOMA ANNULARE

*Granuloma annulare* is a nodular, non-itchy eruption in the skin, tending to form ringed lesions. The cause is unknown. Histologically there is a focal degeneration of the collagen giving it a ground-glass appearance. Around this area is an infiltrate of histiocytes, lymphocytes and fibroblasts. There is a deposition of mucin between the collagenous bundles. The elastic tissue is degenerate. A few epithelioid cells and foreign body giant cells may be present. Children and young adults are mostly affected. The mildest cases occur on the knuckles, elbows or feet as skin-coloured, painless and non-itchy nodules without epidermal changes. Soon the nodule takes on a ringed shape or may extend in one direction and resolve in another, so causing crescentic lesions. A few patients have extensive and numerous lesions on the shoulders, buttocks and elsewhere, as well as at the more usual sites.

The lesions tend to continue indefinitely or may disappear without scarring at one site, only to break out elsewhere. They are, however, not known to be of any systemic importance and are consistent with good general health.

Diagnosis is from periarthritis nodosa, annular sarcoid, tinea circinata and necrobiosis lipoidica (*q.v.*). Nodules of the first-named are painful. The second is usually erythematous and not characteristically situated on the knuckles. The third is an epidermal, ringed eruption with scaling.

*Granuloma annulare* tends to disappear after minor trauma has been applied. Adhesive dressings, carbon dioxide snow or slush applications, or biopsy may all have this effect. Treatment is unnecessary except on cosmetic grounds. There is no effective systemic treatment.

### ERYTHEMA ELEVATUM DIUTINUM

*Erythema elevatum diutinum* occurs as the Bury type or as the Hutchinson type. The Bury type is a firm, raised, dusky disc or ring of erythema. It may represent the end stage of granuloma annulare. The Hutchinson type consists of many firm nodules in a dusky background, scattered widely over the trunk and limbs. The lesions urticate on friction, heat or excitement. They persist indefinitely and end up as fibrous nodules. The cause of the Bury type is unknown. The Hutchinson type may arise from the persistent effects of an urticariogenic antigen leading to a refractory phase of the vessels so that damage occurs to the vessel walls. Histologically in the Bury type there is a dense dermal, mainly neutrophilic, infiltrate especially around the vessels. Sometimes eosinophils predominate (one form of eosinophilic granuloma). In the Hutchinson form a hyaline degeneration of the reticular fibrils around the vessels may be seen (toxic hyaline). Later, fibrosis replaces the inflammatory process.

Both conditions are chronic, but the Hutchinson type is of more serious import because of the distressing itching and smarting.

Treatment is symptomatic and largely ineffective. In the Bury form, carbon dioxide snow is worth a trial. In the Hutchinson form, antihistamine drugs may reduce the itching and urtication.

### NECROBIOSIS LIPOIDICA

*Necrobiosis lipoidica* is a condition in which lipoid deposition occurs in areas of degenerate or necrobiotic collagen. Diabetes mellitus is often present or may subsequently develop. Ill-defined areas of poorly staining, somewhat basophilic collagen are present in the dermis. The collagen bundles are disorderly and disrupted. In and around the area is an infiltrate of lymphocytes, histiocytes and fibroblasts. A few epithelioid and foreign body giant cells may be seen, and sometimes foam cells. The blood vessels show fibrosis and endothelial proliferation, often with thromboses. Stains for fat show much extracellular lipoid material.

The lesions usually appear on one or both shins but are occasionally seen at the ankles, on the feet or hands, or elsewhere. They consist of slightly depressed plaques of shiny atrophic, waxy yellow skin, with well-defined margins and dilated venules showing clearly. The centre may ulcerate. On the hands the appearance differs, the lesion resembling granuloma annulare.

The malady often becomes inactive after a time but it never regresses. Diagnosis is from other atrophic conditions and from granuloma annulare. In the latter, the histological changes are very similar but more focal and vascular changes are not visible. Mucin deposits are found but no lipoid, as in necrobiosis. There is no effective treatment.

### AMYLOIDOSIS

*Amyloidosis* can affect the skin in three ways: primary systemic amyloidosis; primary cutaneous amyloidosis (lichen amyloidosis); secondary systemic amyloidosis.

Primary systemic amyloidosis affects the skin, particularly of the face, with non-itchy, waxy, yellowish, semi-translucent nodules and plaques. Petechiae may be present. In addition there is extensive involvement of voluntary and involuntary musculature, the cardiovascular system and the gastro-intestinal and genito-urinary tracts. Macroglossia occurs. There may be multiple myelomata and Bence Jones proteinuria. Radiographic examination of the bones and sternal biopsy are helpful in diagnosis.

Amorphous deposits of amyloid are scattered throughout the dermis. In secondary systemic amyloidosis the skin is very rarely affected. In primary cutaneous amyloidosis the lesions usually occur on the legs as very itchy lichen planus-like nodules—conical, brownish or violaceous verrucose lesions which may coalesce to form large plaques. Deposits of amyloid are present in the upper dermis. There is no effective treatment.

### CALCINOSIS

*Calcinosis cutis* may be the result of hypercalcaemia due to hyperparathyroidism, excessive vitamin D (calciferol) therapy, chronic kidney disease or gross destruction of bone as in osteomyelitis or malignancy. The skin is rarely affected, most deposits occurring in the kidneys, lungs or stomach. Far commoner is normocalcaemic calcinosis cutis secondary to some degenerative process in the skin, hypoderm, muscles or tendons. Scleroderma or dermatomyositis are often present but sometimes no cause can be found. The depositions mostly take place in the fingers, wrists, elbows and feet, and can be felt as hard masses bulging the skin, often white and sometimes ulcerating. Treatment is of the primary condition when this is possible.

## GOUT

*Gout*.—In this disorder of purine metabolism, white nodules due to deposits of urates (tophi) are found in the cartilage of the ears and in the subcutaneous tissues around joints, particularly the metacarpophalangeal joints of the great toes.

## MYXÆDEMA

*Myxædema*.—In generalised myxædema the skin is dry, pale and thickened. In circumscribed (cutaneous) myxædema, which occasionally develops after operations on the thyroid or with thyroid adenomata, firm, raised, dome-shaped, waxy, skin-coloured or yellowish nodules and plaques form, mostly on the anterior aspects of the legs, sometimes also on the face or arms. Histologically the lesions contain a large amount of mucin. Treatment is ineffective.

## EPIDERMAL TUMOURS

## BASAL CELL PAPILLOMA (SENILE OR SEBORRHŒIC WART)

Basal cell papillomata are light to dark-brown, roughly papillated excrescences with non-infiltrated bases and a greasy candle-wax texture. They occur with increasing frequency after the age of 40 and affect especially the scalp, the face and the trunk. They can easily be scraped off, exposing a raw fleshy base.

*Ætiology and Pathology*.—Their cause is unknown. They are believed by some to be infective; by others to be a late *nævroid* condition.

Histologically there are small epithelial cysts, due to invagination of the epidermis. There is also acanthosis, with prolonged rete ridges. The dermis shows little inflammatory reaction.

*Course and Prognosis*.—These lesions are benign but they may become secondarily infected.

*Treatment*.—For small, superficial lesions, brief (1 second) applications of carbon dioxide snow are effective. Larger lesions are best dealt with by curettage and cautery under local anaesthesia.

## SQUAMOUS CELL PAPILLOMA (JUVENILE OR INFECTIVE WART; VERRUCA)

*Ætiology and Pathology*.—Warts are infective epidermal tumours caused by a virus. They are auto-inoculable and may appear in linear form in scratch marks. They are commonest in childhood and young adults, though elderly persons may be affected.

Histologically there is focal acanthosis and gross hyperkeratosis with a variable degree of inflammatory infiltrate in the dermis. The epidermo-dermal junction is intact with no evidence of invasion of the dermis. Mitoses may be numerous.

*Clinical Picture*.—Warts are described on a morphological basis as plane, acuminate, filiform, digitate, etc., and from their situation as genital, plantar, etc. On the scalp they tend to be digitate; in the beard area filiform; on the faces of children plane; on the hands and knees grey-brown circular excrescences (common warts, *verruca vulgaris*), except around or under the nails where they may resemble hangnails or corns, with considerable discomfort. On the genitalia warts are usually acuminate (*condylomata acuminata*) and on the soles of the feet they are painful, inverted, embedded in hyperkeratosis and perhaps confluent in a mosaic pattern.

*Course and Prognosis*.—This is extremely variable. Warts may disappear

without treatment or they may spread. They are amenable to suggestion in a proportion of cases. They may recur even after the most careful curettage.

Diagnosis may have to be made from one or other of keratosis, corn, callus, molluscum contagiosum, molluscum sebaceum, squamous carcinoma, papillary mole or naevus, subungual exostosis, acanthosis nigricans, condyloma latum, verrucose lichen planus and lupus verrucosus (*q.v.*). Histological examination is sometimes necessary.

**Treatment.**—A waiting policy is sometimes justifiable because a proportion of warts disappear spontaneously. On the scalp and beard area a combination of curettage and cautery is best. Plane warts on the face or hands may be dealt with by daily applications of 1 per cent. brilliant green in collodion salicylic acid: fractional X-ray exposures are sometimes used but simple suggestion may prove just as effective.

On the hands, if suggestion and local keratolytics and caustics fail, recourse may be had to curettage and cautery under local anaesthesia, or to carbon dioxide snow applications 30 to 90 seconds on each occasion, depending on the size and situation of the lesions, at intervals of 2 to 3 weeks. Carbon dioxide snow is especially useful for paronychia and subungual warts because it causes less deformity than curettage and cautery.

On the genitalia, podophyllin 20 per cent. in liquid paraffin is the treatment of choice. The application is made on gauze to the penis or vulva. It is applied at bedtime and removed on rising, the affected area being cleaned with liquid paraffin. A similar application is made the next night but after this at least a week should elapse before any further treatment of this sort is given. Podophyllin causes a brisk inflammatory reaction after which all or most of the warts are shed. A second course of treatment a week later may dispose of the remnants. Sometimes this treatment fails to relieve extensive vulvar warts and then curettage and cautery under general anaesthesia may be necessary.

Plantar warts may occasionally disappear spontaneously but usually it is necessary to treat them either by caustics, podophyllin 25 per cent., formalin 10 per cent. or by carbon dioxide snow applications, 30 to 90 seconds at each treatment. X-ray treatment is contraindicated; it succeeds in only about 60 per cent. of cases, a success rate equalled by many simpler measures and far exceeded by curettage and cautery. Further, if X-ray treatment fails, the tissue is left to some degree devitalised: repeated X-ray treatment can cause sloughing of the deeper tissues, with much suffering and deformity, and perhaps necessitating grafting.

Curettage and cautery offers something above 90 per cent. prospect of success. The injection of the local anaesthetic is a difficult part of the procedure. For this purpose the patient lies prone on the operating table; this provides flexion of the foot and relaxation of the plantar fascia, and also directs a timid patient's attention away from the field of operation. The injection is made slowly, if possible through thin skin at the side of the foot. After thorough curettage, the horny collarette is trimmed away and the whole area is cauterised.

### MOLLUSCUM CONTAGIOSUM

A virus infection of the skin, characterised by globular, slightly umbilicated nodules.

**Ætiology and Pathology.**—The condition is acquired by direct contact, non-venereal or venereal.

Histologically there is a symmetrical proliferation of the epidermis in oval or pear-shaped lobules with degeneration of the epidermal cells, caused by large cytoplasmic inclusion bodies, homogeneous and eosinophilic, which push the nuclei aside (molluscum bodies). The granular layer is thickened and a mass of horny material forms the central area of the tumour.

**Clinical Picture.**—Pearly, yellow, pink or skin-coloured umbilicated nodules occur singly or in groups. They may occur anywhere on the skin, and transference may take place from the breast of a mother to the face of her suckling, or in the anogenital region during coitus. Secondary infection may cause a lesion to become grossly enlarged, ulcerated and purulent, or necrotic.

**Diagnosis** from warts is made with a hand lens.

**Treatment.**—A phenolised probe or pointed orange stick is forced into each lesion; or the tumours can be curetted off. Antibiotics are ineffective, as a rule, but one or two successes have been claimed.

### EPIDERMAL CYSTS (WENS)

Milia are pinhead-sized white cysts in the epidermis. They are usually multiple and are found with acne or on apparently normal skin on the face; they may also develop over some pathological condition such as epidermolysis bullosa or pemphigoid.

Large epidermal cysts are often found on the scalp, behind the lobes of the ears, on the face, scrotum and elsewhere. A few of them are sebaceous cysts which vary in size from a pinhead to a walnut and show a dimple, representing the follicular opening.

**Ætiology and Pathology.**—Epidermal cysts are possibly derived from the lanugo hair follicles and consist of a whorl of epithelial cells. Sebaceous cysts are believed to be naevoid. They may occur in large groups in *steatocystoma multiplex*. The cysts are lined with squamous epithelium and contain horny and sebaceous material.

**Diagnosis** is from dermoid cyst, lipomata and cystic acne (*q.v.*).

**Treatment.**—The cyst is incised and its odourless contents are expressed. In epidermal cyst this is sufficient but in sebaceous cyst the offensive cheesy contents are first expressed and then the capsule is pulled out with artery forceps. If secondary infection has occurred, it is only possible to incise the cyst, and removal of the capsule has to be deferred until inflammation has subsided.

### DERMOID CYST

These rare tumours occur in the mid line of the body or at the outer end of the brow. They are skin-coloured and not dimpled. The cyst is lined with keratinising cells and may contain rudimentary sweat glands and pilosebaceous follicles as well as layers of keratin, sebaceous material and sometimes hair, cartilage or bone.

**Treatment** is by removal if desired.

### IMPLANTATION CYST

These occur in the skin or more often in mucous surfaces following an injury which carries epidermal cells through a break in the surface.

**Treatment** is by excision.

### BASAL CELL CARCINOMA (RODENT ULCER)

**Ætiology and Pathology.**—The cause of these tumours is unknown. They usually occur in the fifth, sixth or seventh decades but occasionally appear in early adult life. The majority arise in the area enclosed by two lines drawn from the tip of the ear to the eyebrows and from the lobe of the ear to the mouth, but no area of the skin is immune except the palms and soles: rodent ulcers may develop on the scalp, the chest or abdomen, or on the limbs. Apparent precipitating causes include sunlight, heat, mechanical trauma and the ingestion of inorganic arsenic.

Histologically there is a proliferation of basal cells without evidence of invasion,



Globular clumps of darkly staining basal cells are seen. The cells may remain undifferentiated or may show differentiation towards horny or glandular structure (keratotic, adenoid and cystic rodent ulcers). The cellular mass expands horizontally and vertically. If expansion is mostly horizontal (superficial rodent ulcer) the tendency to ulceration is less marked: if it expands vertically the mass finally reaches a size in which the nutrition of its more centrally and superficially placed cells is inadequate and ulceration results.

**Clinical Picture.**—The appearance of rodent ulcers is extremely variable, depending on the situation, superficiality or depth, and presence or absence of ulceration or infection. Types include: (1) the button-like nodule; (2) the pigmented nodule; (3) the rodent ulcer; (4) the superficial type; (5) the cicatricial type; (6) the morphœa-like scalp lesion; (7) the cystic type. Rodent ulcers may be multiple.

The most common form is a pearly nodule which expands to form a button-like tumour with small vessels coursing over its surface. Sometimes the nodule is more globular and cherry-like. It may be skin-coloured, grey or brown. The rodent ulcer may bore deeply from the earliest stages (ulcus terebrans) or a nodule may only start to ulcerate after attaining a certain size, 1 cm. in diameter or more. In the first form there is a slightly raised rolled edge to the ulcerated area. In the latter, the ulceration is at first a relatively inconspicuous feature in the centre of the nodule and gradually extends.

The superficial basal cell carcinoma may be multiple. It usually occurs on the trunk and often there is a history of prolonged medication with Fowler's solution. It has a rolled edge, so slightly elevated that it is not always easy to recognise it except with the aid of a hand lens. The lesion resembles psoriasis, being a circumscribed, irregularly red, oval patch of abnormal scaling, perhaps with some serous crusting in places. The cicatricial basal cell carcinoma is also usually superficial but leaves a scarred and somewhat atrophic skin in the area behind its extending edge. On the upper forehead and scalp basal cell carcinomata tend to develop horizontally and resemble morphœa ("card"-like basal cell carcinoma). Rarely, rodent ulcers are clinically cystic. This type tends to be dome-shaped with a shelving edge and there may be considerable pigmentation.

**Course and Prognosis.**—The course varies according to the situation, depth and amount of differentiation. The superficial type may slowly extend parallel with the surface for many years. The ulcus terebrans erodes early and deeply, with the result that in a year or two important subcutaneous structures may be destroyed. In these cases, death may occur from hæmorrhage or secondary infection. Metastases from basal cell carcinomata are very rare.

**Diagnosis.**—Rodent ulcers must be differentiated from granulomatous and reticulotic conditions, from Bowen's disease and from psoriasis. The long duration and hard, pearly edge, sometimes somewhat serpiginous, usually makes the diagnosis easy. Syphilitic ulcers are of short duration in relation to their size. In some cases the diagnosis is not possible on clinical grounds and reliance has to be placed on biopsy and histological examination. This also applies to the differentiation between recurrences of rodent ulcers and radiation necrosis or ulceration.

**Treatment.**—This consists of surgery with plastic repair when necessary, X-irradiation or radium, or, in a few superficial examples, destruction by carbon dioxide snow. Surgery, to be effective, must include an area of apparently normal skin all round the lesion, at least 0.75 cm. wide. This may be easy in some places, impossible or too disfiguring in others. Surgery is a necessity in dealing with recurrences where further X-irradiation is thought to be inadvisable; it may entail extensive plastic repair.

X-irradiation is best for lesions in situations which render excision difficult. The total dosage used by radiotherapists varies. A total of 3600 r, fractionated so as to give 720 r daily, for 5 days, gives a better cosmetic result than 3600 r at one

treatment. Some prefer a total dosage of 4500 r, claiming that recurrences are less likely, but it is probable that more recurrences are due to insufficient coverage of the apparently normal zone around the lesion than to insufficient dosage. Basal cell carcinomata spread along the lymphatics beyond the visible edge and it is this clinically imperceptible spread that leads to recurrence unless a zone 0.75 cm. to 1 cm. wide is irradiated as well as the visible tumour.

Radium is sometimes more useful than X-rays and can be used as moulded surface applications or as needles or seeds of radon.

Carbon dioxide snow is sometimes used for superficial rodent ulcers on the trunk; applications of 90 seconds' duration are made under firm pressure. The resultant reaction has to be treated like a burn.

## SQUAMOUS CELL CARCINOMA

A tumour which is more rapidly growing than the basal cell carcinoma and which may give rise to metastases.

**Ætiology and Pathology.**—Squamous cell carcinomata are of varying grades of malignancy. Some tend to form horn and are of low malignancy; in others the cells remain undifferentiated and the lesions are more malign.

**Clinical Picture.**—The lesions are firm and nodular with shelving edges, and rapidly ulcerate or form cauliflower-like growths. There is no rolled edge. The sites most often affected include the face, lower lip, ear and the backs of the hands. Squamous carcinomata are usually preceded by one or other of the precancerous conditions mentioned in the next section. They rarely arise on apparently healthy skin; usually the preceding pathological condition is brought about by excessive and prolonged solar irradiation, by past X-ray treatment or by some other physical irritant. Glandular metastases occur early, particularly from the ear, lip or hand.

**Course and Prognosis.**—The lesion extends at first within the dermis and then invades the hypoderm. At this stage spread by the lymphatics to the lymph nodes is more likely. These lesions are, as a result, much more likely to be fatal than are basal cell carcinomata.

**Treatment** is by excision or X-irradiation. On the lip and ear wedge excision offers the best prospects. At other sites, too, surgery is preferable to X-rays because the cells may be relatively radio-insensitive. Sometimes a combination of excision and irradiation is used. Block dissection of the lymph nodes draining the area may be necessary. Biopsy may be performed on skin sites if it is considered necessary but on the vermilion surface of the lip it is inadvisable. Here, V excision should be done and histological study made of the excised material.

## SECONDARY CARCINOMA OF THE SKIN

This occurs by lymphatic spread from a breast cancer or as cutaneous metastases usually from the breast (rarely from stomach, uterus, lungs, prostate or ovary).

In the first form, there is a hard, red but pitting area of skin with a well-marked border (carcinoma erysipelatoides; cancer en cuirasse). It usually occurs in the axillæ or on the chest, perhaps following a radical mastectomy.

The metastatic form occurs as one or several firm, white nodules in the skin, the nature of which may be suspected or only discovered by biopsy.

**Treatment** is symptomatic because the primary lesion may still be present, or other inaccessible secondaries may exist.

## PRE-MALIGNANT AND BORDER-LINE CONDITIONS

Kerato-acanthoma (molluscum sebaceum) is a benign neoplasm of the skin which, though histologically resembling a squamous and horny carcinoma, has a self-limited

natural history ending in spontaneous resolution at about 3 months. Its histological structure is that of a symmetrical and molluscoid squamous horny carcinoma.

Tar warts are possibly a variety of kerato-acanthoma but are more uncertain in their course, some being shed while others go on to carcinoma. Kerato-acanthoma sometimes arises on normal skin whereas squamous carcinomata arise at sites of keratoses and other epidermal abnormalities. The lesion is button-shaped with almost vertical edges whereas in squamous carcinoma the edge is shelving. In the centre of the button is a horny plug. Ulceration does not occur. If nothing is done, the nodule shrinks up and disappears, leaving an irregular crater with thickened lips of epidermis.

**Treatment.**—Thorough curettage of the lesion usually gives a better cosmetic result than X-ray treatment or waiting for spontaneous clearance. If doubt exists as to the diagnosis the lesion should be treated as for squamous carcinoma either by wide excision or by adequate X-irradiation.

### BOWEN'S DISEASE

This precancerous condition may occur on the face, body or limbs.

**Pathology.**—There is an irregular acanthosis, and large cells with dark nuclei and vacuolation of the cytoplasm are scattered through the epidermis. They are similar to the cells seen in Paget's disease of the nipple.

**Clinical Picture.**—The lesions are usually itchy, pink and brown, scaly or papular patches, sometimes slightly exudative, with well-marked but not rolled edges.

**Course and Prognosis.**—If untreated, a termination in squamous carcinoma is likely after an interval of months or years.

**Diagnosis** from superficial rodent ulcer is by the absence of a rolled edge: from psoriasis by the absence of lesions elsewhere, the chronicity of the lesion at one site, the itching and the absence of typical psoriatic scales. From mildly infected eczematous dermatitis the differential diagnosis may be impossible on clinical grounds alone and biopsy is then advisable.

**Treatment** is by carbon dioxide snow, a firm application lasting 90 seconds. This causes an inflammatory reaction, sloughing of the affected area and replacement of the pathological skin by a smooth scar. X-ray treatment may also be used in doses equal to or greater than those used for skin cancers. Sometimes excision is more suitable.

### PAGET'S DISEASE

A pathological condition of the nipple and its ducts, occurring with or soon followed by carcinoma of the nipple ducts.

**Pathology.**—There is parakeratosis with irregular acanthosis and clear "Paget cells" scattered in the stratum mucosum.

**Clinical Picture.**—There is scaling and pinkness of the skin around one of the nipples, with slight palpable thickening. The nipple may be, in part or totally, destroyed in the process or it may be retracted. It is clearly smaller than the other nipple. Lymph nodes are not usually palpable in the axillæ and no abnormality can be felt in the breast.

**Course and Prognosis.**—Carcinoma of the duct coexists with Paget's disease or soon follows it. The malady, if untreated, leads to metastatic carcinomatosis.

**Diagnosis** is from eczema of the nipple. This may be secondary to scabies, or in adolescents and young women it may be a manifestation of the asthma-prurigo syndrome or of neurodermatitis. In either of these conditions, infiltration of the lesions is absent and the nipple is intact and equal in size to the other nipple. Eczema of the breast may also develop from maceration by milk and the use of rubber dress protectors by lactating women.

**Treatment** is by mastectomy. Lymph node dissection is usually unnecessary. X-irradiation is contraindicated.

#### QUEYRAT'S ERYTHROPLASIA

This is a rare condition similar to Bowen's disease but affecting the glans penis or the vulva.

**Clinical Picture.**—There is a clear-cut, shiny, pink, slightly infiltrated and elevated patch.

**Diagnosis** is from psoriasis and chemical balanitis. In doubtful cases biopsy is indispensable.

**Treatment** is by X-irradiation.

#### ACANTHOSIS NIGRICANS

This occurs in a juvenile benign form and in an adult malignant form.

**Ætiology and Pathology.**—The juvenile form is of unknown ætiology, possibly nævoid. The adult form is nearly always associated with a carcinoma, usually of the stomach.

The histology of both types is the same and consists of marked hyperkeratosis and papillomatosis with an irregular acanthosis and hyperpigmentation in the melanoblasts and melanophores.

**Clinical Picture.**—The skin of the flexures is darkened, thickened and lies in velvety folds. In severe cases of the adult form the lips, gums, tongue and œsophagus may also be affected. Clinical examination may reveal evidence of a new growth but sometimes the most careful search gives negative results, yet at post mortem a neoplasm is discovered.

**Course and Prognosis.**—The juvenile form is benign but the adult form nearly always ends in death from the associated visceral neoplasm.

**Diagnosis** is from warty nævi which are usually unilateral and linear and not confined to the flexures. Darier's disease has a somewhat similar distribution but is usually more widespread, the individual lesions are harder and the histology is distinctive.

**Treatment.**—Laparotomy is justifiable even if a visceral neoplasm cannot be located by clinical methods.

#### KERATOSIS SENILIS VEL SOLARIS

This occurs mostly on the exposed surfaces of the skin, except the form that may develop after inorganic arsenic medication which occurs more on the trunk than on the exposed parts.

**Ætiology and Pathology.**—Damage to the skin by excessive solar or X-irradiation or by the ingestion of arsenic is the chief factor. Age is of secondary importance, the lesions occurring in children with xeroderma pigmentosa, in relatively young persons who have been much exposed to the tropical sun, but rarely occurring even in extreme old age unless there has been considerable exposure to the sun throughout life.

Histologically there is hyperkeratosis and parakeratosis. Acanthosis precedes a frank prickle-cell carcinomatous proliferation.

**Clinical Picture.**—Ill-defined or clear-cut, dirty grey, hard, rough and scaly areas of skin are seen on the face or on the backs of the hands.

**Course and Prognosis.**—At any time keratoses may take on malignant properties; on the other hand, they may continue for years without this change occurring.

**Diagnosis** is from seborrhœic warts. Keratoses are hard, rough and dirty grey

in colour, while seborrhœic warts are soft or firm, of candle-wax texture, and with a shiny brown surface which is often papillated.

**Treatment** is by freezing with carbon dioxide snow for 15 to 30 seconds, provided there is no infiltration of the base. Once the base has become infiltrated, the lesion should be treated as a squamous carcinoma (*q.v.*) with or without preliminary biopsy.

#### CUTANEOUS HORN

This is a keratosis in which horn formation is carried out to excess.

**Clinical Picture.**—A horn grows either from an area of squamous papillomatous change or from an area of squamous carcinomatous change. In the former the base is not infiltrated, in the latter it is hard and elevated.

**Treatment** depends on the changes taking place in the base. If they are simply papillomatous, curettage of the lesion through its base and cautery are usually sufficient. If there is a suspected carcinomatous base, the lesion should be widely excised or dealt with by radiotherapy with or without a preliminary biopsy.

#### LEUCOPLAKIA

This is keratosis of a mucous surface and, like keratosis on the skin, it may remain innocent or develop into carcinoma (see "Diseases of the Lips and Mouth").

#### NÆVOID AND ORGANOID EPIDERMAL TUMOURS

These are tumours either present at birth or first appearing later in life but running a benign course.

##### NÆVUS SEBACEUS (JADASSOHN)

This is a yellow, slightly raised, firm nodule with a papillated surface usually occurring on the scalp or face and present at birth.

**Pathology** shows mature sebaceous glands.

**Course and Prognosis.**—At or after puberty a basal cell carcinoma may develop on a nævus sebaceus. Apart from this, the lesion remains static through life, except for any secondary infection that may occur from trauma by a comb or some other means.

**Treatment** is by excision if desired. Cautery or diathermy are unlikely to be effective. For carcinomatous changes, excision, possibly with grafting, or radiotherapy is necessary.

##### SENILE SEBACEOUS NÆVUS

This is probably a delayed nævus. Like the nævus sebaceus it consists of mature sebaceous glands. It occurs on the forehead or face of persons of 50 or over as yellowish, somewhat translucent nodules. No treatment is necessary but the cautery can be used to destroy it.

##### ADENOMA SEBACEUM (PRINGLE)

This is not an adenoma but a sebaceous nævus with hyperplasia of blood vessels and connective tissue. The lesions occur on the part of the face near the nose as yellow-brown or purplish nodules with telangiectasia. The condition is associated with epilepsy, mental deficiency, nodular sclerosis of the brain and tumours of the kidneys, heart and other organs (epiloia). The brain and retinal tumours are gli-

mata; those of the heart rhabdomyomata, and those of the kidneys angiomas, fibromata, adenomata or mixed tumours. No treatment is necessary for the skin condition, but the nodules can be destroyed with the galvanocautery.

#### FORDYCE CONDITION

This consists of ectopic sebaceous glands in the mucous surfaces of the lips or of the cheeks. The lesions are yellow, pinhead or larger, soft nodules, the histology of which is of a sebaceous glandular nature. No treatment is necessary. Reassurance may be necessary that the lesions are not luetic, tuberculous, cancerous or lichen planus. The condition is so common as to be regarded as physiological.

#### SYRINGOCYSTADENOMA PAPILLIFERUM

This occurs as a skin-coloured or yellowish papilliferous lesion with crusting on the scalp. It is an adenoma of apocrine ducts. It may occur together with sebaceous naevus and, like the latter, may be complicated by basal cell carcinoma. Treatment is preferably by excision. Destruction by galvano-cautery is likely to be followed by a recurrence.

#### HYDRADENOMA PAPILLIFERUM

This occurs on the labia majora and perineum as a solitary skin-coloured nodule of split-pea size or smaller. Malignancy does not develop. The condition is an adenoma of apocrine glands.

#### APOCRINE EPITHELIOMATA

These are of two varieties: in syringoma, differentiation of the cells is towards apocrine duct cells; in cylindroma, differentiation of the cells is towards apocrine gland cells.

*Syringomata* occur mostly in women as multiple skin-coloured or yellowish, soft nodules of pinhead size and larger on and around the eyelids, on the chest and abdomen, and sometimes elsewhere. No treatment is necessary but for cosmetic reasons they may be treated with carbon dioxide snow or the galvano-cautery.

*Cylindromata* (turban tumours) occur as rounded, smooth elevations on the scalp and sometimes on the face and upper trunk, beginning in young adults and slowly enlarging up to the size of grapes, sometimes giving the scalp a cerebral appearance. Treatment is ineffective because the extent of the lesions makes surgery impracticable and radiotherapy is of no use.

#### TRICHO-EPITHELIOMATA (EPITHELIOMA ADENOIDES CYSTICUM) (BROOKE'S DISEASE)

These occur as multiple, skin-coloured nodules resembling basal cell carcinomata, developing in early adult life on the scalp and face. It is a familial disorder. The tumours contain numerous horn cysts and rudimentary hair. Some areas may closely resemble basal cell carcinoma and occasionally after many years these tumours take on the properties of rodent ulcers.

**Treatment.**—The tumours are usually too numerous for surgery and they are radio-insensitive. Active treatment is therefore best deferred unless malignancy develops in any one nodule, when either radiotherapy or surgery is necessary.

## CALCIFYING EPITHELIOMA (MALHERBE)

This is a rare solitary, movable, sharply demarcated, often encapsulated tumour situated in the lower dermis. Histologically there are basal cells adjoining pale "ghost" cells, with a foreign body giant cell reaction nearby. Diagnosis is made histologically from a calcified sebaceous cyst, which has squamous cells adjoining the cyst cavity. Treatment is by excision.

## CHONDRODERMATITIS NODULARIS CHRONICA HELICIS

This condition presents clinically as a painful nodule on the helix. It is best considered here although it is uncertain whether it is inflammatory or neoplastic. It usually occurs in men, it may be bilateral, and it interferes with sleep by causing discomfort when the head rests on the pillow.

**Pathology.**—There is diffuse inflammation in the corium. It has been suggested that it is a form of glomus tumour.

**Treatment** is by wedge excision including a portion of cartilage. Anything less leads to recurrence.

## TUMOURS OF THE DERMIS

## MOLES

A mole (pigmented, fleshy, sometimes hairy *nævus*) is an elevated light or dark-brown, firm, fleshy nodule occurring singly or scattered over the face. A papillated form also occurs.

**Pathology.**—There are orderly, circumscribed clusters of *nævus* cells in the dermis, separated from the epidermo-dermal junction and showing no mitotic activity. Mixed dermal and epidermo-dermal junctional *nævi* also occur in which the active junctional component is potentially malignant.

**Course and Prognosis.**—Moles tend to enlarge as age advances and they also get more hairy. Folliculitis may develop and cause tenderness and swelling, but malignant degeneration rarely, if ever, occurs.

**Treatment** is unnecessary except as a cosmetic matter. The hairs may be removed permanently by diathermy or electrolysis and this is often sufficient. Excision may be performed but destructive procedures of cautery, carbon dioxide snow or diathermy are inadvisable; they may result in ugly scarring and cause incomplete removal. Operations on moles necessitate removal of the dermis in full depth.

## LENTIGO MALIGNA

This is a state of premalignant proliferation of lentigo (*q.v.*) in the plane parallel to the surface. It is to malignant melanoma much as Bowen's disease is to squamous carcinoma. The lesions appear in elderly persons as a very dark brown impalpable expansion of a lentigo. There is no lymph node enlargement.

**Pathology.**—There are no *nævus* cells in the dermis but there is great irregularity and dropping off of the cells at the epidermodermal junction into the dermis. The basal layer is markedly pigmented and there are many clear cells.

**Treatment** is by wide excision. A margin of 1 cm. or less may be followed by recurrence in the scar.

## MALIGNANT MELANOMA

This, the most malignant of all tumours, arises from lentiginous, lentigo maligna or from mixed or junctional *nævi*. It may also arise from the choroid.

**Pathology.**—There is extreme disorganisation of the epidermodermal junction with much mitotic activity in atypical nævus cells. Beneath is a dense inflammatory infiltrate, invaded by strands of the pigmented nævus cells. Often the epidermis becomes permeated by tumour cells and disintegrates, leading to the characteristic bleeding or ulceration of these lesions.

**Clinical Picture.**—Any mole or lentiginous macule should be regarded with great suspicion if it enlarges, becomes darker, bleeds, scabs or becomes ulcerated or painful. The classical malignant melanoma is a dark brown or bluish-black, soft, easily bleeding nodule. If it arises from a lentigo maligna there is a flat, surrounding, impalpable, dark zone of a somewhat lighter tint than the melanoma itself. Regional lymph nodes may be palpably enlarged or there may be extensive lymphadenopathy beyond the reach of the diagnostician's finger, for example in the iliac chain. Some melanomata are light brown and a few are skin-coloured (amelanotic) and perhaps difficult to recognise even on histological grounds from anaplastic carcinoma.

**Course and Prognosis** of melanomata is grave in the extreme. Even if removed at the first recognition, metastases are only too often found already to have occurred. Once a melanoma has taken on malignant proliferation therefore, the prognosis should be guarded; there may be no recurrence after operation or metastases may declare themselves after a technically perfect operation. Metastasis may take place in the lymph nodes, in the liver or lungs, or in the brain, giving rise to symptoms of a cerebral tumour, sometimes long after the primary lesion has been removed.

**Treatment.**—Without performing a biopsy, a suspected melanoma should be very widely and deeply excised. On no account should the lesion be manipulated by forceps in the process of removal. Sometimes, for example with Hutchinson's melanotic "whitlow", amputation is a better plan. More drastic block dissections of the regional lymph nodes are sometimes carried out. Melanomata are non-responsive to X-ray treatment, but X-rays are sometimes used before excision to check mitotic activity during the time of removal.

#### BLUE NÆVUS (MONGOLIAN SPOT)

This is a button-like, firm, slaty-blue nodule usually found in the sacral region.

**Pathology.**—Deep in the dermis are spindle-shaped cells containing melanin and lying with their long axes parallel to the surface. The epidermis is normal, but with the upper dermis it acts as a light filter and so gives the nævus its bluish tint.

**Course and Prognosis.**—The lesion is benign and static. No treatment is necessary but excision can be carried out if the patient wishes it.

#### KELOID

A keloid is a pink or white, firm, raised tumour, often with claw-like extensions beyond the limits of the original scar. Histologically there is fibroblastic proliferation in the early stage and dense fibrosis in the later stages. Keloids may form for no obvious reason or at sites of ingrowing hairs, acne, wounds, tattoo marks, vaccination scars or burns. Predisposition, both racial and personal, is marked, the coloured races being most affected and some white persons more than others.

Acne keloidalis nuchæ is probably a keloid due to ingrowing hairs. True acne keloids occur on the face and trunk.

**Treatment.**—Repeated fortnightly carbon dioxide snow applications, 10 to 30 seconds on each occasion, may flatten the lesions; or excision followed by radiotherapy to the scar may prove effective. Excision alone is usually most disappointing, recurrence taking place.



### FIBROMA DURUM (SCLEROSING HÆMANGIOMA, 'DERMATO-FIBROMA, HISTIOCYTOMA, 'FIBROMA EN PASTILLE)

These deeply situated, firm, globular tumours occur in the skin of the legs more than anywhere else. They may be single or multiple. The colour may be pink, light brown, bluish or skin-coloured, depending on the amount of vascularisation, lipid or hæmosiderin deposition, or fibrous tissue. They are usually painless.

**Pathology.**—The histological appearance varies with the degree of maturity. Early tumours contain a preponderance of histiocytes and endothelial cells; older tumours contain fibroblasts and fibrous tissue. Infantile xanthomata, the yellow nodules known as nævo-xantho-endothelioma, are histiocytomata.

**Treatment.**—Histiocytomata do not recur after excision.

### FIBROMA MOLLE (FIBROMA COLLI OR SKIN TAGS)

Fibroma molle is a soft, fleshy, sometimes pedunculated tumour, often found on the necks and axillæ of middle-aged women. The histology is that of normal connective tissue. It is possible that these lesions represent a forme fruste of von Recklinghausen's disease.

**Treatment.**—Destruction or removal by means of the galvano-cautery gives excellent results.

### DERMATO-FIBROSARCOMA PROTUBERANS

This is a locally recurrent form of fibroma. One or several grouped nodules, skin-coloured or purple, form an irregular mass which may ulcerate. There is local invasion of tissue but metastasis is unusual, except after many years. True metastasising fibrosarcoma is very rare on the skin.

**Treatment.**—Local excision should include a wide area of apparently normal skin if recurrence is to be avoided.

### MYXOMATOUS DEGENERATION CYSTS (SYNOVIAL CYSTS)

These occur mostly on the fingers near the distal interphalangeal joints. They are tense, translucent and globular and contain mucinous fluid. The wall of the cyst is made of fibrous tissue.

### COLLOID MILIUM

This is a pinhead-sized, translucent, yellow nodulation, usually of the forehead. The slimy contents are degenerate collagen and the cysts are lined with collagen.

### NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

In this malady there are numerous soft skin-coloured or brownish-purple tumours, mostly pedunculated, varying in size from pinhead size to masses the size of an orange (*molluscum fibrosum*). Yellowish-brown macules of varying sizes and shapes (*café au lait spots*) are also present.

**Pathology.**—Wavy nerve sheath fibrils in loose strands and whorls are interspersed with reticulum fibrils and collagen. Mucoïd degeneration may occur. The *café au lait spots* show an increase of melanin pigment.

**Clinical Picture.**—The fully developed clinical picture is characteristic but formes frustes also occur in which the diagnosis may be more difficult. In addition to the skin lesions there may be nodules on the peripheral nerves and in the central nervous system, in the chest or abdomen and under the periosteum.

**Course and Prognosis.**—Malignant change is rare in the skin lesions but more common in the visceral ones.

### KAPOSI'S IDIOPATHIC HÆMORRHAGIC SARCOMA

This condition is probably a benign angiomatosis and is not sarcomatous. Histologically, there are spindle cells and numerous dilated blood vessels with extravasations.

**Clinical Picture.**—Brown or purple nodules develop, usually on the feet, sometimes on the hands or on other parts of the skin. Visceral lesions are common, particularly in the lungs and abdominal organs and lymph nodes. The skin lesions are not tender. They first appear in early or middle adult life, mostly in Jews, slowly enlarge and then become static or regress. They may ulcerate.

**Course and Prognosis.**—The course is usually benign though occasionally sarcomatosis has been reported as a terminal feature.

**Treatment.**—Radiotherapy may diminish the size of the lesions. Apart from this, dusting powders to the feet and measures directed to preventing or controlling ulceration are indicated. Watch must be kept for symptoms of visceral involvement.

### OTHER SARCOMATA

Liposarcoma, myxosarcoma, osteosarcoma, rarely occur in the skin.

### LEIOMYOMA

Leiomyoma may be a solitary tumour or it may occur in groups.

**Clinical Picture.**—The tumours are split-pea sized, smaller in the grouped form or larger in the solitary type. They are yellowish-brown and very tender to the touch, particularly the grouped form. The grouped leiomyomata arise from the arrectores pilorum muscles and the lesions may occur on the face, trunk or limbs, particularly the extensor surfaces. Solitary leiomyomata may arise from involuntary muscle in the skin of the breasts, scrotum or labia majora, or from vascular musculature (angiomyomata).

**Treatment.**—The only effective treatment is excision.

### LIPOMATA

These are soft, freely movable, often ill-defined tumours in the subcutaneous tissue. They may be single and massive, for example in the neck, or multiple. The latter variety may be painful (Dercum's disease).

**Treatment** is by excision when necessary.

### HÆMANGIOMATA

#### NÆVUS FLAMMEUS (PORT WINE STAIN)

This is a hæmangioma of statically dilated vessels, present at birth and often persisting through life, although some small lesions on the eyelids and face may disappear after a few weeks of extra-uterine life.

An hæmangioma at the nucha is very common (Unna's nævus, physiological nævus). Other sites commonly affected are the mid-line of the forehead and one half of the face or even one half of the whole or part of the body and limbs. In this case there may also be asymmetry, the limbs of the affected side being smaller than those on the sound side (hemiatrophy). The vessels in nævus flammeus may be barely visible, or obvious capillaries or large purple venules, perhaps with nodular excrescences.

**Course and Prognosis.**—*Nævus flammeus* usually persists for life, except for the transient form on the face. Some of the darker port wine stains may become more irregular and scaly as time progresses.

**Treatment.**—If there is a diffuse pinkness without blood vessels visible to the naked eye, a trial of thorium-X applications is justified, 1500 e.s.u. in spirit being painted on at fortnightly intervals for about 12 applications. Photographic control is advisable and if after 12 treatments there is little or no improvement, it is not justifiable to continue with this procedure. Elevated areas may be destroyed and flattened with the galvano-cautery. For the rest, cosmetic coverage offers the best prospects, particularly in women. Some cosmetic firms provide a service in large cities whereby patients with blemishes can by individual trial be supplied with a cover preparation most suited to their complexions. In men, the problem is more difficult and the patient may prefer to leave his lesion uncovered. Plastic surgery is rarely feasible.

#### NÆVUS VASCULOSUS (STRAWBERRY MARK; CAVERNO-CAPILLARY NÆVUS)

This has a characteristic natural history. It may be present at birth or it may appear within the first 2 weeks of extra-uterine life as a bright red, flat or slightly raised, pinhead-sized nodule, which steadily enlarges until about 8 or 9 months of age, when its growth stops and its gradual regression begins, the lesion finally disappearing without trace or with slight scarring at about 5 years of age.

Sometimes these hæmangiomas develop on a markedly raised area of venous tissue, but the ultimate prognosis is equally good. Histologically there is vascular proliferation in a fibrous or fatty stroma.

Strawberry nævi may occur anywhere on the skin but rarely cause serious inconvenience unless they involve the mouth or the anus, an ear or a finger. Large hæmangiomas or those at sites exposed to trauma or a great deal of movement, may become ulcerated and infected.

**Treatment.**—Simple capillary and caverno-capillary hæmangiomas are best left to run their natural course which ends in resolution at about 5 years of age. Periodic inspection and measurement or photography with reassurance of the mother are usually sufficient. It is wise to inform the mother that a waiting policy will give the best results in the long run, whereas any interference will cause some scarring and, if the lesion is on the scalp, loss of hair. Radiotherapy of a strawberry nævus near the nipple of a female infant is likely to be followed by nondevelopment of that breast, and irradiation of a lesion near a joint may interfere with the growth of a limb. Applications of carbon dioxide snow, made in the first few months while the hæmangioma is growing, may be followed by a ring-shaped recurrence around the scar.

If there is ulceration, infection should be controlled with a suitable antibiotic and the lesion subsequently dressed with tulle-gras until the ulcer is scarred over. If hæmorrhage occurs it can be controlled by a pressure pad.

Rapidly growing hæmangiomas around the mouth may have to be treated; injections of hot water or sclerosing chemicals, excision or radiotherapy can be used, depending on what is considered most suitable.

#### STELLATE HÆMANGIOMATA

These small "spider" nævi appear on the face or hands in young children. They may become much more numerous in pregnancy and in the presence of liver disorders. There is a central venule with radiating capillaries.

**Treatment.**—The galvano-cautery point is applied cold to the central vessel, the current is switched on and the point withdrawn when the patient flinches.

## SENILE HÆMANGIOMATA (CAMPBELL DE MORGAN SPOTS)

These pinhead-sized or larger red spots occur more and more after the age of 40, particularly on the trunk and face. On the scrotum they often have a rough surface (angiokeratomata). They have no significance as regards the general health and need no treatment.

## FAMILIAL HÆMORRHAGIC TELANGIECTASIA (OSLER)

In this disorder numerous hæmangiomas and telangiectases occur on the skin and mucous membranes; the latter may cause hæmorrhages from the nose, mouth, stomach, kidneys, vagina or rectum.

**Treatment.**—Individual lesions can be destroyed with the galvano-cautery.

## ANGIOKERATOMA (MIBELLI)

These are warty angiomas which occur on the extremities of young subjects. Angiokeratoma corporis diffusum are similar lesions, but with rather less wartiness on the trunk and external genitalia. There may also be proliferation of Bowman's capsules in the renal glomeruli, of the vascular musculature and of the heart muscle.

## GRANULOMA TELANGIECTATICUM (GRANULOMA PYOGENICUM)

This is a rapidly growing hæmangioma which soon becomes eroded and infected. It presents as a pink, shiny, orange pip-sized, exuding and bleeding nodule. Histologically there is great proliferation of capillaries and of fibroblasts.

**Treatment** is by galvano-cautery destruction.

## GLOMUS TUMOUR (GLOMANGIOMA)

These very painful nodules are formed from the neurovascular glomus, an arterio-venous anastomosis. They are usually single, flat or raised lesions on the finger tip, nail bed or occasionally elsewhere, for example on the forearm.

**Treatment** is by wide excision.

## LYMPHANGIOMA

Lymphangiomas may be circumscribed and superficial or widespread, cavernous and deep. In the former, translucent, superficial lemon-coloured or red vesicles are present in a group at birth or soon after. The surface of the vesicles may be slightly warty. Histologically there are dilated lymph spaces.

**Treatment** is unnecessary but excision is sometimes performed.

In lymphangioma cavernosum there is also hypertrophy of the connective tissue, causing macrocheilia, macroglossia or enlargement of part or the whole of a limb. In this form treatment other than drastic surgery is rarely possible.

## JUXTA-ARTICULAR NODES

These are painless, firm, subcutaneous fibrous nodules, occasionally found near the elbows or knees or other joints in tertiary syphilis. Non-syphilitic juxta-articular nodes also occur, as in acrodermatitis chronica atrophicans (Pick-Herxheimer).

## PARAFFINOMA

Paraffinoma is a nodular, fibrotic, subcutaneous thickening somewhat resembling morphæa, but due to injection of paraffin or camphorated oil, the former sometimes

having been used in an attempt to iron out creases and saggings in the ageing skin and the latter having been used as a vehicle for certain subcutaneous injections.

Histologically there is a "Swiss cheese" appearance of cavitation, indicating where the oily substance was contained, and around these spaces is an inflammatory and foreign body giant cell reaction with fibrosis. The presence of the oil within the spaces can be demonstrated in frozen sections.

**Diagnosis** is from lipophagic granuloma and morphœa on histological grounds.

**Treatment** is difficult and usually inadvisable. Sometimes excision and grafting is justifiable.

## CUTANEOUS RETICULOSES

### MALIGN RETICULOSES

These serious systemic, infiltrative disorders may be ushered in by general pruritus, furunculosis, nonspecific eruptions, urticarial, pruriginous and eczematized lesions, parapsoriasis en plaque, poikiloderma, purpura, erythroderma or cutaneous or subcutaneous obtuse, dome-shaped, plum-coloured or skin-coloured nodules which may ulcerate. When large "tomato tumours" form, the clinical description of "mycosis fungoides" is sometimes used. It is at present not possible satisfactorily to classify these maladies.

**Pathology.**—Biopsy from the cutaneous nodule shows a polymorphic infiltrate in Hodgkin's disease and mycosis fungoides. The Sternberg-Reed giant cells are pathognomonic of Hodgkin's disease and in the infiltrate there are also neutrophils, many eosinophils, plasma cells, histiocytes, fibroblasts and immature reticulum and stem cells.

In "mycosis fungoides" the infiltrate is similarly polymorphic but Sternberg-Reed cells are absent. Small accumulations of lymphocytes and histiocytes are present in the epidermis (Pautrier micro-abscesses).

**Clinical Forms.**—Hodgkin's disease may present with pruritus, furunculosis, a nonspecific eruption, or tumours or ulcers having the specific pathology of the disease. Tumours on the face may give a leonine appearance.

In lymphatic leukaemia, erythroderma (l'homme rouge) is the commonest form but this may be preceded by pruritus and nonspecific, eczematoid lesions, by parapsoriasis en plaque and poikiloderma or by itchy pink plaques resembling urticaria. The leukaemia may develop late in the course of the disease. Large, fungoid tumours may form (mycosis fungoides) with or without leukaemia. Infiltrative skin lesions have also been described in monocytic leukaemia and, rarely, in myeloid leukaemia.

**Course and Prognosis.**—These maladies are all fatal after intervals varying between a few months and several years. Death is usually due to pulmonary complications, marrow destruction or involvement of other organs.

**Diagnosis.**—Reticulosis must be considered a possibility in all persistent forms of generalised pruritus, furunculosis, nonspecific eruptions, parapsoriasis en plaque, poikiloderma, erythroderma, tumours and ulcers of the skin. Often the diagnosis can only be established after a long period of observation and after repeated biopsies.

**Treatment.**—General pruritus of Hodgkin's disease may be relieved by X-irradiation of the epigastric region. Erythroderma may be subjectively relieved by corticotrophin. Earlier, more superficial plaque-like erythematous infiltration may respond well to weekly paintings with thorium-X 1500 c.s.u. per ml. for as many treatments as may be necessary. The tumours are usually radio-sensitive at first, responding to two or three exposures of 250 r each at weekly intervals. As the disease progresses, the tumours tend to become more and more radio-resistant.

## BENIGN RETICULOSES

FOLLICULAR LYMPHOCYTOMA (LYMPHADENOSIS BENIGNA CUTIS;  
SPIEGLER-FENDT SARCOID)

This occurs as one or more dome-shaped nodules on the scalp, face, ears, nose, breasts, genitalia or elsewhere.

**Pathology.**—The nodules consist of nests of lymphocytes.

**Course and Prognosis.**—There is some doubt about the benignity of this condition. It is believed that after years the condition may develop into a fatal reticulosis.

**Treatment.**—The lesions usually flatten and disappear after two or three X-ray exposures of 250 r each at weekly intervals.

## MILIARY LYMPHOCYTOMA

This is a condition of pinhead-sized, translucent nodules in groups, which arise on the malar region or forehead. Each consists of a circumscribed nest of lymphocytes. The condition is not a reticulosis but is apparently an unusual reaction to light.

**Treatment** is ineffective. Light-screening creams should be prescribed, if only to prevent worsening.

## DISEASES OF THE HAIR

## CONGENITAL CONDITIONS OF THE HAIR

These include pili torti (spiral twisting of the hair); monilethrix (beaded hair, the shaft being constricted, with absence of the medulla at regular intervals, as a result of which the hair breaks off short); congenital ectodermal defects in which the scalp hair may be delicate and fine, or woolly or absent (congenital alopecia). In albinism, the hair is white.

## ACQUIRED CONDITIONS OF THE HAIR

## CANITIES (WHITENESS OF THE HAIR)

This may be physiological from the age of about 40 years onwards. It may also be pathological and premature in endocrine disorders including hyperthyroidism and Simmonds' disease. There may be partial or general whitening of the hair that regrows after alopecia areata or in the involvement of hairy areas by vitiligo. The hair may also become white after severe emotional disturbance.

**Treatment** is by suitable dyes which may be of the harmless type, for example, henna; or potentially harmful, for example, paraphenylenediamine. Before using the latter, a patch test should be performed to determine the presence or absence of sensitivity to the chemical. It should never be applied to a scalp on which any cuts, abrasions, scabs or redness exist.

## NON-CICATRICIAL ALOPECIA (BALDNESS)

This may be local or general; all the hair may be lost from a given area or there may be sparseness of the hair on the site (alopecia diffusa).

*Alopecia areata* is a complete loss of hair from a circumscribed area of the scalp or the beard. More extensive forms result in the loss of all the hair from the scalp (alopecia totalis) and in the worst cases the hair of the beard, lashes and brows, axillæ and pubis, and even the glabrous hair may fall (alopecia universalis).

**Ætiology and Pathology.**—The cause is unknown but emotional factors are

prominent in about two-thirds of the cases. The condition may represent an hysterical symbolisation. Histologically, there is an inflammatory infiltrate around the hair follicles which leads to atrophic changes of variable degree; after the milder forms, regrowth of hair may occur, but after the severer forms the loss may be permanent. In long-standing alopecia, the inflammatory infiltrate is absent and the follicular atrophy more marked.

**Clinical Pictures.**—In simple alopecia areata, there are oval or circular, completely bald, shiny patches, which by confluence may form polycyclic areas. There is no sign of inflammation and an absence of scurf. At the margin of recent and extending patches, "exclamation mark" (club-shaped) hairs are visible. These are short hairs with their ends of greater diameter than the portion level with the surface of the skin. First attacks of the condition often occur in children and young adults. Ophiasis is a variety of alopecia with serpentine lesions.

**Course and Prognosis.**—Recovery is usual from first attacks and localised lesions, but becomes increasingly unlikely with each recurrence. Sometimes one patch develops while another is regrowing. The band-like forms affecting the occipito-temporal regions and alopecia totalis are of poor prognosis. When regrowth occurs the new hair is at first fine and often white.

**Diagnosis.**—In children, alopecia areata has to be differentiated from tinea capitis and from trichotillomania. Tinea capitis presents as scaly patches with short, broken hairs looking thicker than the adjoining healthy hairs and with frayed ends. The inflammatory reaction may be insignificant or frankly folliculopustular. Wood's light examination and microscopy makes the diagnosis clear. The "black dot" ringworm due to *T. violaceum*, in which the hairs break off flush with the surface of the skin, may resemble a regrowing alopecia. Microscopy is necessary for the differentiation. Trichotillomania, an habitual tugging, twisting and manipulation of the hair, is usually situated in the frontal or temporal regions; the hair loss is only partial and a history of hair-tugging will be obtained if the parent is asked this question.

In adults, alopecia areata has to be differentiated from various forms of cicatricial alopecia (*q.v.*).

**Treatment** is supportive. A stimulating liniment may be rubbed in daily or a second-degree erythema exposure to ultra-violet irradiation given once a week. Psychotherapy is seldom effective. Foci of sepsis and eyestrain are no longer regarded as of aetiological significance.

The term *alopecia diffusa* implies a diffuse thinning of the hair over part or the whole of the scalp.

*Androgenic alopecia* is the commonest variety, occurring in most males from about the age of 40 onwards and, in some, as early as 20 years of age. The hair becomes thinner and finer in the bifrontal and vertical regions but remains in its former texture and thickness on the rest of the scalp. Genetic (racial and familial) influences are important in its aetiology, also the fineness of the hair. There is at present no means of checking its progress except by control of the coincident scurf or mildly infective folliculitis (*q.v.*). Massage may do more harm than good and ultra-violet irradiation has no effect. Estrogens, too, in practical doses, are ineffective.

Women also are sometimes affected with this type of hair loss after the menopause, and there may also be hirsutes of male distribution. Occasionally alopecia of androgenic type occurs after pregnancy; in these circumstances, non-destruction of androgens by the liver is suspected as the cause.

In *myxedema*, the hair over the whole scalp is thinned, fine, dry, limp and lustreless, but may recover some of its former texture by suitable dosage with thyroid extract.

In *nutritional deficiencies*, particularly of vitamins A and C, the phrynodermatous process may involve the scalp, causing loss of hair and a finer texture of those that remain.

*Defluvium capillorum* is a term used for conditions of temporary or permanent, occasional or recurrent, falling of the hair from causes known or unknown, including acute infections, emotional stresses, exfoliative dermatitis, toxic processes and nutritional deficiency states acting indirectly through endocrine and metabolic mechanisms.

In *infective* ("seborrhæic") *dermatitis*, the hair loss of masculine distribution that is so often present is accentuated by the folliculitis.

In *secondary syphilis*, there may be an irregular but diffuse loss of hair, giving a "moth-eaten" appearance to the scalp.

*X-irradiation* is often used to bring about epilation of patients suffering from ringworm of the scalp. A single X-ray exposure of 400 to 450 r causes shedding of the hair after 3 weeks, with complete regrowth starting in another 3 weeks. Further exposures, or a single exposure of more than 450 r, may cause permanent epilation, with the development after a few years of the picture of *chronic radiodermatitis* (atrophy, telangiectasia, pigmentation and depigmentation).

*Certain toxic substances* have a direct action on the hair papillæ. One of these, thallous acetate, was used some years ago to bring about temporary epilation, but its use has been almost completely abandoned owing to the small margin between the therapeutic and the toxic dosage, the latter causing albuminuria, blindness, coma and even death. The use of this substance is strongly to be deprecated.

#### FRAGILITAS CRINIUM

Breaking of the hairs at various distances from the scalp must be differentiated from *defluvium capillorum*. The hairs show frayed and split ends and sometimes frayed nodose swellings on their shafts (*trichorrhexis nodosa*). The cause is undue drying and degreasing of the hair which may follow the excessive use of shampoos. Bleaching agents may also be responsible. The treatment is preventive, by avoidance of these substances in excess. Once it has occurred, it may be helpful to prescribe a lotion of salicylic acid 2 per cent., oil of rosemary 2 per cent., castor oil 12½ per cent. in industrial spirit, for use as a hair dressing.

#### PILI INCARNATI

Ingrowing hairs, resembling folliculitis barbæ of mild degree (*q.v.*).

#### CICATRICIAL ALOPECIA

Scarring baldness has a large number of causes, including :

Physical traumata—cuts, burns, X-rays, radium.

Chemical traumata—caustics, etc.

Exanthemata—variola, varicella, zoster.

Drug intoxications—lichenoid mepacrine eruption.

Fungous infections—kerion, favus.

Granulomata—syphilis, lupus, sarcoidosis, leprosy, halogen eruptions.

Reticuloses—lymphocytomata or lymphoblastomata; Hodgkin's disease.

New growths—rodent ulcers.

Nævoid conditions—nævus sebaceus, hydrocystadenoma papilliferum (both present as bald areas with yellowish papillomatous outgrowths).

Skin diseases—lupus erythematosus, lichen plano-pilaris, morphœa, folliculitis decalvans, acne varioliformis, pseudo-pelade.

A few of these may be described in some detail.

Radiogenic alopecia presents as poikiloderma, that is, a polymorphic and patchy picture of atrophy, telangiectasia, depigmentation and hyperpigmentation. It is occasionally seen in patients who have been treated by X-rays for ringworm of the



scalp in childhood. The condition is irreversible and, after several years, keratoses and squamous carcinoma may develop.

Varicella, variola and zoster may show macular bald areas at the sites previously occupied by the vesicles.

The lichenoid gold or mepacrine dermatosis presents as one of its features a patchy folliculitis of the scalp, beard, eyebrows and lashes, which is followed by baldness either temporary or permanent. The history of drug treatment and the lichenoid features elsewhere help to supply the correct diagnosis.

Favus may present with scutuliform crusts with an offensive odour or as folliculitis decalvans (*q.v.*). Affected hairs fluoresce pale blue under Wood's light and spores and mycelium are visible within the hair shafts on microscopic examination.

Syphilis, in addition to the "moth-eaten" alopecia at the secondary stage already mentioned, may in the tertiary stage cause cicatricial alopecia at the sites of gummata which, in this situation, often develop a heavy secondary infection.

Leprosy may give rise to baldness in its nodular and in its maculo-anæsthetic forms.

Lupus vulgaris rarely involves the scalp, and when it does the face is usually heavily affected as well with the characteristic "apple-jelly" nodulation.

Reticuloses may cause obtuse skin- or plum-coloured, dome-shaped swellings, with baldness on the scalp, or occasionally more diffuse pink infiltrated nodulation.

Rodent ulcer, when it affects the vertex, differs considerably from the button-like lesions seen on the face. The scalp lesions are flat or even slightly depressed, scleroderma-like plaques, perhaps with some crusting around the edges, which also have a slight translucency and pearly appearance.

Lupus erythematosus causes red, bald patches, with central atrophic scarring and marginal infiltrated redness with follicular plugging and adherent scales.

Lichen plano-pilaris causes irregular areas of baldness and itchy, acuminate, violaceous, follicular papules with shiny tops.

Morphea causes an oval or linear waxy, shiny, bald area with a lilac halo.

Folliculitis decalvans is a coccal folliculitis causing atrophy of the follicles and atrophic scarring with baldness. Often the central area is bald apart from a few scattered hairs but shows no active inflammation; towards the margin of the bald area are scaly follicular papules and sometimes a few pustules. The condition can be controlled to some extent by appropriate antibiotics.

Acne varioliformis leaves depressed, hairless scars around the hair margin.

Pseudo-pelade presents as irregular and angular areas of scarred baldness with tufts of hair remaining amidst the bald patches. The condition sometimes represents the end stage of lichen plano-pilaris of the scalp.

*Ulerythema ophryogenes* is a rare, scarring folliculitis of the eyebrows, of uncertain ætiology. Sometimes it may be a manifestation of lupus erythematosus, sometimes of coccal folliculitis profunda (sycosis).

*Perifolliculitis capitis abscedens et suffodiens* is a rare condition of fluctuant swellings on the scalp with sinuous tracks, multiple sinuses and considerable loss of hair. Culture may be sterile. The condition is analogous to hydradenitis suppurativa, and is most difficult to relieve. It may be necessary to open up the tracks and allow them to heal by granulation.

#### HYPERTRICHOSIS (HIRSUTES)

The localised form occurs as coarse hairs growing from a mole, which is usually small and nodular but sometimes extensive and plaque-like. They rarely need treatment unless they occur on exposed surfaces, when the patient may ask for something to be done on cosmetic grounds. One of two courses should be adopted—either the hairs are destroyed individually by electrolysis or the whole mole is excised and the

wound stitched or grafted. Interfering traumatic procedures, such as cautery or carbon dioxide snow freezing, are to be deprecated: the cosmetic results are poor and the depth of the lesions means that only excision can remove it all.

Very rarely local hirsutes occurs over the sacrum without pigmentation, apparently as a vestigial tail.

*General hypertrichosis* involves the areas of masculine coarse hairs, the upper lip and beard area, the chest, mid-line of abdomen and subumbilical triangle, and the extensor surfaces of the limbs. Gross hypertrichosis is sometimes a source of embarrassment in the male: in the female, minor degrees may be equally distressing.

*Etiology.*—The majority are genetic (racial and familial) in origin and no doubt related to a functional endocrine imbalance which is, at present, incapable of adjustment. If the moon face, obesity, purple striae, hypertension and glycosuria are present (Cushing's syndrome), investigation should be made for pituitary or adrenal cortical neoplasia.

The administration of adreno-corticotrophic hormones may bring about acne and hirsutes.

Acne vulgaris is often accompanied by hirsutes of moderate degree.

*Treatment.*—If there is no hypertension, glycosuria, moon face, striae or obesity, and normal 17-ketosteroid excretion, the condition can be regarded as genetic and is a functional endocrine disorder, incapable (at present) of relief except by local epilatory methods.

For coarse hairs, electrolysis carried out by an expert gives the best results, but in inexperienced hands noticeable pinpoint scarring may follow. If the hirsutes is widespread and finer, electrolysis entails many tedious treatments and it is better to use some simpler method of masking the condition. Bleaching with peroxide of hydrogen (neutralised) followed by exposure to daylight, is often valuable. Shaving is often the ideal method and does not, as is supposed by some, lead to coarsening of the hair. Unfortunately, it carries with it a discouraging sense of performing a masculine act and many women refuse this suggestion for that reason, although they are prepared, illogically, to use pumice, the equivalent of pre-historic man's razor. Chemical depilatories are more useful in the axillae than on the face, where any inflammatory reaction they might cause would be more unfortunate.

Epilation by wax has a small sphere of utility for localised patches as a temporary measure. Plucking, too, is commonly performed for this purpose but, if persisted in, may end in some traumatic epidermal proliferation of the ostia of the follicles.

X-rays should never be used for cosmetic epilation of women's faces, breasts or limbs because of the likelihood of chronic radiodermatitis developing and of subsequent keratoses and epitheliomata.

## DISEASES OF THE NAILS

The nails may be affected in various ways by local or general conditions, congenital or acquired.

### PARONYCHIA

Paronychia, or inflammation of the nail fold, is due to micro-organisms gaining entry through a break in the cuticular barrier, and it may be acute or chronic.

The acute form (paronychial whitlow), due to coccal infection, presents as a red, tender, cushion-like swelling on one or both sides of the nail fold. Yellowish discoloration, due to pus formation, is soon apparent. A painless epidermal variety may be the unsuspected source of various staphylococcal infections of the skin.

Treatment is by systemic penicillin in the earliest stage or by avulsion of the nail and a paronychia flap at the later stage. The epidermal variety is easily dealt with by removal of the overlying epidermis and cleansing with 1 per cent. cetrimide.

If a paronychia whitlow persists, neither resolving nor suppurating, consideration should be given to the possibility of its being an example of Hutchinson's melanotic whitlow (onychia maligna), a highly malignant condition masquerading as an infection and necessitating amputation (see Melanoma).

*Chronic paronychia*, like the acute form, is due to destruction of the protective cuticle on the nail plate. This happens following the use of powerful detergents, strong alkalis and soaps, constant exposure to water, the use of cuticle removers, and clumsy manicure. Through the gap thus made pass detergents, soaps, alkalis and water which cause a chemical paronychia with alkalinity of the fold: this predisposes to infection by organisms normally present on the skin, such as monilia and *Staphylococcus saprophyticus*.

The condition presents as persistent, reddened, cushion-like swellings around the nail fold, with a space between the fold and the nail into which a probe can be passed for a few millimetres. There may be occasional exacerbations with a slight discharge of thin pus. The nail plate is usually deformed (onychia) by irregular transverse ridging and grooving, with some discolouration. Sometimes a nail becomes detached from its bed.

**Course and Prognosis.**—Untreated, the condition tends to persist indefinitely.

**Treatment.**—Wet work and the use of detergents and alkalis must be reduced to a minimum. Rubber gloves, if used, should be worn for not more than 10 minutes at a time. A water-repellent barrier cream may be applied around the folds immediately before doing any essential wet work.

Active treatment consists of the application of pigmentum magentæ to the nail fold twice a day by means of a camel-hair brush. This may succeed in the milder cases but, in more severe ones, a course of X-irradiation (150 r fortnightly up to a total of 600 r) is often most effective.

The patient must continue to take precautions against damage to the cuticle after the condition has healed.

Tuberculous paronychia is very rare. Its treatment is the same as that of cutaneous tuberculosis elsewhere.

### INGROWING TOE NAIL (UNGUIS INCARNATUS)

This nearly always affects the great toe and is due to a faulty technique of cutting the nail whereby a lateral sharp spur is left which cuts into the flesh: tight socks and shoes also play a part. The condition presents as a painful swollen area to one side of the toe near the free edge of the nail. A purulent infection is common, or a granulomatous condition.

**Treatment.**—In the early stages, corrective chiropody may be sufficient but once a purulent or granulomatous condition has developed it is necessary to remove half the nail and to excise a wedge of tissue at the site of ingrowth to enable the nail to grow without cutting into the flesh.

*Hangnails* are skin tags alongside the nail, the result of faulty manicuring, a tic, or chapping. The tag as it tears becomes of increasing depth. The diagnosis is from paronychia warts (*q.v.*). The treatment is to cut off the tag and to apply an antiseptic and a collodion dressing.

*Subungual hyperkeratosis* is usually due to psoriasis, dermatitis or some other skin disorder. Tinea must be excluded by microscopic examination.

*Subungual exostosis* presents as a painful swelling beneath the nail, with some

hyperkeratosis. The condition is differentiated from a subungual wart by X-ray examination, and the treatment is surgical.

*Subungual warts* (see Warts).

### DISORDERS OF THE NAIL PLATE

Affections of the nail plate, secondary to disease of the matrix, are many and various. The nails may undergo atrophy or complete destruction (acquired onychia), or hypertrophy, the latter either as a simple thickening following trauma (onychauxis) or as ram's-horn-like masses (onychogryphosis or "claw nails"). For convenience, the thickened nails may have to be removed but the new nails will be just as thick. Excision of the nail beds is sometimes advisable but it is a delicate surgical procedure to remove all the bed proximally and laterally without opening the distal interphalangeal joints.

Congenital abnormalities include absence of the nails (anonychia), rudimentary nails, ectopic nails (onychoheterotopia), spoon-shaped nails (koilonychia), extreme thickening (pachyonychia congenita).

Tics affecting the nail and its surrounds include nail biting (onychophagia) and picking (onychotillomania), one form of hangnail, and knuckle chewing.

Dystrophy (dullness and roughening) of the nails may be due to ringworm, psoriasis, dermatitis, lichen planus, syphilis, tuberculosis, leprosy or unknown causes. Ringworm should always be suspected when one or a few nails are discoloured, irregular, friable or honeycombed. Microscopy, repeatedly if necessary, enables the diagnosis to be confirmed.

Psoriasis of the nails usually occurs with psoriasis elsewhere so that the diagnosis is simple, but it may affect the nails alone. It presents as "thimble pitting" of the nails, there being anything from a single pit to uniform involvement of all the nails. In its more severe forms, it causes yellow opaque, brittle thickening of the nails, usually distally or laterally, sometimes over the whole plate. The nails may be raised and shed by psoriasis of the nail bed.

Dermatitis around and in the nail folds leads to pitting and transverse or longitudinal grooving of the nails.

When dystrophy of the nails is not explicable as of fungous, psoriatic or dermatitic origin, the Wassermann reaction should be tested and examination directed especially to evidence of syphilis or of lichen planus elsewhere. Median canaliform dystrophy is a permanent thickened ridge running along the centre of the nail and due to previous chemical or physical trauma to the part of the matrix supplying this portion of nail.

*Splitting of the nail tips into lamellae* (onychoschizia) is usually caused by powerful detergents or alkalis; occasionally, nail manicure preparations and varnish removers are responsible.

*Transverse groovings and ridgings* of the nails are spoken of as Beau's lines. They may arise in one or more nails from dermatitis, psoriasis and other skin conditions, or they may indicate some recent illness, for example pneumonia, which has led to a temporary impairment of the nutrition of the nail. They take about 6 months to "grow out" and, from their situation on the nail, the date of previous ill-health can be roughly estimated.

*Longitudinal grooving and ridging* of the nails is very common and of no significance in minor degrees; but when severe and accompanied by splitting of the nails it is dignified by the name of onychorrhexis and attention should be paid to the avoidance of degreasing and dehydrating substances.

*White spots* on the nails (canities unguium or leuconychia) are of no diagnostic significance or import, except that they indicate areas of imperfect cornification, possibly the result of injury.

*Longitudinal bands of variation in colour*, either lighter or darker, may result from local pigmentary changes in the matrix.

*Koilonychia* may be congenital and of no serious import. When acquired, it often indicates a chronic malnutrition of the matrices from iron and vitamin B deficiency. A general cause cannot always be found and local ischæmic processes are sometimes responsible. Damage to one or more fingers may cause a somewhat similar deformity, except that the nails are not thin as they are in nutritional *koilonychia*.

*Clubbing of the fingers* includes an increased curvature of the nails, both in the longitudinal and transverse axes, and an increased springiness of the nails on their beds. It is associated with suppurative lung conditions and cyanotic congenital heart disease, etc. There is often also hypertrophy of the distal phalanx (hypertrophic pulmonary osteoarthropathy).

*Detachment of the nail* from its bed may start proximally (onychoptosis) from hæmatoma or paronychia, or distally (onycholysis) as in psoriasis. Onychomadesis is a term applied to shedding of all the nails (sometimes recurrently), starting proximally. The causes of this phenomenon include vasospastic states, skin diseases beneath the nails, for example exfoliative dermatitis or psoriasis, chemical contact, injury, syphilis, diabetes or scarlet fever in its peeling stage.

*Usure des ongles* is a term applied to wearing away of the free border of one or more nails as the result of occupational friction or even merely rubbing with the finger tips.

#### CONDITIONS OF THE NAIL BED

Conditions of the nail bed observed through the plate include the "splinter hæmorrhages" of lupus erythematosus, purpura, hæmatomata, cyanosis, stains of various chemicals and racial pigmentation.

### DISEASES OF THE LIPS AND MOUTH

The lips and mouth are affected in many skin diseases which have been described elsewhere. It remains to describe a few other conditions affecting the lips and mouth.

#### CHEILITIS

*Commissural cheilitis* (angular stomatitis) causes redness, slight crusting and fissuring. It may be a form of infective (flexural) dermatitis; or a manifestation of deficiency of iron and vitamin B; or due to falling in of the angles of the mouth and a resultant extension of the moist surface, arising from lack of teeth or from dentures which are too narrow and shallow; or it may be due to salivation resulting from hypersensitivity to vulcanite or acrylic denture material, to tooth paste, mouth wash or fruit juices. It should be remembered that frambæsiiform syphilides may develop in this situation or at the cleft of the chin.

*Cheilitis exfoliativa* is a peeling of the vermillion surface of the lips usually due to contact with a sensitiser. In severe forms there is œdema, vesiculation and crusting, perhaps going on to fissuring. Eosin in lipstick is the commonest cause; this may act either by causing a contact eczematous reaction or by causing sensitisation to ultra-violet rays. In the former, both lips may be affected. In the latter, the lower lip alone suffers. Rarer causes include nail varnish, tooth paste, mouth washes, fruit juices, essential oils, nicotine, mentholated cigarettes, chemicals handled at work and a lip sucking and chewing habit.

*Cheilitis glandularis* is a rare condition of unknown cause. The mucous glands are enlarged and there is a glairy exudate, with some crusting. Treatment is by cautery destruction of the swellings.

*Macrocheilia* may be congenital or acquired. The latter is usually due to lymphatic obstruction secondary to streptococcal cellulitis, the infection gaining entry through

a fissure; but syphilis and tuberculosis are also sometimes responsible for this elephantiac condition.

Conditions of the lips dealt with elsewhere include lupus erythematosus, lichen planus, psoriasis, keratoses, leucoplakia, urticaria, erythema multiforme, granuloma pyogenicum, syphilis, tuberculosis, recurrent herpes and tumours. Mucous (retention) cysts occur on the mucosal aspect.

### STOMATITIS

Inflammation of the mouth may cause diffuse redness, erosions, blisters, submucosal hæmorrhages or ulcers. The tongue may exfoliate. In more chronic forms redness is inconspicuous and there is leucoplakia.

**Ætiology.**—Lesions appear in the mouth in infections with syphilis, tuberculosis, streptococci, monilia, Vincent's angina, herpes simplex, zoster, varicella, variola, etc. Lesions also appear in intoxications by many drugs (*q.v.*) and heavy metals. Nutritional deficiencies (scurvy, pellagra) cause hæmorrhage and inflammation. Blood disorders such as leukæmia, agranulocytosis, pernicious anæmia, hæmophilia, metabolic disorders such as diabetes mellitus and uræmia, may all cause lesions in the mouth. Finally, certain idiopathic skin diseases may be responsible, particularly lichen planus, lupus erythematosus, erythema multiforme, pemphigus, Behcet's syndrome, Lipschütz disease and rare maladies such as epidermolysis bullosa, Darier's disease and acanthosis nigricans.

**Syphilis.**—Primary lesions may occur on the lip, tongue, palate or tonsil and mucous patches and "snail track" ulcers may appear anywhere in the mouth. Gummata may develop in the palate or tongue or there may be a syphilitic glossitis with irregular leucoplakia.

**Tuberculosis** (see page 1241).

**Streptococcal stomatitis** may complicate tonsillitis. There is a patchy or generalised cherry-red and swollen condition of the gums.

**Monilial stomatitis** (thrush) produces soft white, rapidly spreading raised patches. This malady may develop in infants or in adults who are taking antibiotics or using antibiotic mouth washes.

**Vincent's angina**, due to symbiosis between a spirochæte and fusiform bacillus, causes grey patches in a red, raw, bleeding surface; it particularly affects the gingivo-buccal margin or gingival sulci. Gangrenous stomatitis (cancrum oris) is a very rare form of Vincent's infection in extremely debilitated children.

**Herpetic stomatitis** first affects infants 2 to 3 years old. This primary infection may be followed by a delicately balanced host-virus relationship with recurrences of aphthous stomatitis when debilitated. There are painful swollen erosions (aphthæ) on the cheeks, gums or tongue.

**Zoster** (see p. 1247).

**Varicella** (see p. 1248).

**Variola** (see p. 160).

**Stomatitis medicamentosa.**—Iodides may cause hæmorrhages or bullæ; many other drugs may cause bullæ, erosions, ulcers and lesions resembling lichen planus or erythema multiforme (see Drug Eruptions).

**Stomatitis due to heavy metals.**—Mercury in sufficient dosage causes salivation with gross swelling of the gums and tongue, often accompanied by nephritis. Lead causes a blue-black discolouration of the gums opposite areas of marginal gingivitis (pyorrhœa). There may also be ulceration. Silver causes a blue-grey pigmentation or an increase of melanin pigmentation. Bismuth may cause a similar discolouration, and gold may cause stomatitis and pigmentation. These metallic pigmentations have to be differentiated from that of Addison's disease and racial pigmentation which may occasionally be seen on the gums of white persons with some coloured ancestry, as well as in the mouths of coloured people.

*Scurvy* causes swelling, redness and friability of the gums and purpura or hæmorrhage. In *pellagra* the tongue is centrally stippled, beefy and raw at the narrow tip and sides. In *leikæmia* and *agranulocytosis* there may be purpura, hæmorrhages and secondary infection; in *pernicious anæmia* the tongue is smooth and glazed; in *hæmophilia* hæmorrhages may occur within the mouth. In untreated *diabetes mellitus* the tongue is large, red, dry, glazed and fissured and there may be gingivitis. In *uræmia* there may be oral ulceration and gingivitis. *Lichen planus* has been described elsewhere; buccal lesions occur most commonly and the lips, gums and tongue may also be affected in this malady. *Lupus erythematosus* occasionally affects the mucosal aspects of the cheeks; there are shiny red eroded areas with ulceration and leucoplakia.

*Erythema multiforme* (see p. 1257).

*Pemphigus* (see p. 1288).

*Behcet's syndrome* begins with ulceration of the mouth, ulceration of the genitalia or serious eye changes of conjunctivitis, keratitis or hypopyon iritis. One site may be affected months or years before the others. There may also be nodules in the skin or acuminate papules. The eye changes end in blindness. The cause is unknown and there is no effective treatment. Before the eyes are affected it is doubtful if this malady differs from *periadenitis mucosæ necrotica recurrens* of Sutton, or from *ulcus vulvæ acutum* recurrens of Lipschütz, both of which are described as causing ulceration of the mouth and vulva.

*Epidermolysis bullosa* of the skin may be accompanied by eroded oral lesions which go on to leucoplakia.

## LEUCOPLAKIA

*Leucoplakia* (mucosal dyskeratosis) is chronic stomatitis.

**Ætiology and Pathology.**—Leucoplakia may be caused by physical or chemical irritation, or it may be the result of various diseases within the mouth, including lichen planus, lupus erythematosus, syphilis or drug intoxications.

Histologically there is hyperkeratosis and parakeratosis and slight acanthosis.

**Clinical Picture.**—Leucoplakia may be smooth, irregular or verrucose. The smooth type is common on the buccal mucosa and is relatively benign, but on the lower lip it may be the precursor of carcinoma. The irregularly raised and depressed form is often syphilitic and precancerous. It occurs especially on the tongue and within the angles of the mouth. The verrucose form also is potentially carcinomatous. The habit of cheek chewing may cause a pseudoleucoplakic roughness and whitening just within the commissure.

**Diagnosis** from lichen planus is sometimes difficult and in fact may not be possible even on histological grounds. Lichen planus usually presents as polygonal white spots, feathery streaks or foliate tracteries, and atrophy with slight depression of the surface is more likely to be present than elevation, as in leucoplakia. At the vulva leucoplakia may be secondary to friction. Friction may also cause a white peeling condition, with fissuring of the perineum and perianal region: this, however, is not leucoplakia but lichenification, modified by the moist flexural situation. Leucoplakia only occurs on mucous surfaces. The distinction is important because it is unnecessary to excise the white skin of the perineum and perianal region in such a case on the grounds that it is a precancerous condition on the skin as well as on the vulva. Excision, if it is carried out, should be limited to the mucosa of the vulva.

**Treatment.**—Leucoplakia is best treated by bland applications such as normal saline mouth washes and hydrous ointment to the vermilion surface of the lip. Smoking, hot drinks and condiments are best avoided. No further action is necessary except periodic inspection for the earliest evidence of neoplastic proliferation. If this is seen, excision of the affected area should be carried out forthwith. Radiotherapy is inadvisable.

## GLOSSITIS

Ætiological factors in this condition are alcohol, smoking, condiments and gastrointestinal and metabolic disorders (Plummer-Vinson syndrome, sprue, pellagra, pernicious anæmia, diabetes mellitus). Electrogalvanism from metals of different electro-potentials in dental prostheses can cause a metallic or salty taste, salivation, tingling, shocks, eroded gums or tarnished teeth.

*Moeller's glossitis* (glossodynia exfoliata) is rare. It chiefly affects women, causing severe burning pain which makes feeding difficult. There are red patches of denuded filiform papillæ and white leucoplakic nodules.

*Glossitis rhomboidea mediana* is a lozenge-shaped elevation in the mid-line about the middle third of the tongue, well defined anteriorly but fading posteriorly into the circumvallate papillæ. It is due to the persistence of the tuberculum impar and is of no serious significance but is sometimes discovered accidentally by the patient who may think it is cancerous.

*Glossodynia*.—This may be symptomatic of irritation from heat, alcohol or trauma; of avitaminosis, pernicious anæmia, leukæmia, drug intolerance (especially phenolphthalein), electrogalvanism, xerostoma or cancerphobia. It may also occur from changes in the temporo-mandibular joints, usually due to lack of teeth resulting in abnormal stresses on these joints.

*Lingua geographica* is often accompanied by soreness. In this idiopathic condition there is a wandering superficial exfoliation which slowly changes its distribution day by day, producing reddened, denuded areas. It is benign and patients' fears of cancer can be allayed with confidence. Treatment is palliative, with normal saline mouth washes or, better still, by ignoring it. It tends to persist indefinitely.

*Lingua plicata* (scrotal tongue) is a congenital malformation of deep sulci running in various directions. Its significance is that it may lead to accumulations of food debris in these folds. Careful hygiene is advisable, perhaps using a wool-tipped probe to clean out the sulci.

*Lingua nigra* has two forms. The black "hairy" tongue is an hypertrophic condition of the filiform papillæ giving the centre of the tongue in its anterior third an appearance like a black dog's matted coat. The use of antibiotics may aggravate it by encouraging the growth of yeasts in the interpapillary spaces. The non-hairy black tongue may be caused by chewing tobacco or tooth paste, dyed sweets, certain drugs, chromogenic bacteria, fungi, or metallic sulphides. The tongue is dark in Addison's disease.

*Tumours of the tongue* include papilloma, carcinoma, hæmangioma and lymphangioma, lipoma, fibroma, sarcoma, chondroma and mucous cysts.

*Macroglossia* occurs in primary systemic amyloidosis and lingual keratoses in some cases of Darier's disease.

BRIAN F. RUSSELL.

## TROPICAL SKIN DISEASES

**Introduction.**—In the tropics and subtropics skin diseases are of major importance. In addition to those which are peculiar to hot countries, the skin diseases of temperate climates are commonly encountered there and for a variety of reasons often assume more serious significance. This was very evident in white troops fighting in the tropics in the War of 1939-1945.

Skin texture and pigmentation are important, and generally fair-skinned blond individuals do not stand hot climates as well as dark-complexioned people. Albinism and acquired leucoderma are both associated with lack of protective pigment in the skin and depigmented areas, especially in fair-complexioned individuals, and may



show abnormal cutaneous response to sunlight, with vesicular inflammation. Bright tropical sunlight is especially injurious in conditions of solar sensitivity, such as lupus erythematosus. Leucoderma has often a peculiar and sinister significance in dark-skinned people; not only on account of the great disfigurement it produces, but also because of its superficial resemblance to the depigmented patches of nerve leprosy.

Owing to the heat and humidity a considerable strain is placed on the sweat glands. The relatively alkaline reaction of sweat favours secondary pyogenic infection, as does the friction of soiled, sweat-sodden clothing. In arid desert country the skin becomes clogged with dust, and the bites of blood-sucking insects are specially prone to be associated with secondary bacterial infection. Skin diseases which are often regarded as a contraindication to tropical service include severe ichthyosis, lupus erythematosus, prurigo æstivalis, seborrhœic dermatitis, severe acne vulgaris, leucoderma and psoriasis (Fergusson). Severe and recurrent attacks of miliaria rubra may necessitate the sufferer abandoning the tropics. So may extensive tropical anhidrosis which is characterised by a goose-fleshlike appearance of the skin with local failure of sweating. O'Brien regards this condition as resulting from chronic occlusion of the sweat glands following successive attacks of miliaria rubra, and records that if more than 50 per cent. of the sweat glands be blocked in this fashion a state of tropical anhidrotic asthenia results.

Certain drugs which are used mainly or exclusively for the treatment of tropical disease may give rise to rashes. The use of photosensitising drugs should be avoided, and the possibility of aggravating acne remembered when using emetine-bismuthiodide in amœbic dysentery. The employment of mepacrine to prevent malaria may occasionally lead to tropical lichinoid dermatitis; it indicates an idiosyncrasy to the drug, the administration of which should cease.

The tendency for urticaria, eosinophilia and other allergic manifestations to develop in individuals with systemic helminthic infestations should be always remembered. Parasitic invasion of the skin may be associated with skin eruptions, such as "ground itch" caused by ankylostome larvæ and "swimmer's itch" by bilharzia and other cercariæ. Similarly, creeping eruption may result from migrating larvæ, such as *Ankylostoma braziliense* or the larvæ of bot flies of the genus *Gastrophilus*. Warbles or furuncle-like lesions discharging fly larvæ may be produced by flies of the genus *Hypoderma* or *Gastrophilus* laying their eggs under the dermis.

A variety of fungoid infections is common in the tropics. Their course is liable to be complicated by secondary pyococcal infection and parasitic achromia, due to depigmentary action of the fungus. Secondary leucoderma is not uncommonly seen in fungoid infections in dark-skinned natives.

Again, native customs may modify such conditions as keloid, which is very prevalent in parts of Africa where the negroes often purposely irritate wounds to produce tribal markings of a keloid nature.

Certain skin diseases, specially prevalent in, or peculiar to, the tropics and sub-tropics, which have not been considered in previous sections are described below.

## PRICKLY HEAT

**Synonyms.**—Miliaria rubra; Lichen tropicus.

**Definition.**—Prickly heat is an acute form of heat rash associated with excessive sweating in hot, humid climates.

**Ætiology.**—It particularly affects Europeans of obese diathesis, has a predilection for the covered parts of the skin, especially where there is friction from the clothes, and rapidly disappears on leaving the tropics by aeroplane or in cool weather. Probably it results from a mechanical blockage of the ducts of the sweat glands with keratin or sodden inadequately cornified cells of the stratum corneum. Bacteria

and yeast-like fungi have been incriminated, but they are only merely secondary invaders. According to O'Brien, sebaceous deficiency causes physical changes and closure in the keratin ring surrounding the sweat duct; occlusion follows, and rupture of the sweat duct and the formation of miliarial vesicles ensue; each sweat gland involved is said to remain obstructed for some time after the acute attack has subsided.

**Symptoms.**—The eruption consists of small glistening, superficial vesicles with a well-marked red areola and inflamed red papules which feel like grains of sand; it may involve the trunk, limbs, forehead and almost any part of the body. The pricking, burning sensation and great itching may be sufficient to prevent sleep, and secondary bacterial infection may result from scratching.

O'Brien records that repeated attacks of prickly heat may lead to extensive chronic sweat gland obstruction and tropical anhydrotic asthenia.

**Treatment.**—**PREVENTIVE.**—Previous suntan, loose clothing and working or sleeping in air-conditioned rooms or in the open air reduce the liability to prickly heat. Only light clothing should be worn and when possible it should be changed twice daily. Soap should be used with moderation when washing.

**CURATIVE.**—After a tepid bath the application of corrosive sublimate solution (1/1000) containing Eau-de-Cologne is helpful. Alternatively, the following lotion is useful: R acid-salicyl. gr. 30, hydrarg. perchlor. gr. 2, Sp. vini rect. 2 oz., Aq. dest ad. 6 oz. Subsequently a dusting powder, such as zinc oxide, boracic acid and starch in equal parts, or boracic acid and menthol, affords some symptomatic relief. In chronic cases, O'Brien advises desquamation of the stratum corneum by daily applications of 10 per cent. salicylic acid in 90 per cent. alcohol for 2 or 3 days, followed by inunctions of lanoline twice daily, and later once weekly to restore the lipoid deficiency.

## CRAW-CRAW

A West African native name (Kra-kra) applied to any itchy, papular or pustular eruption of the skin.

**Ætiology.**—O'Neill found filarial embryos in this eruption resembling scabies, but they were probably *Microfilaria streptocerca*, which Macfie has since commonly found in the skin of West African negroes. There is still doubt regarding its ætiology.

**Symptoms.**—The papules are hard and horny, occur chiefly in the limbs, and are very itchy: scratching and secondary infection lead to a pustular dermatitis with enlargement of adjacent lymph glands.

**Diagnosis.**—The condition must not be confused with scabies or coolie itch; no acari are obtained and no burrows seen. Cutaneous onchocerciasis has also to be differentiated.

**Treatment.**—Pustules are opened, ulcers scraped and crusts removed, then disinfected with 1 in 1000 sublimate solution or carbolic lotion and subsequently dressed with boric acid ointment.

## DESERT SORE

**Synonyms.**—Veldt Sore.

**Definition.**—A chronic septic sore, somewhat resembling impetigo contagiosa, occurring on exposed, hairy parts of the body and affecting individuals living in hot, dusty, arid regions; the causative organism is generally a hæmolytic streptococcus.

**Ætiology.**—The disease has a widespread geographical distribution in hot, dry, sandy or desert country, being known as veldt sore in South Africa, barcoo rot in Northern Australia, and desert sore in Egypt, Mesopotamia and Iraq, where many thousands of troops acquired the disease in the War of 1914–1918. It was equally prevalent in the campaigns in Egypt, Palestine and the Western Desert (1940–1943),

where it caused considerable loss of manpower. Laboratory and field investigations then indicated that the sores were due to infection of the skin following minor injury, such as scratches, abrasions and insect bites on exposed parts of the body. The infecting agent was almost invariably a hæmolytic streptococcus, often associated with a pyogenic staphylococcus (Keogh *et al.*). In one or two minor outbreaks virulent diphtheria bacilli were isolated, but this finding is infrequent; the cutaneous infection probably originated from latent or patent faucial or nasal diphtheria in the first instance. Nor was there any discoverable relationship between these sores and deficiency of vitamin C in the rations, or latent scurvy as measured by urinary excretion tests. The origin and persistence of these sores were largely connected with the difficulty of keeping the skin clean in a hot and dusty climate when arduous physical work had to be performed and little opportunity existed for bathing, washing clothing or sterilising blankets. Often the troops were crowded together under conditions when droplet spray infection of clothing and skin would occur; some 7 per cent. of troops harboured in their throats the same serological types of hæmolytic streptococcus as were isolated from the sores.

**Symptoms.**—The desert sore commences as a small vesicle or group of vesicles containing clear fluid which soon becomes turbid and yellow. The lesions are situated on the dorsum of the hand and forearm and elbow when sleeveless shirts are used or the sleeves rolled up; around the knees and on the thighs when shorts are worn; and they also occur on the dorsum of the feet, the ankles, legs and face. The vesicles, which are painful and surrounded by a dull-red erythematous zone, soon rupture and a circular or oval punched-out ulcer is formed. Its base, which is composed of granulation tissue exuding yellowish-green pus, is often covered by dark-grey pseudo-membrane, which rapidly re-forms if separated. The edges are dull red at first but later bluish in colour. In some instances undermining occurs, and the ulceration may rapidly extend into fresh tissue at a time when the ulcer appears to be healing satisfactorily. Desert sores are generally multiple; they may cause considerable pain and lead to deterioration in general health, especially if septic complications ensue. They may take months to heal, and often leave a thin scar. Septic complications include cellulitis, lymphangitis, adenitis, bursitis and septicæmia.

In those comparatively rare outbreaks in which true virulent diphtheria bacilli are demonstrable in the local lesions, faucial diphtheria and carriers are generally prevalent and the cutaneous diphtheria has probably originated from droplet spray infection of traumatised skin. Diphtheritic palsies, such as paralysis involving the palate, arms, legs, iris and muscles of accommodation, were recorded in the War of 1914–1918. In campaigns in Palestine and the Western Desert, a few such cases were encountered in the War of 1939–1945, but it was always doubtful whether the exotoxin causing such paralyses had been derived from the cutaneous membrane or from coexisting unsuspected faucial or nasal lesions.

**Treatment.**—**PROPHYLACTIC.**—Efficient prophylaxis depends on prevention of skin infection by personal hygiene and adequate first-aid treatment of minor skin traumata. Bathing, or a bath or shower after the day's work, adequate changes of well-washed clothing, and sterilisation of sheets and blankets are important. The surrounding skin area should be shaved, the wound epilated and washed with a disinfectant soap or 2 per cent. freshly prepared lysol solution, followed by methylated spirits or iodine. Elastoplast should then be applied and left *in situ* some 4 to 7 days.

**CURATIVE.**—If seen in the vesicular stage the vesicle should be pricked with a sterile needle, the raised skin cut away, hairs in the sore removed and a moist eusol dressing or diluted ammoniated mercury ointment applied. Ambulatory patients who have resisted treatment, those with multiple deep ulcers or sores around the ankle, elbow and knee joint, where movement prevents healing, and those in which septic complications have ensued should be admitted to hospital for treatment. Rest is an important factor in the recovery of such patients, and splinting may be necessary if multiple

deep ulcers exist in the vicinity of joints. The sores should be cleansed, treated with a 1/1000 solution of aminacrine (5-amino-acridine) and covered with non-adhesive dressing, such as "tulle gras", which is coarse curtain net impregnated with petroleum jelly (99 per cent.), and balsam of Peru (1 per cent.). The application of Flavogel—a water-soluble preparation of aminacrine in starch and tragacanth—is a satisfactory alternative treatment. Dressings should not be done more frequently than once daily, and small sores may be strapped and left much longer. In the large chronic ulcers, skin grafting is indicated to reduce the time of healing. Septic complications, such as cellulitis, call for the usual treatment, and oral sulphonamides or penicillin are indicated when there is evidence that streptococcal infection is spreading to surrounding tissues or lymph glands. Diphtheritic sores are a special problem. Skin grafting, combined with large doses of penicillin and diphtheria antitoxin parenterally, produce the best results.

## TROPICAL ULCER

**Synonyms.**—Ulcus tropicum; Naga sore; Phagedenic ulcer; Tropical sloughing phagedena.

**Definition.**—Tropical ulcer is a gangrenous, sloughing ulceration of the skin and subcutaneous tissues which may involve underlying muscle, tendons or bones; it generally occurs in the humid tropics, runs an intractable, chronic course; fusiform bacilli and spirochaetes are frequently demonstrable in the discharges.

**Ætiology.**—In contradistinction to desert sore this disease is generally, but by no means always, confined to the damp, steamy, tropical jungles occurring most often within latitudes of 35° N. : 10° S. It is common in underfed, debilitated and diseased populations, may affect people of any age and either sex, and occasionally assumes epidemic proportions, especially amongst coolies or native labourers on the plantations, and native tribes who eat a vegetarian diet containing only protein of low nutritional value. Meat- and fish-eating tribes are rarely affected, and outbreaks among the Somalis occur when the supply of camel's milk is low. Some have regarded deficiencies in vitamin D, calcium, nicotinic acid and riboflavine as factors in its development. All agree that skin trauma is essential, and that malnutrition and lack of personal cleanliness predispose to the condition.

*F. fusiformis* and spirochaetes are commonly demonstrable in the ulcer (70 per cent.) and less frequently staphylococci, streptococci and bacilli of various types. The condition is directly transmissible by inoculation of ulcer pus from man to man, or the direct application of pus to the scarified skin over the external malleolus; it is also recorded following the direct inoculation of anaerobic cultures of *F. fusiformis* into a traumatised area of dermis. Though the ætiology remains doubtful the available evidence indicates *F. fusiformis* is the probable cause.

**Pathology.**—There is coagulation necrosis and sloughing of the skin and subcutaneous tissue, and separation of the slough leaves a foul acute ulcer with an adherent yellow base. Vascular changes are said to occur even early in the disease and to consist essentially of thickening and narrowing of the lumina of vessels, which may sometimes be obliterated and sometimes recanalised; arteries, veins and capillaries are all to some extent implicated (Golden and Padilla).

**Symptoms.**—Phagedenic ulcers generally occur on the dorsum of the foot and the lower two-thirds of the front of the legs. The thighs, the hands and forearms are rarely affected. Ulcers are generally single but may be multiple, and old scars indicating previous lesions may be present.

The disease originates as a sero-sanguineous bleb which soon ruptures leaving a dirty grey slough. This process rapidly extends, forming a foul sloughing ulcer with granulation tissue sides and adherent yellowish-grey base which may attain several inches in diameter, and gives rise to considerable pain and perhaps intermittent

fever, toxæmia and anæmia. Sometimes there is spreading gangrene, and the ulcerative process involves surrounding or deeper structures like the toe nails, muscles, blood-vessels, nerves and especially periosteum, bone and joints. Epidemics are recorded in which extension to tendons and bones occur in one-third of the cases. Three stages are recognisable: (1) spreading sloughing ulceration, (2) a stage of tissue equilibrium when destruction and growth of granulation tissue are equalised and (3) healing. Often these ulcers persist for months unless properly treated; one factor delaying healing is inadequate epithelial proliferation even after a healthy granulation tissue base has formed. Excessive fibrosis and adhesion of scar tissue to bone is another cause of failure.

**Prognosis.**—Ulcers generally heal with modern treatment but the time taken varies with the facilities available for treatment, the size and condition of the ulcer and the resistance of the patient. In acute fulminating cases, unless penicillin be available, death may occur from toxæmia or septicæmia, and amputation may be necessary to save life.

**Treatment.**—**PREVENTIVE.**—In Europeans protection of the legs with gaiters or puttees is advisable in jungle countries, and shorts should not be worn. First-aid treatment of minor skin traumata is essential. A well-balanced diet would probably prevent epidemics developing in native populations.

**CURATIVE.**—Continuous rest in bed is desirable but is frequently not practicable; with natives, the leg may have to be tied to some fixed apparatus to enforce this. A well-balanced nutritious diet adequate in high class protein and vitamins should be given; any existent vitamin-deficiency should be treated. Cod-liver oil, calcium and certain vitamins of the B<sub>2</sub> complex have been specifically advocated.

In the rapidly ulcerating stage complete débridement is an essential preliminary to any treatment. Sloughs should be removed and the ulcer irrigated—preferably by diluted hydrogen peroxide. Various treatments have been advocated. Antiseptics such as carbolic, copper sulphate, eusol and proflavine have been widely used in the past; a paint consisting of copper sulphate 2 drachms, phenol 1 drachm, glycerin 1 oz., has proved useful. Others prefer the application of hypertonic or isotonic magnesium sulphate to clean the ulcer. Alternative treatments which have the advantage of avoiding daily dressings are to apply Z.I.P.P. to the ulcer and then put the leg up in a plaster cast (Cornell and Buchanan), or to firmly bandage with Elastoplast after dusting with iodoform powder. Should septic dermatitis develop, other treatment must be substituted without delay.

The most promising of all recent treatments is penicillin. In Europeans and in acute fulminating cases this should be given intramuscularly in appropriate dosage, but this routine is generally not feasible in natives both on account of expense and because they object to multiple injections. Excellent results have been reported with local penicillin applied as a powder, in solution on gauze dressings or as a cream. It should be continued for 2 or 3 days after fusiform bacilli and spirochaetes have disappeared and the ulcer has become clean. Oral chlortetracycline and chloramphenicol have recently been used successfully, especially in early lesions, which heal rapidly under such treatment and do not frequently relapse. *Chlortetracycline*: 500 mg. 3 times a day for 2 to 10 days. *Chloramphenicol*: same dosage for 7 days.

Whatever the treatment once the ulcer has become clean, skin grafting including "pinch" grafts accelerate recovery. In chronic ulcers where there is much fibrosis and the ulcer base has become adherent, complete excision followed by skin grafting may be necessary.

## TINEA

Ringworm infections abound in the tropics, some being confined to special regions, while others are much the same as in temperate climates. The chief ones are:

(1) *Tinea cruris* or dhobie's itch; (2) Hong Kong foot or ringworm of the foot; (3) *T. unguium*; (4) *T. imbricata*. The first two are due to the *Trichophyton*, *Epidermophyton inguinale*: they are not peculiar to warm climates and are described elsewhere (pp. 1236, 1237).

**TINEA UNGUIUM.**—A mycotic infection of the nails affecting Europeans from the Far East: it may last for years and be associated with ringworm elsewhere. The nail-bed is involved, leading to brittleness, ridging and opaqueness of the nail. Diagnosis is made by demonstrating *Epidermophyton inguinale* in scrapings mounted in liquor potassæ. The application of a 2 per cent. watery solution of copper sulphate or treatment with X-rays may prove helpful. In severe cases the nails may have to be removed before cure is effected.

**TINEA IMBRICATA (Tokelau).**—A form of ringworm mainly indigenous in the Eastern Archipelago and South Pacific, and characterised by non-inflammatory raised brown spots, giving rise to flaky tissue-paper scales which are free centrally, but attached at their peripheral bases, producing a rosette-like appearance. These circles are about  $\frac{1}{4}$  in. in diameter and as adjacent ones form they cause a characteristic festooned appearance. The fungus, *Endodermophyton concentricum*, is readily demonstrable in the scales: it affects the face, trunk and limbs, but the palms, soles, scalp, axillæ and crutch generally escape.

The local application of linimentum iodide (B.P.), chrysarobin ointment (2 per cent.), or of resorcin (1 drachm) in tinct. benzoin co. (1 oz.) are curative. Clothing should be boiled to prevent reinfection.

**PITYRIASIS VERSICOLOR or Tinea Flava** is common in the tropics, producing pale, yellowish-brown scurfy patches on the pigmented negroid skin, especially on the face, neck, arms and chest. Castellani holds that the yellow patches met with in his Ceylon cases differed from the brownish patches long recognised as being caused by *Microsporon furfur* in the European disease, and has named the tropical variety *Tinea flava* and the causal fungus *Malassezia tropica*; the black variety, which is caused by *Cladosporium masoni*, Castellani calls *Tinea nigra*.

The skin should be washed daily with green soap in spirit, followed by the application of a saturated aqueous solution of sodium thiosulphate. In severe cases, ung. hydrarg. ammon. dil. should be applied daily. Sterilisation of the clothing is necessary to prevent reinfection.

## PINTA

**Synonyms.**—Mal de los pintos; Caraate.

**Definition.**—A skin disease characterised by pigmentation, depigmentation and hyperkeratosis caused by the *Treponema carateum*.

**Ætiology.**—The disease is found in tropical America and is specially common in Mexico and Colombia. It occurs almost exclusively in dark-skinned races and is caused by the spirochæte, *T. carateum*, which morphologically resembles *T. pallidum* and is demonstrable in the lesions. Syphilis, however, does not appear to confer immunity. Transmission probably occurs by direct contact or through flies feeding on open sores.

**Pathology.**—So far visceral lesions have not been described. In the skin there are mild chronic inflammatory changes with disturbances of the melanophores and thickening of the corium. Sections of the early lesions have revealed *T. carateum* in the epidermis.

**Symptoms.**—The first stage is said to consist of a papule followed by a secondary stage when flat erythematous lesions known as pintids appear. The late or tertiary stage is characterised by patches of pigmentation mainly involving the back of the hands and wrists, or the feet and ankles, and spreading to other parts of the body.

The patches are generally symmetrical, rough, dry and raised; they vary in colour and progress finally to leucoderma. Hyperkeratosis also is liable to involve the palms and soles. There may be considerable itchiness and, if fissuring occurs, an offensive serous discharge is liable to result. The Wassermann and Kahn reactions are generally positive in the later stages of the disease.

**Treatment.**—The treatment is similar to that of syphilis, neo-salvarsan and similar arsenical drugs being specifics.

## PIEDRA

Piedra or trichosporosis is a disease common in Columbia and British Guinea in which hard, gritty, black nodosities form around the hair of the scalp; it is caused by the *Trichosporon giganteum* and may be confused with ordinary *Trichomycosis nodosa*.

## CREEPING ERUPTION

**Synonyms.**—*Larva migrans*; *Myiasis linearis*; *Hautmaulwurf*.

**Definition.**—A peculiar linear, slightly raised red eruption, gradually creeping forward in a sinuous or straight line, the posterior end fading away.

**Ætiology.**—The condition may be produced by *Gastrophilus* or other fly larvæ wandering under the skin, but more commonly it is due to filariform larvæ of the cat and dog hookworm, *Ankylostoma braziliense*, which have accidentally invaded man.

**Symptoms.**—The symptoms vary in different individuals and include smarting pain and intense itching along the raised line which first shows red spots, and later hard round red papules 2 to 5 mm. in diameter; vesiculation or pustulation may occur. Unless treated the condition persists for a long time.

**Treatment.**—Freezing the anterior end of the line where the larva is located, with an ethyl chloride spray for 2 minutes, is suitable for the type due to canine ankylostomes. Oleum chenopodii applied locally, either pure or diluted, with 3 parts of castor oil has been favourably reported on. If the lesions are produced by fly larvæ, the skin should be dried, cleaned with alcohol and cleared with cedar wood oil. By means of a hand lens the larva can be seen as a spherical white mass at the end of its burrow. Novocaine should be applied before local cauterisation.

## ULCERATING GRANULOMA

**Synonyms.**—*Granuloma venereum*; *Granuloma inguinale*; *Granuloma inguinale tropicum*; *Ulcerating Granuloma of the Pudenda*; *Serpiginous Ulceration of the Genitals*.

**Definition.**—A very chronic ulcerating condition of uncertain ætiology occurring in the tropics, involving the genitals, perineum and groins.

**Ætiology.**—The disease occurs in the West Indies, Guiana, Brazil, Puerto Rico, parts of India and Africa, the Pacific Islands and Northern Australia. Both sexes are affected, but not before puberty, and all races are susceptible. Donovan and many other observers have found a short, oval bacillus specially located within the mononuclear cells; it is a non-motile, capsulated bacterium of the rhinoscleroma group, but though found with frequency in the lesions there is still doubt as to its real ætiological significance. The disease itself is probably contracted during coitus.

**Pathology.**—The condition resembles an infective granuloma, and microscopic

section of the nodules situated at the edge of the sore shows infiltration with plasma and round cells containing poorly staining nuclei, in which phagocytosed bacilli may occur in clumps. The granulomatous tissue is very vascular, while in the older areas fibrosis and scarring are marked. Spread is by direct continuity and the lymphatic system is never involved.

**Symptoms.**—The disease begins on the genitals as a flat papule which desquamates, leaving a red granulation-tissue surface which bleeds easily: this superficial ulceration extends serpigiously producing offensive pus. As the process advances the older areas cicatrise, but this scar tissue readily breaks down again. The disease is auto-inoculable so that adjacent parts such as the scrotum and thighs, or the surfaces of the labia become infected. Ultimately the whole of the penis, scrotum and groins in the male, and the clitoris, vulva, labia, vagina, perineal and perianal region in women become involved, and, if unchecked, the urethra and rectum as well. Though skin ulceration extends slowly over a period of many years, the process accelerates once the mucous membranes are involved, and here there is little tendency to heal. Until the terminal phase the general health remains good and the local lesions give rise to a minimum of pain and discomfort.

**Complications.**—These include recto-vaginal fistula, urethral stricture, septic cystitis and pyelitis. The lymph glands are only implicated if there is secondary coccal infection. Cicatrisation may block the lymphatics and cause pseudo-elephantiasis of the genitals.

**Diagnosis.**—Ulcerations due to syphilis, tubercle or lupus vulgaris may be confused, and where the glans penis is involved with fungating granuloma, epithelioma may be suspected.

**Prognosis.**—This has greatly improved by modern treatment; formerly the condition was hopeless, frequently lasting for life.

**Treatment.**—**PREVENTIVE.**—As the disease is generally contracted by illicit intercourse with native women this should be avoided or appropriate prophylactic measures taken.

**CURATIVE.**—Formerly, the trivalent antimony compounds like tartar emetic, Anthiomaline and stibophen (Fouadin) were widely employed and regarded as specifics. Intravenous injections of tartar emetic were administered as in schistosomiasis (p. 321), only a longer course of injections and a greater total dosage was given, i.e. gr. 50 to 150. Streptomycin, chlortetracycline and chloramphenicol have proved considerably more satisfactory than antimonials in treatment. Most cases, even those resistant to antimony, respond to these antibiotics, and surgical excision and skin grafting should not be necessary. *Streptomycin*: 1.0 g. intramuscularly every 6 hours for 5 days will cure most cases. Pain is relieved in 24 to 48 hours in most cases and healing takes place within 4 weeks. Relapses after streptomycin therapy are few and will usually respond to further treatment with this antibiotic, or to chlortetracycline or chloramphenicol. *Chlortetracycline*: 250 mg. orally every 6 hours may be given until healing is complete. A total dosage of 15 to 20 g. is usually required. *Chloramphenicol*: up to 3.0 g. orally per day may be given in divided doses. Dosage for 10 to 12 days is usually adequate.

BRIAN MAEGRAITH.



## SECTION XVIII

# DISEASES OF THE NERVOUS SYSTEM<sup>1</sup>

## INTRODUCTION

THE diagnosis of a case of central nervous disease involves answers in turn to the two questions: Where is the lesion? (the topographical diagnosis), and What is the lesion? (the pathological diagnosis).

*Where is the lesion?*—The central nervous system is not susceptible of examination by direct methods, and all that can be examined are the functions of its various parts. The first step is to determine as accurately as possible what disturbances of function are present (sometimes called physiological diagnosis); inferences can then be drawn as to what structures in the brain, spinal cord or nerves are affected, and consequently as to the site of a local lesion. In occasional cases confirmatory localising information is obtained by special techniques, such as radiographic examination and electro-encephalography, and in some cases these methods may even provide the only evidence of the location of the disease.

*What is the lesion?*—In endeavouring to determine the nature of the disease present, we are in general dependent on information obtained from sources other than the examination of the nervous system, namely: (1) the history of the case; (2) the general examination of the patient and (3) special tests.

(1) In no department of medicine is careful and expert history-taking more important. The same physical sign has very different significance according to whether it has come on suddenly, with moderate quickness or very gradually. (2) A general examination of the patient should never be omitted. Disease of the lungs, heart, blood vessels, blood, liver and abnormalities of the skin are all of great diagnostic significance in relation to nervous disease. (3) Of the special tests, ophthalmoscopic examination comes first and is always performed at the same time as the functional examination of the nervous system. It often provides most important evidence of the nature of the disease. The examination of the cerebro-spinal fluid and the Wassermann reaction of the blood frequently help to reveal the kind of disorder present. Radiographic examination, its power now enlarged by special techniques, may be equally diagnostic. Electro-encephalography is a relatively new aid, of which the diagnostic value is gradually increasing.

*Symptoms and their Modification.*—This brings us to a brief consideration of the ways in which lesions within the nervous system may disturb its functions. The functions of a region of the brain that is directly involved in a disease-process may be deranged in either of two ways. They may be stimulated to over-activity or they may be diminished or abolished. We may thus speak of "*irritative*" or "*excitatory symptoms*" on the one hand, and of "*paralytic symptoms*" on the other, a Jacksonian fit being an example of the first, while hemiplegia is an instance of the second. Thirdly, impairment or abolition of one function may cause serious derangement of another. A lesion of the posterior columns of the spinal cord gives rise not

<sup>1</sup> While this section has been largely rewritten, the authors have made use of much of the material of previous editions and desire to express their indebtedness to the original authors. The authors also thank Messrs. Butterworth & Co. (Publishers) Ltd. for permission to make use of parts of Dr. Purdon Martin's article on Neurosyphilis in *The British Encyclopædia of Medical Practice*.

merely to an impairment of the sense of position—the function which those columns subserve—but also to a severe disturbance of the motor functions. But the ataxia which results is clearly produced by the activity of the intact motor structures working in the absence of adequate sense of position, and is an indirect or secondary effect of the lesion, which is brought out only when the motor structures come into action.

A final group of symptoms are those which we speak of as “release phenomena”. When the coma of a hemiplegic patient has passed off he is left with paralytic symptoms, namely, the hemiplegia. In a few weeks the paralysed limbs become spastic, their tendon jerks increase and clonus makes its appearance. These symptoms of persistent over-action of intact nervous mechanisms freed by the lesion from the normal control of physiologically superior mechanisms are what are called “release” symptoms. Such symptoms may persist indefinitely and in some instances may entirely dominate the clinical picture.

The symptoms produced by a lesion depend primarily on its localisation, *i.e.* on the nervous structures damaged by the lesion, and from this aspect they are considered in some detail in a later portion of this section (p. 1357). But it must be recognised that the symptoms may also be profoundly influenced by the pathological nature of the lesion. A suddenly arising lesion, such as an arterial occlusion or hæmorrhage or a direct injury, is apt to produce a much more severe and definite local disorder of cerebral function than a slowly developing lesion of similar extent. Indeed, it is often a matter of surprise to observe the degree to which the brain can adapt itself to structural changes which are brought about gradually. Thus the intracranial cavity may come to accommodate a large new growth which compresses and markedly deforms the brain without giving rise to any objective symptoms or to any abnormal physical signs discernible on examination. It is similarly known that a cerebral or cerebellar abscess is commonly present for some weeks before it reveals its presence by signs or symptoms; this is its period of clinical latency.

Again, a tumour within the brain, while it may give rise to symptoms of increased intracranial pressure, such as headache, vomiting and papillædema, may yield on examination few or no localising signs, and this is not necessarily because it is in what is known as a “silent area” of the brain, but simply because the essential nervous elements have not been seriously damaged by it. For instance, a glioma, being a tumour of the interstitial elements, may cause a minimal disturbance of observed nervous function even when large regions of the brain of known and specific function are directly involved by it.

As another example of the modification of symptoms by the nature of the lesion, a general disturbance may follow a local lesion as a result of what is known as *diaschisis* or *shock*. We see this mode of disorder in the coma which accompanies a cerebral hæmorrhage. In this state the cerebral hemispheres are for the time being out of action as a whole—even those parts not actually damaged by the lesion. Such shock symptoms are necessarily transient.

Finally, we have to recognise that with space-occupying lesions within the skull or brain there may ultimately arise indications of local disorder of function of parts of the brain remote from the lesion. These may be spoken of as *false localising signs* and may result from such processes as œdema, “*contre-coup*” pressure or interference with the circulation of blood or cerebro-spinal fluid.

From what has been said it will be apparent that while the first step in neurological diagnosis is the recognition of the disorders of function present, the localisation of a lesion (the *topographical diagnosis*) and the determination of its nature (the *pathological diagnosis*) are usually something more than a simple essay in the applied anatomy and physiology of the nervous system, and that the complete diagnosis calls for a knowledge of the natural history of the different disease processes—that is of the pathology of nervous diseases—and for clinical experience.

## DISORDERS OF THE CRANIAL NERVES

### THE OLFACTORY NERVE AND TRACT

Small olfactory nerve filaments arise from special receptors in the olfactory portion of the nasal mucosa, and joining together into small nerves pass through the cribriform plate of the ethmoid bone to end in the two olfactory bulbs. From each olfactory bulb an olfactory stalk passes backwards on the inferior surface of the frontal lobe of the brain and ends in two roots, lateral and medial, on either side of the anterior perforated spot.

Loss of the sense of smell (anosmia) is frequently due to disease of the nasal mucosa, and only occasionally is it of diagnostic value in cases of nervous disease or injury. It occurs in cases of head injury, especially if the patient has fallen upon his forehead or upon his occiput, and is usually due to tearing of the olfactory nerves, with or without fracture of the cribriform plate. In most cases the loss of smell is permanent.

Unilateral or bilateral anosmia may result from meningeal tumours arising from the olfactory groove and pressing on the inferior surface of one or both frontal lobes, and it occasionally results from basal syphilitic meningitis.

Flavours are actually appreciated by the sense of smell, so that a patient who has lost this sense is apt to think that he has lost his sense of taste as well, but if the sense of taste is retained he will still be able to appreciate the primary flavours—salt, sweet, bitter and acid.

### THE OPTIC NERVE

The optic nerve is developed as a cerebral tract and retains something of that character throughout life. The primary visual neurones are situated entirely in the retina: it is the neurones of the second order whose fibres form the optic nerves and tracts. Disturbances of these structures are frequent and are of great importance in many kinds of nervous disease.

The optic nerve head or optic disk can be seen with the ophthalmoscope and is the only part of the central nervous system which can be examined by inspection. Congenital abnormalities of the optic disk are not uncommon, the most important being the presence of opaque nerve fibres. When viewed with the ophthalmoscope a bundle of opaque nerve fibres is seen as a glistening white streaky mass appearing to stream out from the nerve head into the adjacent parts of the retina. The fibres may be limited to one quadrant, or may be all round the disk. The acquired disturbances of the optic nerve give rise to four principal syndromes: (1) papillædema, (2) optic neuritis or neuro retinitis, (3) retrobulbar neuritis and (4) optic atrophy.

#### PAPILLÆDEMA

The term denotes an œdema of the optic papilla or nerve head, and the significance of such œdema lies in the fact that it is almost invariably due to raised intracranial pressure; it is frequently the only objective sign of that state, and it is important that the student should be familiar with it in all its stages. Before there is any actual œdema of the optic nerve head the principal veins of the retina may appear distended, and the disk appears somewhat redder than its normal colour. Then the margin of the disk becomes blurred in its upper and inner quadrant or in its uppermost portion; this blurring extends around the disk and at the same time the cup of the disk becomes filled up. The disk becomes much redder than normal and may be of almost the same colour as the retina. The disk continues to swell and bulges slightly into the

eye, and this swelling can be measured with the ophthalmoscope relative to the surrounding retina in terms of dioptres; a swelling of 4 dioptres is common but higher degrees of swelling are rare. As the swelling increases the disk margins become still more blurred and some hæmorrhages and exudate may appear. With the increase of swelling the arteries appear to sink down as they pass off the disc on to the retina, and the retina close to the disk, especially on the macular side, may show some swelling or tendency to fold. When the rise of intracranial pressure is slow, the œdematous disk is less highly coloured than when the pressure rises quickly and the œdema is more acute. In the early stages of papillœdema there is little disturbance of vision, but when the swelling becomes severe the patient begins to complain of some blurring of vision and of transitory severe disturbance of sight (*amaurosis fugax*) associated with stooping or with physical effort.

If the intracranial pressure is high and is not soon relieved, the sight eventually fails, the disk becomes paler and takes on a somewhat waxy appearance, and gradually subsides into atrophy. This "consecutive" or "post-neuritic" atrophy can in many instances be recognised ophthalmoscopically by the irregularity of the edges of the atrophied disk, consequent on the preceding swelling and exudation.

#### OPTIC NEURITIS AND NEURO-RETINITIS

Actual inflammation of the nerve head is rare, but the abnormal state of the disk and retina that is associated with renal disease with arterial hypertension is often mistaken for papillœdema due to raised intracranial pressure. The disc is blurred and usually slightly swollen; the swelling of the disk, however, rarely exceeds 2 dioptres while the changes in the retina are pronounced and extensive, and are much greater than those that may be associated with papillœdema.

#### RETROBULBAR NEURITIS

This term is applied when disease, regarded as inflammatory, affects the optic nerve behind the papilla, and, as a rule, the disease is situated farther back than the point, about half an inch behind the eye, where the central vein emerges from the optic nerve.

Local lesions in the substance of the nerve between the globe of the eye and the chiasma are very common, and according to their severity give rise to partial or complete blindness in the corresponding eye. As the central part of the optic nerve is the site of election for such lesions, the visual defect is commonly in the form of a central scotoma. This is the characteristic disturbance and is usually acute or subacute in its onset, but there are a number of associated phenomena. The patient frequently complains of pain on movement of the eyeball and sometimes of pain above the eye. The fundus of the eye usually looks normal, but when the disease comes forward to the papilla redness of the optic disc and blurring of its edges may be apparent. The pupil is usually moderately dilated; it reacts to light but often does not maintain the reaction. These associated phenomena soon pass off and in most cases the central scotoma begins to diminish within a few weeks. The prognosis depends, however, on the cause of the syndrome.

*Disseminated sclerosis* is the usual cause of acute retrobulbar neuritis. With this condition the disturbance is almost invariably unilateral and a great degree of recovery is the rule. Functional recovery may be complete; in other cases a central scotoma for colour, or a small absolute central or paracentral scotoma is left. Characteristically a slight degree of optic atrophy follows, causing permanent pallor of the temporal half of the optic disc.

Bilateral retrobulbar neuritis occurs from toxic causes and also occasionally without discoverable cause, and the outlook for recovery of vision in such cases is

always doubtful. The less severe toxic cases are usually due to tobacco; more severe disturbances are due to such causes as poisoning by wood spirit present in alcohol, by arsenical compounds such as tryparsamide, by lead compounds and by quinine. Retrobulbar neuritis may also be bilateral in neuro-myelitis optica, a rare demyelinating disease closely resembling an acute form of disseminated sclerosis. Leber's disease is a familial malady characterised by retrobulbar neuritis; males only are affected and the symptoms make their appearance after puberty and usually before the age of 25. Repeated attacks may occur and a severe degree of optic atrophy result.

### OPTIC ATROPHY

Optic atrophy is recognised on ophthalmoscopic examination, by a peculiar whiteness and flatness of the disk with a very high contrast at the edge of the disk between disk and surrounding retina, both as regards colour and limitation. The lamina cribrosa—the sieve-like cross-latticing of the strands of the sclerotic through which the bundles of optic nerve fibres pass—becomes visible as a stippling of the temporal region of the disk. The vessels of the retina become atrophied, and are seen to be unduly small. In many atrophies the edge of the disk is sharply cut; but when atrophy follows papillœdema the edge is apt to be fluffy, like that of torn cotton-wool. Optic atrophy is usually classified as "primary" or "consecutive", according to whether the atrophy of the disk is the first observable change or follows upon papillœdema or inflammation of the disk, or optic nerve.

*Ætiology.—Primary optic atrophy.*—1. This is of frequent occurrence in the hereditary or congenitally installed diseases in which primary degeneration of neurones occurs, and, in particular, it occurs in association with the hereditary ataxias. In amaurotic family idiocy, and retinitis pigmentosa, both of which are familial diseases, optic atrophy is consequent upon degeneration of the neurones in the retina. 2. It is one of the common manifestations of syphilis of the nervous system and may occur alone, but much more usually it occurs as part of the syndrome of tabes or of general paralysis. It is not uncommonly met with in congenital syphilis. 3. It results from lesions of the optic chiasma and optic nerve, and is the constant result of long-continued pressure upon these structures. This variety, often called *retrograde optic atrophy*, is usually due to pituitary and other tumours in the neighbourhood of the chiasma, and occasionally to tumours, aneurysms or bony injuries behind or involving the optic foramen. It also results from local disease within the orbit. 4. It may follow the exhibition of certain drugs such as tryparsamide, methyl (wood) alcohol, quinine. 5. It may result from severe hæmorrhage from any part of the body, or from anæmia, and may occur in association with pernicious anæmia and subacute combined degeneration of the spinal cord. Optic atrophy may also result from diabetes, arterial disease (with or without thrombosis of the central artery of the retina) and from glaucoma.

*Consecutive optic atrophy.*—1. This follows the more severe grades of papillœdema, and is due to strangling of the optic nerve fibres by the œdema in the first place, and by the cicatrisation subsequently. Severe degrees of papillœdema may, if pressure be relieved, recover perfectly without atrophy or impairment of sight. 2. It follows inflammation of the optic nerve, and in occasional cases is seen in the late stages of the neuro-retinitis associated with arterial hypertension. 3. Partial optic atrophy of varying degree is an almost constant result of retrobulbar neuritis.

### THE OCULO-MOTOR NERVES

The third nerve supplies the internal muscles of the eye, and all the external muscles of the eyeball with the exception of the superior oblique (which is supplied

by the fourth nerve) and the external rectus (which is supplied by the sixth nerve). Complete paralysis of the third nerve produces a dilated and inactive pupil, complete ptosis and loss of upward, downward and inward movements of the eye; the eye assumes a position of downward and outward strabismus. As a rule diplopia is not complained of because of the dropping of the lid. Many third nerve palsies are, however, partial, and the muscles innervated by the nerve may be affected in different degrees. When diplopia is present it is a crossed diplopia, because the strabismus is divergent; there is secondary deviation of the sound eye and false projection in the visual field.

The fourth nerve supplies the superior oblique muscle. Paralysis produces no obvious strabismus, but in looking outwards or downwards there is a wheel movement of the globe which can be detected by observing the conjunctival vessels when the eye moves. The diplopia is most discomforting, and occurs in every position of the eyes, except on looking up. The diplopia is uncrossed, and the false image is lower than, and with its top tilted toward, the true image.

The sixth nerve supplies the external rectus muscle. Paralysis of it produces a convergent squint and uncrossed diplopia.

These oculo-motor nerves may be affected singly or in various combinations and the paralysis of any one of them may be complete or partial. In some cases the lesion responsible for the paralysis lies within the brain-stem, where it may affect either the nuclei of the nerves or the nerve-fibres in their intra-cerebral course. More often the lesion affects the nerve in its peripheral course—within the cranium, in the neighbourhood of the sphenoidal fissure, or within the orbit. To attempt to give a list of all the possible lesions—inflammatory, neoplastic, hæmorrhagic or traumatic—that affect these nerves would serve no useful purpose, but the following may be noted and certain syndromes should also be recognised. Syphilis is a common cause of third nerve paralysis, by involvement of the nerve in syphilitic meningitis; less commonly the sixth and fourth nerves are affected by the same process. Any of the forms of acute and subacute meningitis may similarly involve one or more of the oculo-motor nerves. Secondary malignant deposits in the meninges or in the brain-stem are not uncommon causes of ocular palsies. Primary intracranial tumours and aneurysms may cause paralysis of any or all of them by direct compression, but intracranial pressure of itself may cause paralysis of the sixth nerve as a result of downward displacement of the brain-stem. Paralysis of the sixth nerve are frequently "rheumatic" (i.e. of undetermined cause) or are associated with generalised arterial disease or with diabetes; the mechanism of the paralysis in such cases is obscure, but recovery within a month or two is the rule. A variable ocular palsy or variable diplopia is often due to myasthenia gravis.

*Syndrome of the sphenoidal fissure.*—All the oculo-motor nerves enter the orbit by the sphenoidal fissure and they are accompanied by the branches of the first division of the trigeminal nerve and the ophthalmic veins, while the second division of the trigeminal nerve enters the infra-orbital canal at the apex of the orbit. All these structures may be involved by a lesion at the sphenoidal fissure, the most common causes being aneurysm of the internal carotid artery at the anterior end of the cavernous sinus, and meningeal tumour. The syndrome usually begins with pain in the eye and forehead. Soon afterwards some proptosis is evident and there is pain on pressing the globe backwards. This is followed by signs of involvement of the oculo-motor nerves. The sixth is the first and sometimes the only nerve involved, and usually its paralysis is followed by that of the fourth, the first division of the fifth, the third and sometimes the second division of the fifth in that order. The final result may be a total ophthalmoplegia with anæsthesia of the eye, corresponding half of the forehead and the cheek, severe pain in the same distribution and unilateral proptosis, but the syndrome is often incomplete. When it is due to aneurysm the condition may largely recover within a few months.

The oculo-motor nerves may be paralysed in the wall of the cavernous sinus, either as a result of thrombophlebitis of the sinus or of an aneurysm of the internal carotid artery.

*Gradenigo's syndrome.*—This consists of paralysis of the sixth nerve and pain of trigeminal distribution associated with middle-ear disease. It has been attributed to localised meningitis at the tip of the petrous bone, but Symonds has pointed out that it may be due to thrombosis of the inferior petrosal sinus. It is usually seen in children, and radical treatment of the ear disease is indicated.

Lesions within the brain-stem may produce combined oculo-motor palsies; other cranial nerves may also be affected or the long projection paths may be involved. Finally, supra-nuclear ocular palsies may arise, as described below. Nuclear palsies may result from tumours, disseminated sclerosis, epidemic encephalitis, tuberculoma and small peri-aqueductal hæmorrhages. The rare condition known as *chronic progressive external ophthalmoplegia* formerly ascribed to degeneration of the oculo-motor nuclei is now believed to be due to myopathic disease of the muscles within the orbit. This disease may begin in young subjects, it is slowly progressive and leads to paralysis of all the external ocular muscles with ptosis which is usually incomplete; the internal ocular muscles are unaffected.

Oculo-motor nerve fibres within the brain-stem may be affected by vascular, neoplastic and granulomatous lesions. Thus a lesion in the cerebral peduncle will produce an ipsilateral third nerve paralysis with hemiplegia on the opposite side of the body (*Weber's syndrome*), and a lesion involving the red nucleus may cause an ipsilateral third nerve palsy with tremor of the limbs on the opposite side (*Benedikt's syndrome*).

#### CONJUGATE PARALYSIS

The uppermost portion of the main third nerve nucleus is concerned with upward movement of the eyes (superior recti), and the inferior recti are represented next in order from above downward. Bilateral lesions involving the upper parts of both nuclei consequently bring about a loss of vertical movements of the eyes, the horizontal movements being retained. The lowest part of each third nucleus is concerned with the internal rectus muscle and is connected with, and partly governed by, the sixth nucleus of the opposite side. A bilateral lesion at the level of the upper part of the pons, by involving these structures, may cause paralysis of horizontal movement of the eyes, vertical movements remaining unaffected. Paralysis of conjugate movements to one side occurs less frequently. The power of convergence is sometimes preserved when conjugate horizontal movement is lost.

#### SUPRA-NUCLEAR OCULAR PALSIES

In some cases, although the patient is unable voluntarily to perform certain ocular movements, it can be demonstrated that the muscles and nerves concerned are not paralysed, and movements of the eyes can be brought about reflexly by appropriate stimuli. The paralysis is, therefore, supra-nuclear and comparable to an upper motor-neurone paralysis. The patient may be unable to deviate his eyes to order, but deviation may be produced by labyrinthine stimulation. Or again, the patient may be unable to follow a moving object with his eyes, but if he fixes an object and his head is rotated passively, his gaze may remain fixed on the object and his eyes thus take up a position of deviation. In rare cases the eyes, when the head is still, may follow an object which the patient fixes intently. The lesions concerned are believed to be situated in the brain-stem, close to the oculo-motor nuclei.

#### ABNORMALITIES OF THE PUPIL

Myosis, or abnormal smallness of the pupil, may be due to paralysis of the cervical sympathetic (p. 1345); minute pupils are sometimes associated with syphilis of the

nervous system, particularly tabes, each pupil being possibly little larger than the head of a pin ("spinal myosis"); myosis occurs also with acute lesions of the pons and it may be met with in advanced age without pathological associations. It is a well-known sign of the action of morphine and it is produced also by the local action of eserine instilled into the eye.

Mydriasis denotes dilatation of the pupil. The sphincter pupillæ muscle is controlled by the small nucleus of Edinger-Westphal, which is the uppermost part of the third nerve nucleus. Mydriasis may, therefore, result from paralysis of the Edinger-Westphal nucleus, and more commonly it is one of the features of paralysis of the third nerve. It results also from the action of belladonna or atropine, or of cocaine whether taken internally or used as eye-drops.

*Inequality of the pupils* has numerous causes. Obviously it may result from any of the causes of unilateral myosis or of unilateral mydriasis given in the preceding paragraphs. Less specifically, it is common in nervous syphilis. It may result from a blow on one eye, or from disease of the eye. It occurs as a transitory phenomenon after the prolonged use of one eye, especially against a bright light, as in using the microscope. It is common with local cerebral lesions of all kinds, including closed head injuries. It is a feature of cases of intradural and of subdural hæmatoma.

*Irregularities of the shape of the pupil* are less common than inequality of the pupils. They may be due to local disease of the irides, but in certain cases of disease of the brain stem, especially syphilitic disease, one or both pupils may be oval in outline without evidence of local disease of the irides. Irregularity of the pupils is common in neuro-syphilis generally and is frequently associated with atrophic changes in the irides, such as are associated with diabetes.

#### ARGYLL ROBERTSON PUPIL

The normal pupil contracts briskly when light falls upon the eye and dilates in darkness: it also contracts in association with accommodation and convergence. The reaction to light is reflex and this reflex response to light may be lost when other reactions of the pupil are retained (reflex iridoplegia). In the particular form of reflex iridoplegia known as the *Argyll Robertson pupil*, the pupil is abnormal in that (1) it does not react at all to light, (2) it is very small and (3) it does not dilate fully under the influence of a mydriatic, while it is normal in that (1) it reacts normally with accommodation-convergence; also (2) reasonably good vision in the eye concerned is an essential part of the phenomenon. Such a pupil is almost invariably due to syphilis of the central nervous system, and is seen most frequently and characteristically in tabes dorsalis. The phenomenon is ordinarily bilateral, but there are often differences in size between the two pupils and usually the pupils are irregular in outline. Atrophic changes in the irides are generally apparent.

The afferent fibres of the light-reflex arc pass back with the visual fibres in the optic nerve and optic tracts, but, whereas the visual fibres end in the lateral geniculate body, the fibres which serve the light reflex pass on to enter the superior corpus quadrigeminum. From there a connection is formed by another fibre with the upper part of the oculo-motor nucleus (Edinger-Westphal nucleus). The efferent fibres of the reflex arc form part of the oculo-motor nerve. Since with the Argyll Robertson phenomenon vision is good, the visual path is evidently intact, and since the pupil contracts with accommodation convergence, the cells and fibres of the third cranial nerve, which innervate contraction of the pupil, must be intact; the arc must therefore be interrupted in its middle portion, *i.e.* between the place where the light-reflex fibres leave the visual fibres, and the oculo-motor nucleus. Degeneration of the fibres forming this middle portion of the arc is not, however, easy to recognise by staining methods and this theory still awaits anatomical confirmation.

The Argyll Robertson pupil, once established, persists in spite of antisyphilitic



treatment. As the tabetic process advances, the accommodation-convergence reaction may gradually be lost; and the pupil thus ceases to show the dissociation of reactions typical of the Argyll Robertson phenomenon, and becomes a fixed pupil.

Modifications of the Argyll Robertson pupil are frequently encountered in diseases of the nervous system. A slight reaction to light may be present in a pupil which otherwise conforms to Argyll Robertson's description. This represents a preliminary stage of the complete phenomenon and its significance is similar.

More frequently the pupil reacts normally with convergence and does not react to light, but it is not small and may even be dilated. Such a pupil is common in central nervous syphilis, but has not the diagnostic significance of the complete Argyll Robertson phenomenon, for it may be due to any lesion interrupting the light-reflex arc in its middle portion. A pineal tumour, for instance, or a tuberculoma or a patch of disseminated sclerosis may cause this abnormality, and it has been described in association with many different nervous diseases. If, however, atrophic changes are present in the iris, the condition is likely to be syphilitic.

#### PSEUDO-ARGYLL ROBERTSON OR MYOTONIC PUPIL

Pseudo-Argyll Robertson pupil (Foster Moore) or myotonic pupil (Adie) is a non-syphilitic abnormal condition of the pupil in which the reactions are all slow, but the light reaction much slower than the convergence reaction. The pupil is of ordinary size or somewhat larger and is usually bigger than the unaffected pupil of the other eye. No reaction is obtained to the light of a torch shone on the eye, but if the patient sits for 10 or 15 minutes in a bright diffuse light the pupil gradually contracts, and if he sits in a dark room it dilates slowly. During accommodation-convergence, contraction of the pupil takes place slowly and continues through an abnormal range of movement, so that as convergence is maintained, the myotonic pupil finally becomes smaller than its fellow. After relaxation of convergence the pupil takes many minutes to dilate to its former size. In pupils of this kind prompt and full dilatation occurs with mydriatics.

The phenomenon is usually unilateral and the iris of the affected eye does not show degenerative changes, such as usually accompany the true Argyll Robertson pupil. Accommodation may be involved in the disturbance and then the patient complains of inability to focus with the affected eye.

**Ætiology.**—The cause of this phenomenon is unknown. It is the more likely to be mistaken for a syphilitic abnormality because in some cases it is associated with absence of some of the tendon-jerks in the limbs. Once established, it persists, but as far as is known at present it is not associated with any progressive disease.

The difference between the true and pseudo-Argyll Robertson pupils may be tabulated as follows:

##### TRUE ARGYLL ROBERTSON PUPIL.

Quite inactive to light or darkness.  
Reacts briskly with convergence.  
Smaller than normal.  
Ordinarily bilateral.  
Usually irregular in outline.  
Iris shows atrophic changes.  
Dilates imperfectly with mydriatics.

##### PSEUDO-ARGYLL ROBERTSON PUPIL.

Reacts slowly to light and darkness.  
Reacts slowly with convergence.  
Larger than normal.  
Usually unilateral.  
Regular in outline.  
Iris looks healthy.  
Dilates fully with mydriatics.

#### PARALYSIS OF THE REACTION WITH ACCOMMODATION

The pupil does not contract when an effort to accommodate is made. Accommodation itself may or may not be present, *i.e.* the ciliary muscle may or may not

be acting. This condition is most commonly seen as an after-effect of encephalitis lethargica, and so is usually associated with the post-encephalitic Parkinsonian state.

Conversely the ciliary muscle may be paralysed and the patient be deprived of accommodation, but the pupil may still contract in association with the effort to accommodate. This occurs in diphtheritic paralysis of which it is one of the earliest symptoms, and it is said to occur sometimes in tabes. It must depend on disease of the centres in the nuclei of the third nerves.

In cases of disease of the third nerve the ciliary muscle is paralysed as well as the iris.

## PARALYSIS OF THE CERVICAL SYMPATHETIC

### *Synonym.*—*Horner's Syndrome.*

So far as the eye and orbit are concerned, the sympathetic is the tonic retractor of the lid, the tonic protruder of the eyeball and the tonic dilator of the pupil, and stimulation of this mechanism results in retraction of the lids or widening of the palpebral fissure, exophthalmos and wide pupil, while paralysis of the cervical sympathetic produces narrowing of the palpebral fissure (cervical sympathetic ptosis), and a small pupil. It is customary to include enophthalmos amongst components of cervical sympathetic palsy, but in many cases this is not recognisable. The excitation is seen in Graves' disease; the paralytic condition is of common occurrence in nervous diseases. The cervical sympathetic is also the tonic vaso-constrictor and secreto-motor nerve of the head generally, but disturbance of this mechanism does not often give rise to characteristic, or important clinical phenomena. A curious lack of expression is, however, sometimes observable in the face on the side of the lesion. Cervical sympathetic paralysis occurs in the following clinical associations: (1) In many lesions of the brain-stem or of the cervical portion of the spinal cord, especially when the last cervical and first dorsal segments or roots are damaged. It is common in syringomyelia. (2) In lesions of the cervical sympathetic trunk by trauma, pressure, growths, etc. (3) It is very common in tabes and nervous syphilis generally, where it appears as partial bilateral ptosis with small pupils. It appears to be due to a primary neuronc degeneration in this condition and never improves.

## THE FIFTH OR TRIGEMINAL NERVE

The fifth nerve arises from the pons by a large sensory and a smaller motor portion. The sensory portion supplies sensation of all forms to the same side of the face and anterior half of the scalp. Its ganglion cells lie in the Gasserian ganglion, which lies near the apex of the petrous bone, and distal to the ganglion the nerve is in three divisions (from which the nerve derives its name). The first, or ophthalmic division, passes forward on the wall of the cavernous sinus and enters the orbit in three branches. It supplies sensation to the forehead and anterior portion of the scalp, to the eye and to the ridge of the nose. The second, or maxillary division, leaves the cranium by the foramen rotundum, passes across the sphenopalatine fossa and enters the infra-orbital canal. Having traversed the canal it emerges on the anterior surface of the maxilla half an inch below the lower rim of the orbit, and its branches spread out to supply the skin of the cheek and upper lip, the mucous membrane of the nose, the upper jaw and the hard and most of the soft palates. The third or mandibular division leaves the cranium through the foramen ovale and enters the infra-temporal fossa; it is accompanied by the motor root, which here unites with it to form a single trunk. It supplies sensation to the skin of the lower lip,

chin and outer part of the cheek, and by its auriculo-temporal branch to part of the auricle and to the temporal area; it also supplies the mucous membrane of the lower lip, lower jaw, floor and sides of the mouth and anterior two-thirds of the tongue. Its lingual branch contains taste fibres from the anterior two-thirds of the tongue, which, however, leave it by the chorda tympani nerve and pass over to the facial nerve. The motor root of the trigeminal nerve innervates the temporal muscle, masseter, buccinator, internal and external pterygoids, mylo-hyoid, anterior belly of the digastric and also the tensor tympani and tensor velipalati.

The fifth nerve may be involved in the pons by tumours and not infrequently by disseminated sclerosis; the Gasserian ganglion may be irritated or compressed by tumour or aneurysm, and it is frequently the site of herpetic inflammation, with a consequent herpetic eruption over the area of the external distribution of the nerve; most commonly only the ophthalmic division is thus affected (see Herpes Ophthalmicus). Organic lesions of the divisions of the nerve or their branches at first cause pain, and then sensory loss with a distribution corresponding to the portion of the nerve involved. Loss of the corneal reflex is often the first indication of involvement of the fifth nerve, *e.g.* in cases of acoustic nerve tumour.

Paralysis of the motor function of the fifth nerve occurs in lesions of the nucleus in the pons, or of any part of the peripheral course of the motor division. The signs of such paralysis are not apparent to the patient, who experiences no difficulty in mastication, provided the lesion be unilateral. To the observer the jaw deviates to the side of the paralysis when the mouth is opened, on account of the action of the unopposed external pterygoid of the sound side. The masseter, as felt by the finger on its anterior edge, does not harden on biting, nor do the temporal muscles harden, and wasting of these muscles may be evident. The floor of the mouth does not stiffen on the paralysed side when the mouth is forcibly opened.

Bilateral involvement of all the muscles supplied by the fifth nerve is the rule in all cases of progressive muscular atrophy when the bulbar nuclei are affected.

### TRIGEMINAL NEURALGIA

**Synonym.**—Tic Douloureux.

**Definition.**—A malady characterised by paroxysms of intense pain of a sharp stabbing nature within the distribution of the trigeminal nerve, without sensory loss or other evidence of organic disease of the nerve.

**Ætiology.**—The cause of trigeminal neuralgia in most cases is unknown. The vast majority of patients are over 50 years of age, and most of them are arteriosclerotic and have high blood pressure. Females are affected more frequently than males. A number of cases in younger people are due to disseminated sclerosis, and there is also a form different from the chronic trigeminal neuralgia of elderly people which occurs temporarily in young subjects from exposure to cold, and may recur.

**Symptoms.**—The chief feature of the malady is pain, which may be general throughout the area of distribution of the nerve, but which is more commonly confined to one of the three divisions of the nerve and often to one branch of a division. It is characteristic for the pain of neuralgia to commence locally, and subsequently to spread in each attack and gradually, in the course of the disease, permanently to invade a larger area. Two different kinds of pain occur, the sharp and paroxysmal and the dull continuous pain. The paroxysmal pains are sudden in onset and in cessation. They have a lightning-like character, and are described as piercing, knife-like or as if the affected region were penetrated by red-hot wires.

Though often quite spontaneous, these pains may be brought on by movements of the face and jaw or by touching the surface, or by a cold wind. The sufferers typically describe them as brought on by eating and talking and washing the face, and may wear a scarf round the head to protect the affected side of the face from the

wind. Mastication may become so difficult as to render the feeding of the patient a matter of anxiety. The paroxysms are brief, seldom lasting longer than 1 or 2 minutes, but they may recur frequently, and the patients usually describe different degrees of liability to them at different times.

When the paroxysms are occurring in a severe case the patient remains for a period, which may be from a few minutes to several hours, paralysed under the fear of pain, unable to move a muscle lest a spasm more dreadful than the last should occur. The paroxysmal pains are usually followed, if severe, by a more lasting dull continuous pain often of a boring character, and sometimes such pain becomes absolutely continuous. The skin over the affected region is sore and tender after the paroxysm, and the patient may be unable to bear brushing the hair or shaving the face. The pain may be of every degree of severity, from mild momentary starts to continuous incapacitating pain, interrupted only by excruciating attacks of agony which render life a burden.

The distribution of the pain is usually in one or two divisions of the nerve. The first division is rarely affected primarily, but pain may spread into it from the second division. If the pain begins in the second division it may, after a time, affect the third, and vice versa. The lightning-like onset of the agony often causes convulsive spasm of the face and of the body and limbs. The tender points of Valleix or "trigger-zones" are constantly present during the attack and for some time afterwards. When the second division is affected a little œdema develops under the orbit when paroxysms are frequent. When the third division is affected unilateral furring of the tongue occurs. Fortunately the attacks usually cease at night.

**Diagnosis.**—The quality of the pain is characteristic, and when trigeminal neuralgia is present the diagnosis is not often missed, especially if a paroxysm is witnessed. The usual mistake is to regard as trigeminal neuralgia pain that is due to some other cause, and since there are very many conditions that give rise to pain in the face the opportunities for error are numerous. Unless the pain is brought on by eating and talking and washing the face, it is almost certainly not due to trigeminal neuralgia. Pain that is constant or of a continuous character is not due to trigeminal neuralgia, and some other cause should be sought. Disease of the frontal sinus and glaucoma should be kept in mind. Local painful neuroses or "psychogenic" pains are continuous though subject to fluctuation, and when at their worst they often spread to the other side of the face, as trigeminal neuralgia never does.

A similar neuralgia occurs in the glosso-pharyngeal nerve, but is much rarer; the pain is induced by the movement of swallowing and is felt in the ear or throat.

**Course.**—In the early stages remissions lasting months or years are usual, but in old patients remissions if they occur are likely to be brief. In all cases the remissions become shorter as time goes on and unless the affected division of the nerve is destroyed the neuralgia persists for the rest of the patient's life. In occasional cases the disease is bilateral.

**Treatment.**—In the first place it is essential to make sure that all possible causes of local irritation in the region of distribution of the fifth nerve are absent, or, if present, adequately dealt with. Secondly, it is important to remember that in its early stages, the malady shows complete remissions of long duration. These remissions do indeed tend to become shorter after some years, but their occurrence suggests that in planning treatment it is essential to consider the circumstances of each individual case. Thus, if a patient who may be expected to enjoy a long period of freedom from pain can be tided over the present attack by medical means, it is clearly not wise to give an alcohol injection immediately.

In the hope that remission will occur, medicinal treatment should be given a trial provided the pain is not too intense. Tinct. gelsemii in doses of 10 to 20 minims is an old-fashioned and seemingly effective remedy, and may be combined with

phenazone gr. 10 in solution or aspirin gr. 10 in emulsion, and with liq. arsen. min 2. This should be taken regularly three or four times daily when the attacks of pain are prevalent, and the number of doses may be reduced when the frequency of pains diminishes.

If after a few weeks of such treatment the neuralgia is still severe more effective measures should be employed without delay. One affected branch of the nerve may be destroyed temporarily by injection of alcohol into it, the corresponding area of the face being thereby rendered anæsthetic. The permanence of the relief obtained by a successful peripheral injection varies and is usually longer when the third division is concerned than when the second is the affected one. The operation is at all times a tricky one, requiring great skill on the part of the operator, and subsequent injections become more and more difficult. Alternatively, the Gasserian ganglion can in most patients be injected with alcohol, but while this gives a permanent result it has the disadvantage that the whole of the affected side of the face is rendered completely anæsthetic, including, of course, the eye, in which severe trophic keratitis will quickly develop unless adequate precautions against its occurrence are taken at the time of the injection. However, injection of the ganglion is an excellent treatment in skilled hands. In general the most successful treatment is operative sub-total division of the sensory root of the fifth nerve proximal to the Gasserian ganglion. This renders the area of the second and third divisions anæsthetic and allows sensation to be retained over most of the area of the first division, thus avoiding risk to the eye, and the effect of the operation is permanent. The practice of different physicians in recommending this operation varies considerably, but it has been performed successfully on patients of all ages, and the mortality nowadays is low. In the case of a patient under the age of 50 years, in whom the neuralgia seems established, operation should be advised at once, since the patient may still have many years of life before him, and the neuralgia will never leave him for more than a few months. With older patients each case must be considered on its merits.

The operation of stripping the dura from the Gasserian ganglion and its immediate vicinity is under trial and has given good results over a short period.

## THE SEVENTH OR FACIAL NERVE

The seventh nerve supplies all the muscles of the face, the platysma and the muscles of the scalp. It is a purely motor nerve, but the taste fibres which convey taste from the anterior two-thirds of the tongue join it by way of the chorda tympani nerve and are incorporated in it for part of its course. Fibres which excite salivary secretion are also associated with it at one part.

The facial nerve may be paralysed in cases of pontine tumour or hæmorrhage, or in association with tumours or syphilitic meningitis in the cerebello-pontine angle, or by inflammation or operative intervention in the middle ear; it may be paralysed within the facial canal as a result of herpes of the geniculate ganglion; inflammation or compression of the nerve within the stylomastoid foramen is the cause of the common "Bell's" palsy and enlarged glands behind the angle of the jaw, or a tumour of the parotid gland or traumatic lesions may be responsible for paralysis of the nerve just before it divides into the branches which distribute it over the face. Bilateral facial paralysis not infrequently occurs in acute infective polyneuritis.

Paralysis of the face due to a lesion of the facial nerve or its nucleus causes, as a rule, equal paralysis or uniform weakness of all portions of the affected half of the face. If the lesion is in the pons the sixth nerve is usually affected as well. When the lesion is at the internal auditory meatus, or in the middle ear, or at the geniculate ganglion the taste fibres are involved, and taste is lost on the anterior two-thirds of the tongue on the affected side.

## 1. BELL'S PALSY

**Synonym.**—Common facial paralysis.

**Definition.**—Paralysis of the facial nerve coming on acutely and not associated with any other lesion.

**Ætiology.**—The pathogenesis of Bell's palsy has been the subject of considerable discussion, but the work of Ballance and Duel confirmed that the nerve was compressed just within the styloid foramen. Inflammation of the fibrous tissue around the nerve outside the facial canal is believed to cause swelling of the nerve, with the result that the nerve strangulates itself at the foramen. The inflammation of its fibrous sheath may have spread some millimetres up the facial canal before this occurs, because Ballance and Duel found scarring and contraction of the sheath extending for 4 or 5 mm. when the lower portion of the canal was opened up. As the chorda tympani nerve leaves the facial canal 2 to 3 mm. above its termination, the lesion may extend up far enough to involve it.

Bell's palsy may occur at any age, but is commonest between 20 and 50. The sexes are equally affected and no predisposing factors are known.

**Symptoms.**—The onset is usually rapid and sometimes even sudden. Pain of a neuralgic character below the ear, behind the mastoid process or referred to the occipital region, is common, but it does not last more than a few days, and sometimes pain is entirely absent. On deep pressure upon the styloid region behind the ramus of the jaw on both sides, one can almost always elicit the fact that there is tenderness on the paralysed side, and sometimes obvious swelling of this region may be felt. The first sign of the facial paralysis is that the patient feels the face to be stiff when he attempts to move it. Subsequently, the paralysis appears rapidly, and the face is drawn over to the opposite side. The paralysed side is motionless, according to the degree and distribution of the paralysis, if incomplete, and, if complete, is expressionless. The eye cannot be closed, and there is epiphora from paralysis of the tensor tarsi. The paralysis at the corner of the mouth causes difficulty in articulation and escape of fluids on drinking, but the patient soon learns to overcome these disabilities. When the paralysis is partial it is nearly always the lower part of the face which is the most affected. The facial muscles soon become hyperexcitable to mechanical stimuli. In nearly all the severe cases, there is loss of taste over the anterior part of the tongue.

There is never any pain in the distribution of the facial nerve. After a time, which may vary from a few days to 2 years, the paralysis begins to recover, and invariably this recovery appears in the upper facial region first.

In not a few cases, however, recovery remains imperfect, and a degree of contracture occurs in the paralysed muscles, with the result that the corner of the mouth ceases to droop, and at rest the asymmetry of the face is not marked, though with movement the limited action of the affected side is apparent.

In rare instances Bell's palsy occurs more than once in the same individual, and not necessarily on the same side. It is conceivable that the true Bell's palsy may sometimes be bilateral, but when bilateral facial paralysis occurs, infective polyneuritis should be suspected and other signs sought for.

**Diagnosis.**—Care in diagnosis is most important since there are many causes of facial paralysis and few of them have as favourable a prognosis as Bell's palsy. Facial paralysis from caries of the temporal bone rarely makes any recovery and it is usually associated with partial deafness. A general examination of the nervous system should be made in every case and if any other abnormal signs are found the facial paralysis is most probably due to some cause other than Bell's palsy. Again, cases of facial paralysis that are slow in their onset are not cases of Bell's palsy.

*Facial paralysis from herpes of the geniculate ganglion.*—Among the not infrequent

causes of facial palsy must be numbered geniculate herpes, to which attention was first drawn by Ramsay Hunt. The herpetic vesicles, preceded by local pain, appear in the external auditory meatus and adjacent parts of the pinna (and sometimes also just behind the pinna) and on the soft palate and anterior pillar of the fauces. When the innervation of the last-named derives fibres from the geniculate ganglion, the clinical picture of geniculate herpes is apt to be a misleading one if it be not thought of. The patient complains of pain in the ear, and in the throat on the same side. As the eruption develops the fauces on the affected side are red and injected, and several small ulcers (ruptured vesicles) may be seen. At the same time, the vesicles appear in the ear, rupture, and give off a watery discharge which may be mistaken for otorrhœa. The pinna may then swell very considerably. After some days, during which the patient may feel ill and be feverish (temperature  $100^{\circ}$  to  $103^{\circ}$  F.), facial paralysis develops and usually becomes complete within 12 hours. Tinnitus, vertigo and a varying degree of deafness are usually present. In milder cases there may be only initial pain in the pinna and the appearance of herpetic vesicles on the pinna without much swelling. It is in the severe cases that an erroneous diagnosis of middle-ear disease with otorrhœa may be made and hazardous and unnecessary steps be taken to deal with this. According to Ramsay Hunt, facial palsy always follows geniculate herpes, and undoubtedly many cases of this kind, where the herpetic eruption is minimal, escape accurate diagnosis.

**Course and Prognosis.**—Recovery of Bell's palsy can in general be promised with some reservation as to its completeness, particularly in elderly subjects. The date of recovery is often difficult to forecast. If at the end of a week after the onset there is the slightest trace of any voluntary power in the orbicularis palpebrarum, which is the "*ultimum moriens*" of the facial muscles, or if any trace of faradic excitability to bearable stimuli remains, then it may be confidently said that recovery will be complete and rapid within 3 months, and that there will be no contracture. Cases in which no complete paralysis occurs in any region of the face usually recover in a fortnight. In complete cases, with complete reaction of degeneration in the muscles, it is difficult to say when recovery will occur or when the effect of contracture will be at an end. Cases which show no loss of taste and, therefore, in which there is no great extension of the inflammatory process up the facial canal, usually recover rapidly.

In cases with imperfect recovery either continuous spasm or intermittent twitching of the partly recovered muscles may occur and may persist indefinitely, causing disfigurement and discomfort.

**Treatment.**—In the acute stage salicylates and iodides may be given internally, and warmth or a counter-irritant such as tincture of iodine applied behind the angle of the jaw. The patient should stay in the house for the first week, and gentle massage may be given to the paralysed side of the face. When paralysis seems to be complete, undue stretching of the paralysed muscles may be minimised by "*splinting*" the face; for this purpose a silver wire, rubber covered where it turns round the lip, may be bent so as to hook round the lip at one end and over the ear at the other, so that the mouth is kept symmetrical during facial movements. Gentle massage should also be continued.

It is customary to give galvanic stimulation to the paralysed muscles, but if it is employed the onset of contracture must be watched for and the applications stopped at the first sign of it.

Ballance and Ducl recommended that at an early stage the lower portion of the facial canal should be opened up and the nerve thus decompressed. This operation should certainly be considered if by the end of a month no sign of recovery has shown itself, either to clinical examination or to electrical testing.

When complete paralysis persists after a year no recovery can be expected and the disfigurement can be relieved by one of the varieties of "*sling*" operation.

## 2. PERIPHERAL FACIAL SPASM

**Synonym.**—Facial Hemispasm.

**Definition.**—A unilateral malady of the facial nerve, in which intermitting spasm of the facial muscles occurs, exactly like that caused by faradism of the facial trunk. Rarely it is associated with a slowly oncoming facial paralysis, and may follow a facial paralysis due to injury.

**Ætiology.**—This malady occurs in adults, and the onset is usually insidious and without known cause. It is most often seen in middle-aged women.

**Symptoms.**—It commences with twitching of some part of the facial musculature, which occurs at first at rare intervals, and subsequently becomes more and more frequent, so as in some cases to be almost continuous. Commencing locally, usually around the eye, it tends to spread so as to involve the whole face in a sudden and hideous contortion. The attacks of peripheral facial spasm may at first glance resemble a Jacksonian fit of the face. The spasms may be so severe and continuous as to keep the eye closed for long periods together, and to interfere greatly with the work and enjoyment of life. The malady is associated with no other symptoms. Cases exist in all degrees of severity, from the mildest, in which an occasional flicker of the face occurs, to the most severe and incapacitating and unsightly malady.

**Treatment.**—In severe cases the only remedy which affords relief is division and alcoholic injection of some of the branches of the facial nerve in the pes anserinus, or possibly of the whole of the nerve at the stylo-mastoid foramen or as it crosses the ramus of the jaw. The resulting paralysis and disfigurement, if a large part of the nerve is divided, will call for a cosmetic operation. As long as the spasm is mild, such treatment is obviously worse than the disease. No other treatment has any effect on the spasm, but sedatives may enable the patient to bear it with less distress.

## THE AUDITORY AND VESTIBULAR NERVES

*The eighth nerve consists of two groups of fibres, different in their functions and in their origins and terminations: one group arising in the cochlea and terminating in the cochlear nuclei in the pons is called the auditory or cochlear nerve; the other, arising from the labyrinth and ending mostly in the vestibular nuclei is called the vestibular nerve.*

Lesions of the auditory nerve (as well as diseases of the cochlea) give rise to two symptoms, nerve deafness and tinnitus.

*Nerve deafness* is distinguished from deafness due to middle-ear disease by the fact that hearing is diminished or lost whether the sound be conveyed by air-conduction or by bone-conduction, whereas in middle-ear deafness the hearing by bone-conduction is increased. Weber's test consists in the application of the base of a vibrating tuning fork to the middle of the forehead, the patient being asked in which ear the sound seems the louder; with middle-ear deafness the sound is heard better on the affected side, while with inner-ear or nerve deafness the opposite is the case or the patient does not appreciate any difference between the two sides. For Rinne's test the fork is applied first to the mastoid process, and when the patient ceases to hear it is held at the external auditory meatus; in nerve deafness the sound may be heard by air-conduction after it has become too feeble to be heard by bone-conduction, while in middle-ear deafness the opposite obtains. As a symptom of nervous disease, nerve deafness is met with in cases of tumour of the eighth nerve, following epidemic meningitis, in syphilis of the nervous system, especially congenital syphilis, and in disease of the lateral region of the medulla.

*Tinnitus* is a subjective sensation of noise in the ears or in the head. It seems to



be due to disease of the cochlea or auditory nerve of a slow degenerative nature, and though at first intermittent, it usually becomes continuous before long. It may also be produced temporarily by certain drugs, of which quinine and salicylates are the commonest.

The sounds commence faintly and at first may be perceived only in stillness and silence at night and later become louder and more persistent, and are often absolutely continuous. The noise complained of may be high-pitched or low-pitched, a piercing whistle or a hiss, or even a rumble; in some cases it is more elaborated and is described "as like machinery", or again, "bell-like".

In the course of time the hearing becomes impaired, and in some patients vertigo occurs and may be associated with periods of aggravation of the tinnitus. Medical treatment produces little benefit, but sedatives such as phenobarbitone, may enable the patient to tolerate the noise better. Division of the eighth nerve often cures the tinnitus, but the patient must be warned both that it may fail to do so and that, in any case, the operation will produce complete deafness on the side on which the operation is performed.

The most prominent symptom which results from lesions of the vestibular nerve (as well as from disorders of the labyrinth) is *vertigo*. The word by derivation means "a turning", and with vertigo of labyrinthine and vestibular nerve origin there is always a sense of rotation, either of the surroundings or of the patient himself; the room may seem to rotate about a vertical or a horizontal axis and there is often a disorder of projection so that when the patient falls it seems to him that the floor has come up to strike his head.

It must be noted that the vast majority of patients who complain of giddiness or dizziness do not suffer from true vertigo. Nearly all those who suffer from functional nervous disturbances complain of what they call dizziness, by which they mean a momentary sensation of unsteadiness; objectively such a patient is not unsteady and this sensation never causes him to fall. Patients suffering from generalised cerebral arteriosclerosis complain of a similar sensation, as also do those who are suffering from the after-effects of head injuries.

With true vertigo, unless it be minimal, nystagmus is always present while the vertigo is going on. Usually the nystagmus is seen with deviation of the eyes towards the side of the lesion, but with irritative lesions of the labyrinth, e.g. for a day or two after operations on the ear and with labyrinthitis the nystagmus is towards the opposite side.

*Tests for vestibular lesions.*—1. Barany's caloric test is made by irrigating the external auditory meatus with either hot or cold water or air. With an intact vestibular mechanism this causes irritation of the vestibular apparatus with the appearance of nystagmus on lateral deviation of the eyes. When the vestibular mechanism is impaired this test fails relatively or completely.

2. If the patient be rotated either by placing him in a special rotating chair, or by turning him round several times in the standing position, lateral conjugate deviation of the eyes immediately after the rotation will show nystagmus in the opposite direction to the rotation, if the labyrinth on that side is intact. It will not appear if the functional activity of the vestibular mechanism is deficient.

## RECURRENT VERTIGO

The causes of recurrent vertigo are various. It is necessary in every instance to make sure that there are no indications of disease of the cerebellum, brain-stem or cerebello-pontine angle, but in the great majority of cases the symptom arises from disease of the labyrinth or vestibular nerve, and the following conditions have been identified: (1) Ménière's disease, (2) vestibular neuronitis (Dix and Hallpike), (3) positional vertigo.

# 1. MÉNIÈRE'S DISEASE

**Definition.**—A malady in which paroxysmal attacks of labyrinthine vertigo occur at irregular intervals, associated with tinnitus and progressive deafness, and due to disease of the labyrinth of a chronic nature.

**Ætiology.**—Ménière's original hypothesis was that hæmorrhage into the labyrinth was the responsible factor, but this is inherently improbable and lacks pathological support. According to Hallpike the essential lesion is a gross distension of the endolymph system together with degenerative changes in Corti's organ and the presence of albuminoid coagula throughout the endolymph spaces. He regards these changes as incompatible with an infective origin, and as probably primarily degenerative in nature.

The precipitating causes of the attacks are unknown, and in the absence of precise knowledge disturbances of fluid balance, allergy and migraine have all been incriminated; in some instances the attacks are associated with diarrhœa.

**Symptoms.**—The majority of cases are much milder than those described by Ménière, and the symptoms may be subject to long remissions.

In the severe cases of the classical type the attacks set in suddenly with a buzzing noise in the ears, followed immediately by intense vertigo, both subjective and objective. The vertigo may be so severe that the patient feels he is hurled to the ground. He often falls as if shot but sometimes he has time to assume the sitting or lying position, before the vertigo reaches its height. Consciousness may rarely be impaired for a few moments. Spontaneous nystagmus occurs to the side of the lesion, and unilateral cerebellar signs on the side of the lesion. The patient becomes nauseated and often vomits repeatedly. The skin is pale and covered with a clammy sweat. The patient lies perfectly still, and in terror lest the least movement should bring on more vertigo. The duration of the attack is usually between 15 minutes and an hour, but the patient may take several hours to recover completely. Sometimes the attacks are excited by sudden movement, such as coughing or sneezing, but they are usually without any such antecedent. They may occur during sleep, and wake the patient. In the milder cases the vertigo is not infrequently present when the patient awakens in the morning and becomes apparent to him as soon as he moves. It is not spontaneous but is brought on by movements of the head, and it is also influenced by the posture of the head, being worse when the affected ear is on the pillow. The vertigo passes off within half an hour or an hour or two.

Ménière's disease is characterised by a slow onset of nerve deafness and by the time the first attack of vertigo occurs an impairment of hearing and some tinnitus are usually present. If the disease is persistent there is a gradual deterioration both of vestibular and of auditory function in the affected ear, and in some cases the labyrinth becomes defunct and the attacks cease.

**Diagnosis.**—This presents no peculiar difficulty for the symptoms are highly characteristic, and although variable in degree are usually quite definite in the first attack. The rapid disappearance of the vertigo is striking. Vertiginous attacks from all other causes must be excluded. In acute cerebellar lesions (including thrombosis of the posterior inferior cerebellar artery) the symptoms are very like those of labyrinthine vertigo, but they are not transitory in a few hours. A careful search of the nervous system for signs of organic nervous disease should in every case prevent any mistake. Vertiginous attacks due to epilepsy rarely cause difficulty in the differential diagnosis because the loss of consciousness and probably the convulsive and other features of the epileptic attack are apparent.

**Prognosis.**—Most cases recover perfectly with slight impairment of hearing, or have long periods of remission. Some cases, however, go from bad to worse in spite of treatment, and progressive deafness ensues with eventual disappearance of the attacks.

**Treatment.**—Sedatives have a pronounced palliative effect. The most commonly used drug is phenobarbitone, and doses of gr.  $\frac{1}{4}$  taken three or four times daily usually bring about prompt amelioration. Bromides in doses of gr. 10 to 15 three times a day are equally serviceable and Gowers advocated the use of sodium salicylate or aspirin. Other measures include a salt-free diet, careful regulation of the bowel to prevent diarrhoea and the use of anti-histamine drugs. Dimenhydrinate (Dramamine) is believed by some to have a selective action as a sedative on the labyrinth.

When medical treatment fails, surgical measures may give relief, the principal operations employed being division of the vestibular nerve, partial removal of the membranous labyrinth and total destruction of the labyrinth of one side.

## 2. VESTIBULAR NEURONITIS

In this condition the cause of the vertigo is believed not to be in the labyrinth, but in the neurones of the vestibular nerve. There is no disturbance of hearing. In a large proportion of cases there is an associated infection in the nasal sinuses or elsewhere, or the onset is associated with some febrile illness. The disorder affects chiefly patients in the age group 30 to 50, without preference for sex.

The attacks of vertigo are similar to those of Ménière's disease but are in general less severe.

Treatment consists in the administration of phenobarbitone, as for Ménière's disease, and the removal of any local or general infection which can be discovered. With these measures the liability to vertigo usually passes off in the course of a few months.

## 3. POSITIONAL VERTIGO (POSITIONAL NYSTAGMUS)

In this variety the vertigo always occurs when the head is put in a particular position, and in most instances the exciting position is with the head back and somewhat tilted to one side. Many of the cases are subsequent to head injury.

The condition can usually be identified by the patient's complaint that he becomes dizzy when he turns his head (face) upwards, but specialised tests are necessary to confirm the diagnosis.

Treatment consists, as before, in the use of phenobarbitone, and in most cases the symptoms pass off completely in 3 to 12 months.

## THE NINTH OR GLOSSOPHARYNGEAL NERVE

Lesions of this nerve involve loss of taste over the posterior one-third of the tongue with some unilateral paresis of the pharynx. It is rarely involved alone; in association with the other nerves taking origin in the neighbourhood, it may be affected by tumours of the lateral region of the medulla, and by syringomyelia.

### GLOSSOPHARYNGEAL NEURALGIA

**Definition.**—A comparatively rare form of neuralgia within the distribution of the glossopharyngeal nerve. It is strictly comparable with trigeminal neuralgia in the quality and severity of the pain, its paroxysmal incidence, the remissions in its course, its provocation by special stimuli and finally by the absence of any discoverable lesion in, or loss of function of, the nerve.

**Ætiology.**—Nothing is known of its ætiology. It is most frequently seen in middle-aged or elderly males. A symptomatic neuralgia of the same distribution is occasionally found in cases of carcinoma of the tongue in which the growth invades the faucial region.

**Symptoms.**—When fully developed, the malady consists in paroxysms of shooting pain of great severity in the region of the throat and ear. The exciting stimulus is commonly the act of swallowing. But just as in trigeminal neuralgia the pain may at first be confined to a single branch of this nerve, so in glossopharyngeal neuralgia, the pain may for long be confined to the tympanic branch, the pain being felt deep in the ear. This pain does not spread to the pinna. In other cases, pain in the faucial region predominates, the pharyngeal branches being affected. As in trigeminal neuralgia, the patient may enjoy long intervals of freedom from pain. During a paroxysm the patient screws up his face and may hold his head in his hand as does the subject of trigeminal neuralgia.

**Diagnosis.**—The presence of neuralgic pain of great severity, provoked by the act of swallowing, and in its general characters and behaviour resembling the very familiar and characteristic paroxysms of trigeminal neuralgia, but different from these in its restriction to the ear and throat, occurring also in the absence of objective signs of a lesion of the cranial nerves; these together are the features which make a diagnosis of glossopharyngeal neuralgia possible and easy.

**Treatment.**—In the early attacks, the same forms of medication as are used in trigeminal neuralgia may be employed. If the pain does not respond to these, then surgical measures are called for and the operation usually performed is avulsion of the nerve high in the neck.

## THE TENTH OR VAGUS NERVE

This is a mixed nerve. The motor fibres supply the voluntary muscles of the soft palate (except the tensor palati), pharynx and larynx in conjunction with the accessory fibres, and also the non-stripped muscles of the respiratory and alimentary tracts.

The sensory fibres of the vagus supply the respiratory tract, the pharynx and œsophagus. Its visceral fibres supply the lungs, heart and abdominal viscera. No sensibility seems to be supplied to the abdominal viscera by this nerve, since with division of the spinal cord above the offshoot of the splanchnic nerves all sensibility in the abdomen is lost.

### LESIONS OF THE VAGUS

The important signs of lesion of this nerve and its nuclei are pharyngeal and laryngeal paralysis and loss of sensibility. Symptoms indicative of lesions of its complicated and mysterious visceral supply are neither well marked nor well understood, and in unilateral lesions seem to be entirely absent; they are therefore not considered.

Lesions of the vagus in the medulla are common. Syringomyelia, when affecting that region, usually involves the nucleus ambiguus, causing unilateral palsy of palate, pharynx and larynx. Thrombosis of the posterior inferior cerebellar artery which supplies that region of the medulla containing the nucleus ambiguus is likely to produce vagus paralysis of the same side. Progressive muscular atrophy, in the form of progressive bulbar paralysis, may affect its cells. Lesions of the nerve roots often occur from tumours of the lateral region of the medulla, and growths outside the medulla arising from nerve roots or meninges, and here the lesion of the vagus roots is associated usually with those of the glossopharyngeal, spinal accessory and hypoglossal. In the neck penetrating wounds and growths may implicate the nerve, and in the thorax tumours, particularly aneurysms and new-growths, are apt to cause paralysis of the muscles supplied by its recurrent branch.

**Unilateral pharyngeal paralysis.**—This is characteristic of all unilateral lesions of

the vagus high up. It is recognised by the low-lying, motionless palate and the loss of sensibility of one side of the pharynx, with loss of the pharyngeal reflex on that side. There is no impairment whatever of deglutition. When the soft palate is elevated, as in saying "Ah!", it is pulled over to the sound side.

*Bilateral pharyngeal paralysis.*—This results from nuclear lesions of the nucleus ambiguus on both sides, and is also common in diphtheria, polyneuritis, myasthenia gravis and progressive muscular atrophy. The whole palate is low and paretic or paralysed, the voice is nasal, there is nasal regurgitation of liquids, the cheeks cannot be forcibly blown out, and there is difficulty in pronouncing final "k" and "g", the words "kick" and "egg" becoming "kich" and "enck".

*Total unilateral laryngeal paralysis.*—Since the superior laryngeal nerve which supplies the crico-thyroid muscle (the chief tensor and adductor of the vocal cords) is given off high in the neck from the ganglion of the trunk of the vagus, it follows that total paralysis of the larynx on one side can only result from a lesion of the vagus between the ganglion of the trunk and the nucleus ambiguus in the medulla. The vocal cord on the paralysed side becomes motionless in the cadaveric position—that is, midway between the abduction and adduction. The larynx is insensitive on the same side. There is some loss of tone of voice but no stridor.

*Unilateral abductor paralysis or recurrent laryngeal paralysis.*—This occurs from all lesions of the trunk of the vagus below the ganglion of the trunk, and from lesions of the recurrent laryngeal branch. The vocal cord on the side of paralysis lies close to the mid-line; it fails to abduct when the patient takes a deep breath; there is no change of voice, but there may be slight stridor on inspiration. The sensibility of the larynx is not affected.

*Bilateral abductor paralysis.*—This condition is occasionally seen as a complication of thyroidectomy and in malignant disease of the thyroid gland. It occurs also in bilateral lesions of the recurrent laryngeal nerves in the thorax, which may occur from aneurysm and new-growths. It is the most dangerous form of laryngeal palsy, as the vocal cords cannot be abducted, and they tend to suck together during inspiration; for this reason bilateral abductor paralysis may cause death from asphyxia, or necessitate tracheotomy.

## THE ELEVENTH OR SPINAL ACCESSORY NERVE

This nerve may be caught with the vagus by lateral lesions outside the medulla, or by lesions in the region of the jugular foramen; but it is more often damaged by injuries to the neck and by operations for the removal of cervical glands. The spinal accessory nerve, as it crosses the posterior triangle of the neck, is very liable to injury, either from blows or from sudden strains, and most of the isolated trapezius palsies are due to local neuritis of the nerve trunk, so arising.

When the sternomastoid is paralysed there is neither complaint by the patient of weakness, nor deformity, nor peculiar attitude of the neck, other muscles compensating for its paralysis. The muscle does not harden when the head is turned to the side opposite to the paralysis, and its reaction to faradism is diminished or lost.

Paralysis of the trapezius, on the other hand, causes great disability in raising the arm above the horizontal level of the shoulder and also difficulty in shrugging the shoulder or approximating the scapula to the middle line behind and therefore also in carrying the extended arm backwards. But the only part of the trapezius that is completely paralysed by disease of the spinal accessory nerve is the highest portion. Instead of its normal nearly straight contour, the neck presents on the affected side a concave curve, and the difference between the two sides is brought out more strongly by a deep inspiration. The other parts of the trapezius are weakened but not paralysed, since they receive additional innervation from the cervical nerves. In consequence

of the weakness the shoulder falls a little, the scapula moves slightly laterally, and by the unopposed action of the rhomboids and levator anguli scapulæ it is rotated, the lower angle moving medially.

## THE TWELFTH OR HYPOGLOSSAL NERVE

The hypoglossal nerve supplies all the muscles of the tongue, both intrinsic and extrinsic.

A lesion of one hypoglossal nucleus in the medulla gives rise to fibrillation and eventual atrophic paralysis of one half of the tongue. When the hypoglossal nerve is divided the fibrillation is usually not apparent but the atrophy occurs more quickly and there is a loss of faradic excitability. In either event the tongue becomes sickle-shaped with the concavity on the paralysed side. There is little impairment of movement within the mouth and no defect of articulation, but the tongue turns to the paralysed side when protruded. Such hemiatrophy of the tongue occurs in syringobulbia and in syphilitic conditions; tumours of the lateral region of the medulla and just lateral to it are rarer causes of it. The hypoglossal nerve may be severed as a result of wounds or operations in the neck.

Atrophic paralysis of the whole tongue occurs when both hypoglossal nuclei are affected, and is commonly seen in progressive bulbar paralysis. Protrusion of the tongue is impossible and articulation is greatly impaired, but this may be partly due to other paralyses which are usually associated.

Upper motor-neurone paralysis of the tongue is not uncommon. A patient suffering from motor aphasia is commonly unable to protrude his tongue, and in bilateral hemiplegia and the condition known as pseudo-bulbar paralysis, the tongue is in a state of spastic paralysis; neighbouring parts are similarly affected, and well-marked dysarthria and dysphagia are frequent. The tongue appears contracted but there is no real wasting and no loss of electrical excitability.

## THE SIGNS OF LOCAL LESIONS WITHIN THE SKULL AND BRAIN

In this chapter we must be content with a brief consideration of the signs and symptoms upon which we depend for the localisation of cerebral lesions. We may take first the various regions of the brain, and secondly, as we have to deal not only with lesions within the brain, but also with lesions within the skull that may be outside the brain itself, we will consider the symptomatology peculiar to lesions in the three cranial fossæ.

## THE CEREBRAL HEMISPHERES

### GENERAL LATERALISING SIGNS

A lesion within or involving one cerebral hemisphere may reveal by the signs it produces whether it is right- or left-sided without affording further evidence of its localisation. Such signs are unilateral loss or diminution of the abdominal reflexes, unilateral accentuation of the tendon reflexes, an extensor response or just perceptible unilateral paresis of movement of the lower part of the face. Fits starting unilaterally, or with turning of the head and eyes to one side may be of similar significance.

## THE FRONTAL LOBES

These consist of the portions of the hemispheres anterior to the coronal sulci (*fissures of Rolando*) and thus include the ascending frontal convolutions and the portions of the hemispheres anterior to them (the "*prefrontal*" areas). The lesions to be met with in the prefrontal areas include tumour, abscess and thrombosis of the anterior cerebral artery, the last named being comparatively rare.

*The syndrome of the anterior cerebral artery* consists of a spastic weakness of the opposite lower limb, especially in its distal part with the appropriate changes in its reflexes. Sometimes there is slight weakness of the corresponding arm which may be associated with forced groping and grasping in the arm on one or both sides. The face is seldom affected. Apraxia of the left arm has been described and there may be some drowsiness and mental confusion.

*The syndrome of frontal lobe tumour.*—The area of the frontal lobes anterior to the ascending frontal convolutions (the prefrontal areas) comprises a considerable portion of the cerebrum and is frequently the site of tumour formation. The symptoms produced vary greatly with the rapidity of growth of the tumour and with other factors imperfectly understood. As a rule, an early, if not the initial symptom, is a change in the patient's mental state. He becomes apathetic and lacking in initiative. The association and flow of ideas tend to fail. He sits about idly, lacks attention and becomes indifferent to cleanliness and other aspects of personal behaviour. He is apt to permit the unimpeded passage of urine and even of feces, and to be totally insensitive to the embarrassments such conduct normally involves. This form of "incontinence" is, in fact, a diagnostic symptom of great value in frontal lobe tumours. Rarely, the patient develops an abnormal facetiousness and euphoria—the so-called "Witzelsucht". These early symptoms may gradually give place to a profound dementia.

Movement is often disordered by the development of apraxia and sometimes by that of forced groping and grasping which, when unilateral, is a useful sign of frontal lobe involvement. When bilateral it is of less localising significance and may be met with in diffuse degenerative or neoplastic lesions of the hemispheres, and in cases of severe internal hydrocephalus. Such grasping and groping has been shown to consist of two components: (i) Volitional grasping movements made by the conscious patient when some object is felt by him in his palm, or is seen by him to approach his hand. These movements wane and cease when consciousness is failing, or when attention is defective. (ii) A true tonic reflex grasp of any object held in the hand, if this object be pulled away in such a manner as to put the flexors of the fingers on the stretch. The flexors tighten as the pull is maintained and their contraction may attain great force, such indeed that sometimes the patient can be pulled out of bed by this involuntary grasp which he is unable voluntarily to relax. This reflex may persist even after consciousness is lost but is abolished by injection of novocaine into the appropriate afferent nerves. Fits are a common feature of frontal tumours and may be generalised from their onset, or start with turning of the head and eyes to the opposite side. Attacks of petit-mal are not uncommon. If the orbital lobule be involved there may be unilateral anosmia, or direct pressure on the optic nerve causing unilateral failure of vision associated with primary optic atrophy. This, when combined with papilloedema in the opposite eye has been described as Foster Kennedy's syndrome. These symptoms will be further considered in connection with the syndrome of the anterior cranial fossa.

As the tumour expands it is likely to encroach upon the projection pathway from the motor cortex with a resulting contralateral hemiparesis, and when left-sided it is commonly associated with a predominantly executive disturbance of speech. Tumours in the medial portions of the frontal lobes may come to involve the corpus callosum and frequently spread through this structure to the opposite hemisphere.

In such cases the patient becomes completely apathetic, silent and immobile, lying with open eyes, but displaying no initiative of any kind.

### SYNDROMES OF THE CENTRAL REGION (REGION OF THE "MOTOR CORTEX")

Hemiplegia is the characteristic symptom of a paralytic lesion in this portion of the hemisphere, and the Jacksonian fit that of an irritative lesion.

The Jacksonian, or focal, fit most commonly originates in the face, thumb or big toe, and thence spreads with varying rapidity until much or all of the corresponding side of the body is affected. It may then become generalised. Consciousness is commonly preserved in attacks which remain unilateral. Such a fit may be accompanied by conjugate deviation of the head and eyes away from the side of the lesion and may be followed by a transient hemiparesis, or in the case of a tumour by a progressive and permanent hemiplegia. The hemiparesis resulting from a destructive lesion near the surface will affect face, arm or leg predominantly according to the site of the lesion. The more deeply this extends into the underlying white matter, the more will the weakness affect the whole half body, since the pyramidal fibres converge from the cortex towards the capsule. Disturbances of cortical sensibility corresponding in distribution to the motor defect are not infrequent and result from simultaneous involvement of the neighbouring post-central convolution.

### PARIETAL LOBES

Irritative lesions in this area may give rise to focal fits heralded by subjunctive sensory disturbances on the opposite side. These are usually described as consisting of numbness, tingling, or pins and needles, and may spread in an orderly manner to other parts of the affected side of the body in the same way as the muscular spasm in discharging lesions of the motor cortex. Destructive lesions in this neighbourhood may be marked by a characteristic series of sensory disturbances. These include defective localisation of tactile stimuli, defective appreciation of two simultaneous contacts (Weber's compass test), defective appreciation of three dimensional space (*i.e.* size and form). There is, in addition, defective power of differentiating minor differences in intensity of painful or thermal stimuli, and a ready fatigue of sensory functions. The simple recognition of such stimuli may be relatively intact. It will be seen that the defects in spatial discrimination which result from these modes of sensory loss lead to that inability to recognise and identify objects held in the hand, or to describe their size, shape or texture which is known as astereognosis. The appreciation of movement and of position is apt to be faulty, and some ataxy commonly results. Disturbances of attention may also occur on the contralateral side of the body together with failure of spatial orientation and of recognition of the body image. In left-sided lesions there may in addition be disorders of the visual speech function, resulting in *dyslexia*, *agraphia* and *acalculia*. Trophic changes, particularly decrease in size of the muscles, may be seen in the periphery of the limbs, and this may be so marked as to amount to true muscular wasting.

### OCCIPITAL LOBES

Lesions of the cuneus and region of the calcarine fissure on the mesial aspect of the occipital lobe result in hemianopia of the opposite field, but central vision escapes. Gordon Holmes showed that if the lesion is limited above the calcarine fissure a quadrantic hemianopia of the lower field results, and if the lesion is below the calcarine fissure the quadrantic defect resulting is of the upper field. Since central vision is represented at each occipital pole, a lesion of either pole causes contralateral,



central, homonymous hemianopic scotomata, vision in the periphery of the field remaining intact. Similarly a bilateral lesion involving both occipital poles will result in bilateral central scotomata, and a bilateral lesion of the calcarine region will produce blindness of both peripheral fields, central vision remaining intact. If the lesion extends deeply into the occipital lobe so as completely to sever the optic radiation to the occipital cortex, complete hemianopia, affecting both the peripheral and central parts of the visual fields will result. The hemianopias resulting from a lesion of the occipital lobes have been distinguished from those due to lesions of the optic tracts by the fact that in the former the pupils react to light thrown on to the blind part of the field (Wernicke's hemianopic pupil phenomenon). To be of practical value this test needs to be made with a very narrow pencil of parallel rays to avoid the effects of dispersal of light within the eye.

On the outer surface of the occipital lobe, a lesion on the left side may sever the connections between the visual centres and the speech centres, and so produce word blindness. Bilateral lesions in this region may be associated with visual disorientation.

Jacksonian attacks are often of great value in the localisation of occipital lobe lesions. When the lesion is situated posteriorly these take the form of undifferentiated visual hallucinations such as flashes of light or coloured figures. When the lesion is situated more anteriorly at the junction of the occipital and temporal lobes the visual hallucinations may take the more elaborate form of visions of people, animals or places. In either case the hallucinations may be accompanied or followed by a transient hemianopia.

#### TEMPORAL LOBES

The considerable portion of the cortex comprised by the temporal lobes includes the cortical representation of the functions of smell, taste and hearing and on the left side, in normal right-handed persons, the function of speech.

The uncinate and hippocampal regions of these lobes are the cortical seats for taste and smell, and the localising symptoms which are rarely absent when lesions in these regions exist are Jacksonian attacks taking the form of hallucinations of taste and smell, nearly always of an unpleasant character. The hallucination is often accompanied or immediately followed by a "dreamy state" in which the patient may experience a feeling of strangeness or of intense familiarity or a panoramic recall of events of his past life. This state of altered consciousness may be accompanied by smacking of the lips, or champing of the jaw. The senses of taste and smell are not lost from a unilateral lesion of this region since they are bilaterally represented in the cerebral hemispheres. Recent clinical and electro-encephalographic researches indicate that discharging lesions in the temporal lobes play an important part in epileptic automatism and the so-called psychomotor epilepsy. It also seems likely that congenital or acquired defects in the temporal lobes may be concerned with the behaviour disorders of aggressive psychopaths.

The outer surfaces of the temporal lobes are concerned with hearing. Lesions here may result in fits which are heralded by crude auditory hallucinations, but owing to the complete semi-decussation of the auditory path unilateral lesions never produce detectable deafness. Bilateral lesions may, however, produce cortical deafness.

In right-handed subjects lesions of the left temporal lobe commonly give rise to serious disorders of speech function. With lesions situated far forward towards the insula the disturbance is predominantly one of spoken speech. With those situated in the posterior portion of the lobe the defect is predominantly one of the reception of speech. Deeply situated lesions of the temporal lobe commonly produce "jargon aphasia". Transitory disturbances of speech may occur in focal attacks originating from lesions in this area.

On account of the wide excursion which the optic radiation makes into the deep

part of the temporal lobe in its course from the thalamus to the calcarine cortex, homonymous field defects, especially of the upper quadrants, are very common in deep-seated lesions of the temporal lobes. Such lesions may also produce a paresis for emotional movements of the opposite half of the face which is relatively greater than the loss for voluntary movements. The occurrence of incontinence of sphincters of a mental type is occasionally seen.

#### INTERNAL CAPSULE

In this region, the chief motor tract is condensed into a small space, and is situated immediately in front of a narrowly localised sensory tract, while not much farther posteriorly, the visual path emerges from the thalamus. Lesions of this region therefore produce severe and widely spread hemiplegia of the opposite side, often associated with hemianæsthesia and not infrequently with hemianopia of the opposite side. From the proximity of the thalamus and corpus striatum, there is often involvement of these structures in a capsular lesion, with appearance of the characteristic spontaneous involuntary movements and sensory loss.

#### THE REGION OF THE FALX CEREBRI

Lesions of this region are likely to affect both hemispheres equally. Tumours opposite the paracentral lobules may cause bilateral crural monoplegia with disturbances of cortical sensibility in the feet if the post-central area is involved. Focal fits starting in one foot may occur. Disturbances of sphincter control are occasionally seen. Tumours arising from the posterior region of the falx may result in bilateral hemianopia. Thrombosis of the superior longitudinal sinus may produce widespread bilateral lesions of the hemispheres, with double hemiplegia in which the face and hands are usually spared.

### BASAL GANGLIA

#### OPTIC THALAMUS

A very characteristic clinical picture results from destruction by thrombosis of this structure which is termed the "thalamic syndrome" of Dejerine and Roussy; there is hemiparesis with spontaneous involuntary movements on the side of the body opposite to the damaged hemisphere. The latter may be of the nature of tremor, intention tremor, choreic, athetotic, dancing or irregular movements. Most post-hemiplegic involuntary movements are due to a lesion of the thalamus. In addition, there is hemianæsthesia, often with a characteristic hypersensitivity to painful, thermal or other stimuli, such as tickling, rubbing, etc., which may produce agonising distress. Sometimes spontaneous, constant and unrelievable pain occurs on the affected side of the body. Emotional movement of the face may be impaired much more than is volitional movement. The thalamic syndrome is not invariably, or even commonly, seen when the lesion is a tumour. In such cases the symptom-complex varies according to whether the growth primarily arises in the thalamus or invades it from its lateral aspect. In the former case it arises in the subependymal glia and spreads laterally. Such tumours are characterised by early mental deterioration, with conjugate ocular palsies. Sensory changes are absent or only terminal in appearance. In the case of tumours secondarily invading the thalamus from its lateral side, sensory changes of the order described under the "thalamic syndrome" of Dejerine and Roussy, and by Head and Holmes, are seen.

## CORPUS STRIATUM

Little is known with certainty of the symptomatology of focal lesions of the large masses of grey matter which form this structure. The syndrome of Parkinsonism is associated with degenerative changes in the globus pallidus of both lenticular nuclei, but such changes are not confined to those organs but involve other areas of the cerebral hemisphere as well. The same is true of chorea and athetosis in which degenerative changes are conspicuous in the caudate nuclei. However a local lesion, usually vascular, in a neighbouring mass of grey matter, the corpus subthalamicum, or corpus Luysii, is followed by very violent unilateral choreiform movements on the opposite side of the body, the so-called *apoplectic chorea* or *hemiballismus*.

## THIRD VENTRICLE AND HYPOTHALAMUS

Lesions occupying this cavity, which are usually neoplastic, may produce symptoms of localising value in addition to those resulting from obstruction of the cerebro-spinal fluid circulation (hydrocephalus). The most important of these are hypersomnia, diabetes insipidus, obesity and alteration in primary and secondary sexual functions of a more variable character than those which occur in lesions of the pituitary body. In the case of the not uncommon "colloid cysts" of the third ventricle, which hang suspended from its roof by a short pedicle, the symptoms, including the obstructive hydrocephalus, may be noticeably intermittent. Where the posterior end of the ventricle is affected there may be disturbance of the pupillary light-reflex.

## BRAIN-STEM

## THE MID-BRAIN

This portion of the brain-stem consists of a small dorsal area, the quadrigeminal plate or tectum and a large ventral area, the cerebral peduncles or *crura cerebri*.

At the level of the corpora quadrigemina the oculo-motor nuclei lie on either side of the aqueduct of Sylvius, and lower down on either side of the middle line, in the floor of the upper part of the fourth ventricle. Lesions of this region cause nuclear ophthalmoplegia—that is, paralysis of both eyes in terms of the conjugate movements upwards, downwards or laterally. From above downwards, lesions of this column of oculo-motor nuclei will produce reflex iridoplegia, loss of convergence, paralysis of upward, downward and lateral movements respectively.

Immediately ventral to the third nerve nucleus and decussating below it lie the superior cerebellar peduncles passing to the red nuclei. Involvement of these structures causes ataxy of the limbs and trunk.

A lesion of the tectal region of the mid-brain produces a characteristic syndrome of nuclear ophthalmoplegia with bilateral ataxy, which is termed *Nothnagel's syndrome*.

In the ventral portion of this region of the brain-stem are the *crura cerebri* with the third nerve perforating each crus to emerge on its inner side, and the optic tract running round the crus as it passes back from the optic chiasma to the lateral geniculate body. A lesion of one crus will cause hemiplegia of the opposite side, and paralysis of the third nerve on the same side. This pathognomonic localising combination is known as *Weber's syndrome*.

Situated a little more dorsally, a lesion of the crus will produce ophthalmoplegia of one eye with tremor and inco-ordination of the opposite limbs. This is known as *Benedikt's syndrome*.

Extension of a lesion outwards from the crus may cause tract hemianopia, in which

the half fields are completely involved and the light reflex lost from the blind fields. Interference with the fillet may cause hemianæsthesia on the opposite side.

### PONS AND MEDULLA

In these regions the motor and sensory tracts, the middle and inferior cerebellar peduncles, the cranial nerve nuclei and the outgoing cranial nerves are closely packed together, and the signs resulting from destruction of these will be various combinations of spastic paralysis, ataxy and sensory loss in the body and limbs—from interference with the long conducting tracts—together with nuclear and peripheral nerve-palsies and anæsthesia in the distribution of the cranial nerves.

If the lesion is unilateral the body and the structures innervated by the cranial nerves will be affected on opposite sides, causing the "crossed paralyses" or "alternate paralyses" characteristic of lesions of the brain-stem. Of these, facial palsy of lower motor neurone type with contralateral hemiplegia is the most frequently encountered, trigeminal palsy and anæsthesia and vagoglossopharyngeal palsy with contralateral hemiplegia being less common. Lesions of the brain-stem below the oculo-motor nuclei cause small pupils (*pontine myosis*) by cutting off those nuclei from the spinal cord, whence the tonic dilators of the pupils—the cervical sympathetic system—emerge. Lesions in the upper part of the pons commonly lead to loss of conjugate lateral movement of the eyes. If the connections of the vestibular nerve are involved intense vertigo may result together with nystagmus at rest and on movement of the eyes. Glycosuria may be met with in lesions in the neighbourhood of the fourth ventricle and the respiratory centre may be involved.

The common lesion involving the medulla is softening of the lateral portion from thrombosis of the posterior inferior cerebellar artery or its branches, the so-called cerebellar apoplexy (see p. 1440). Owing to the smallness of the brain-stem, lesions of an inflammatory or neoplastic character commonly involve both sides of the structure and bilateral symptoms result.

### CEREBELLUM

When lesions of this structure develop suddenly they are apt to produce more striking disturbances of function than when they develop gradually, a point which it is important to remember when the presence of an abscess or a tumour within the cerebellum is suspected. These disturbances are all in the realm of voluntary movement and the several different components of cerebellar ataxy are to be regarded not so much as special disorders of different cerebellar functions, but as expressions of a single disorder, which owe their varying appearance to the varying nature of the clinical tests employed.

*Hypotonia*.—This is particularly marked in acute lesions, but can also be detected in those of slow evolution. It shows itself by marked flaccidity and extensibility of the limb muscles which permit of undue mobility of the joints and leads to a modification of the normal posture of the limbs and, when marked, to the "pendular" form of knee jerk. The hypotonia is largely responsible for the symptom of *dysmetria*. If the patient is asked to extend the arm and pick up some object, such as a glass, or to touch a fixed point, the limb is shot forward with undue force and may overshoot the mark. Similarly the hypotonia may give rise to the *rebound phenomenon*. If the arms be horizontally extended by the patient, and the observer smartly strikes them downwards by a blow on the hand, the arm on the normal side is quickly brought to rest in its original position with the minimum of recoil. On the side of the lesion, however, the hand and arm "bounce" freely and may oscillate two or three times before being brought to rest.

*Dysdiadochokinesis.*—This name has been used to describe the slowness, clumsiness and irregularity with which alternating movements (e.g. pronation-supination of the forearm) are carried out although the simple movement can be performed normally. In carrying out this test it is common to see adventitious movements in the proximal segments of the limb from disturbance of the normal co-ordinated contraction of the adjuvant muscles. To correct this disturbance the patient tends to break up complex movements into their several components, which are carried out successively instead of simultaneously—the so-called "movement by numbers".

*Tremor.*—This is not a resting tremor, but an unsteadiness which develops during movement, and in purposive movements tends to increase in range and severity as the climax of the movement is reached. It is thus essentially an "intention" tremor.

Similarly if the arms are out-stretched, they may show a tendency to droop, which is corrected by a series of jerks which thus gives the form of a tremor.

Again standing there may be irregular oscillations of the trunk and head—the so-called "titubation".

*Gait.*—In bilateral lesions the gait has a reeling, staggering character and in unilateral lesions there is a tendency to sway and deviate towards the side of the lesion. The disorder may vary in severity from a slight unsteadiness to a complete inability to walk or stand unaided. There is a tendency to walk with the legs abnormally separated to lessen the tendency to overbalance and the feet are brought down irregularly with a stamp.

*Speech.*—The articulatory musculature shares the inco-ordination of the other voluntary muscles with a resulting characteristic dysarthria. The defect is known as "scanning" or "staccato" speech. It consists of slowness of articulation, and a tendency to say each syllable of a word as though it were a separate word. The rhythm of speech becomes irregular, some syllables being slurred over, others being enunciated with almost explosive violence.

*Nystagmus.*—Nystagmus is particularly frequent in those lesions of the cerebellum which involve its connections with the brain-stem and the neighbouring vestibular nuclei. In unilateral lesions there is coarse nystagmus on deviating the eyes to the side of the lesion with a finer and more rapid movement on deviation away from the side of the lesion. In bilateral lesions the nystagmus may be symmetrical and if the lesion is confined to the superficial areas of the cerebellar hemispheres nystagmus may be entirely absent. Rarely—usually after acute lesions such as gunshot wounds or operative interference—the phenomenon of "skew-deviation" may appear temporarily; the eye on the side of the lesion being displaced downwards and inwards, the opposite eye upwards and outwards. A slight degree of skew deviation on lateral deviation of the eyes may be seen in deeply seated tumours of the cerebellum.

The cerebellum forms part of the non-sensory afferent nervous system and is concerned with the co-ordination of voluntary movement. It is not a sensory organ and there is no disturbance of any form of sensibility in cerebellar lesions.

## THE ANTERIOR FOSSA OF THE SKULL

The lesion most commonly found in this situation is a meningioma arising from the dural covering of the cribriform plate and growing upwards into the olfactory groove. The earliest sign is anosmia from pressure on the olfactory bulb and tract, unilateral at first and later often bilateral. Unilateral loss of vision associated with primary optic atrophy may later be associated with papilloedema in the opposite eye as an expression of the general rise of intracranial tension. Such a tumour gradually displaces the overlying frontal lobe and may then give rise to mental deterioration and fits, but only in tumours of exceptional size is a crossed hemiparesis observed.

*Aneurysm of the anterior cerebral or anterior communicating arteries may give rise to similar early symptoms, but owing to its limited size papilloedema and the remote pressure effects are not seen.*

## THE MIDDLE FOSSA OF THE SKULL

A rich variety of lesions may arise in or invade this fossa, and the syndromes vary according to the situation of the lesion.

The lesions in the mid-line include pituitary adenomata, tumours of the pituitary stalk, and meningioma of the sellar diaphragm (parasellar and suprasellar tumours). In the lateral parts of the fossa, passing from mesial to lateral, we have to consider lesions in the cavity or walls of the cavernous sinus, and tumours arising from the sphenoidal ridge in its middle and outer parts. Finally, reference must be made to growths invading the base of the skull and either occluding its foramina and producing cranial nerve palsies, or actually invading the cranial cavity. Secondary deposits of carcinoma and epitheliomata of the naso-pharynx are the common lesions of the last-named group.

### REGION OF THE OPTIC CHIASMA AND THE PITUITARY BODY

*The most common lesion in this region is tumour of the pituitary, usually an adenoma. The earliest symptoms of such a tumour are of an endocrine disturbance and vary according to the nature of the tumour. If this is composed of eosinophil cells acromegaly or gigantism will result, whereas if the adenoma is composed of indifferent (chromophobe) cells the endocrine disturbance will take the form of hypopituitarism of which Fröhlich's dystrophia adiposo-genitalis is the common and Lorain's infantilism the rarer type. Basophil adenomata although producing a characteristic group of endocrine symptoms, commonly described as Cushing's syndrome (see p. 516), do not attain a size sufficient to produce symptoms as space-occupying lesions.*

When a pituitary tumour of whatever kind extends outside the cavity of the sella turcica it causes distortion of the optic chiasma and produces one of a variety of visual disturbances. The commonest of these is a bitemporal hemianopia, sometimes starting as bitemporal paracentral scotomata which gradually increase in size till the entire temporal fields are lost. This results from the stretching of the decussating fibres of the chiasma derived from the nasal halves of each retina. In other cases, if the extension of the tumour is forward, unioocular scotoma, hemianopia or blindness may result, while if the extension is backward homonymous hemianopia may result from involvement of the optic tract. It cannot be too strongly emphasised that the form of the visual field defect in pituitary tumours is determined by the position of the local pressure upon the visual pathway and that while a bitemporal hemianopia is the most usual and characteristic defect the others which have been mentioned are frequently seen. Primary optic atrophy in the affected eyes is the rule in pituitary tumours, and papilloedema is not seen unless, as rarely happens, the tumour has attained such a size as to obstruct the third ventricle.

Meningeal tumours arising from the sellar diaphragm, and aneurysms extending backwards from the anterior communicating artery and cystic arachnoiditis may produce identical pressure symptoms, but without the endocrine disorders of pituitary tumours.

Cysts derived from vestiges of Rathke's pouch give rise to endocrine and local pressure symptoms comparable to those of primary intra-sellar tumours, but in addition give rise to papilloedema and internal hydrocephalus from obstruction of the third ventricle (see also p. 1403).

## SYNDROMES OF THE CAVERNOUS SINUS

The commonest acute lesion of this cavity is thrombosis, usually septic. Of the slowly developing lesions saccular aneurysm of the carotid artery is the most frequent, though the cavity may be encroached upon by tumours originating from the mesial end of the sphenoidal ridge. Symptoms consist of paresis of the third, fourth and sixth cranial nerves often leading to complete ophthalmoplegia, anaesthesia in the distribution of the ophthalmic division of the trigeminus and proptosis of the corresponding eye with oedema of the orbital tissues and conjunctiva from congestion of the ophthalmic veins. In rapidly developing lesions unilateral papilloedema may occur, but in those of slow development unilateral optic atrophy from pressure on the neighbouring optic nerve is more often seen.

## SYNDROMES OF THE SPHENOIDAL RIDGE

The dural sinus, which runs along the sphenoidal ridge (*sinus sphenoparietalis*), is one of the sites of election of the development of meningiomata. From the point of view of localising diagnosis this ridge may be divided into three parts, the inner (or clinoidal), the middle and outer.

A meningioma arising from the inner part gives rise in its early stages to a syndrome similar to that of a lesion of the cavernous sinus. Later symptoms referable to pressure on the temporo-sphenoidal lobe may occur (uncinate fits, personality changes and crossed hemiparesis). Papilloedema may result from general increase of intracranial pressure.

A meningioma of the middle part of the ridge may remain for long without clear localising signs, and radiography and ventriculography may be necessary to establish its position.

At the outer end of the ridge a meningioma may produce as its localising syndrome unilateral exophthalmos without squint, some fullness of the temporal fossa with local tenderness on pressure, speech disturbances if the lesion is left sided, together with the general symptoms and signs of raised intracranial tension. The X-ray picture usually reveals densification of bone or even hyperostosis of a part of the ridge and adjoining bone.

## SYNDROMES OF THE BASE OF THE SKULL

The characteristic signs of such lesions are palsies of the cranial nerves, often in groups anatomically close to one another, without any evidence of intracerebral damage or rise in intracranial tension. The common cause is malignant growth, either secondary deposits from remote carcinomata, the lung and breast being the most important, or direct invasion from the naso-pharynx.

## THE POSTERIOR FOSSA OF THE SKULL

*Lateral recess.*—The angle formed by the posterior surface of the petrous temporal bone and the tentorium (cerebello-pontine angle) is a common situation for neurofibromata which grow usually from the eighth nerve, but occasionally from the fifth or seventh. Rarely a meningioma may occupy the same position. Such a tumour presses into the lateral lobe of the cerebellum and the side of the pons. A highly characteristic clinical picture results, consisting of slowly progressive nerve deafness and tinnitus, some facial weakness, usually accompanied by peripheral facial spasm, impairment of sensibility in the area of the fifth nerve with diminution or loss of the corresponding corneal reflex and signs of ipsilateral cerebellar involvement. Such

tumours are of slow growth, and headaches and papillædema are often absent or occur late in the clinical picture.

## APHASIA AND OTHER DEFECTS OF SPEECH

Speech is the most highly developed and recently evolved function of the human being which is capable of direct analysis. Of all man's endowments it is the one which marks him off most clearly from his closest neighbours in the animal world. While in its final expression speech consists of sensori-motor activities of many mechanisms, each simple in comparison with the whole, its roots strike deeply into the texture of the mind and it constitutes the symbolic currency of thought itself; indeed it is doubtful if without speech in this wider sense any but the simplest thoughts are possible. So it is that we find that profound disturbances of speech function are invariably accompanied by disorder of the mind.

Speech in its simplest form is a means of communication of thought between individuals by the production and perception of sounds, but unlike sight or hearing, it is an elastic function, capable of indefinite extension and elaboration both in the race and in the individual. We thus find an almost infinite variation between the simple language of a primitive people and the highly elaborate language of a civilised race; between the speech of an uneducated peasant, for whose simple needs a few hundred words suffice, and that of a master of prose who may use thousands of words to express shades of meaning far beyond the scope of an uncultured person; between the speech of a child and that of the same individual grown to maturity. The growth of speech proceeds *pari passu* with the growth of the mind which employs it for its needs. Furthermore, upon the foundation of the initial symbolic expression of thought in spoken language has been erected in all but primitive races, the further edifice of written speech in which visual symbols replace those of sound. The evolution of speech in the different races of mankind is the province of the science of philology, but its growth in the individual in health and its dissolution in disease make up one of the most fascinating and complex chapters of medicine. As would be expected in a function of such complexity the disorders of speech are many and varied. At one end of the scale are disturbances purely psychological in their origin such as hysterical mutism; at the other are those due to the defects of the executive structures such as the tongue and larynx, and the neuro-muscular mechanisms which control them. To disturbances of this order the term *dysarthria* is applied. Between these extremes lie a group of speech disorders which depend upon physical disturbance of the portions of the cerebrum which form the anatomical substratum of the speech function and to these the terms *aphasia* or *dysphasia* are applied. It is with this order of speech disturbance that we are at first concerned.

## APHASIA

**GENERAL CONSIDERATIONS.**—Few subjects have suffered more from attempts at over simplification than the study of aphasia. Many attempts have been made by the creation of hypothetical "centres" connected with one another by supposedly well-defined tracts, to explain the manifold and often apparently conflicting facts which may be observed in an aphasic patient. Such diagrammatic analyses have been based upon individual cases of aphasia in which particular aspects of speech function have been predominately affected and in which post-mortem examination has revealed damage to a circumscribed area of the brain. Thus, Broca's centre in the cortex of the posterior part of the left third prefrontal convolution was the motor centre for spoken speech, while Exner's centre in a similar position in the second left



prefrontal convolution was the motor centre for written language. The "auditory word centre" in which auditory memories of words were stored was in the cortex of the first and second temporal gyri, while the "visual word centre" in which visual memories for words were impressed was in the cortex of the angular gyrus. These various centres were connected together by to-and-fro pathways which could be separately affected by a lesion. But the attempts to explain the multitudinous and varied phenomena which occur in lesions of the speech centre by assuming damage to one or other of these hypothetical "word centres" or to their connecting paths proved highly unsatisfactory, and the validity of such clinico-pathological correlations was usually undermined by the fact that the majority of cases of aphasia result from vascular lesions in which multiple areas of disease are present or from tumours of wide extent.

Clinical observation shows that as the function of speech in health evolves as a whole from more simple to more complex by a process of gradual elaboration, so in disease it undergoes dissolution as a whole from more complex to more simple. The more critically cases of so-called "pure motor aphasia" or "pure word deafness" are examined the more clear it becomes that, while one particular aspect of spoken speech is particularly affected, the level of speech function as a whole is lowered. Furthermore, in a given case of aphasia the defect of function is not constant, but may vary widely with the activity of the brain as a whole in response to such factors as fatigue, attention, anxiety and the general level of health of the whole individual.

These considerations must constantly be borne in mind in the examination of aphasic patients and in our attempts to generalise from such individual observations and to obtain a clear understanding of aphasia as a whole.

**ANATOMICAL CONSIDERATIONS.**—The function of speech seems to be concerned with the left hemisphere of the brain alone in right-handed persons, and this is explained by the major potential of the left hemisphere for receptivity and education associated with the major use of the right hand through the countless ages of humanity. True left-handedness is usually associated with a transfer of the speech function to the right hemisphere, but there are exceptions to this rule. The possibilities of transfer of the speech function from the left to the right hemisphere is great during childhood, to the extent that no lesion of the speech region of the left hemisphere, however extensive, causes lasting loss of speech in a child under the age of 6 years, provided that sufficient intelligence remains to permit of re-learning. After this age the possibility of such compensation by the right hemisphere from lesions in the left hemisphere seems gradually to diminish and to occur but little after adult life is reached, but even in adult life remarkable exceptions to this rule are seen. Within the left hemisphere speech function has as its anatomical substratum a region of the cerebral convolutions having its centre a little behind the middle of the first and second temporal convolutions. It is limited above by the posterior limits of the Sylvian fissure, occupies probably most of the external convexity of the left temporal lobe, and spreads backwards into the supramarginal and angular gyri, while anteriorly it extends forward, deep to the Sylvian fissure, over all the convolutions of the insula and to the posterior ends of the second and third left frontal gyri.

This "speech region of the brain" comprises not only the cortex but also the subcortical white matter which carries the paths of communication between the speech region and other portions of the brain. Posteriorly it receives an important tract from the visual region of the cortex. An interruption of this tract results in the condition known as "pure word blindness", in which the most conspicuous feature is an inability to appreciate written speech. Upon its deep aspect the speech region of the convolutions receives the temporal projection of fibres conveying auditory impressions, and destruction of this system by a lesion undercutting the convolutions in the centre of the temporal lobe results in serious speech disturbance in which

"word deafness", or inability to appreciate spoken language, is the most important component. In this same region another set of fibres impinges upon the speech area which convey the muscular sense impressions and other sensory impressions which are produced in the movements of articulation, and which are the only guidance which the "deaf mute" has in the knowledge of correct execution of his articulation. A lesion deep in the temporal lobe may interrupt both the foregoing paths and so isolate the speech region from any appreciation of correct execution, with the result that spoken language becomes unshapen and degenerates into a voluble jargon or "jargon aphasia" which is invariably associated with serious mental deterioration and confusion.

In the anterior half of the speech area a tract of white fibres gathers by degrees, and passing forward constitutes the bulk of the "temporal isthmus" which joins the temporal lappet of the insula to the region beneath the middle and inferior frontal convolutions from whence it is connected with the pyramidal path of the left side, and by way of the corpus callosum with the pyramidal path of the right side. This is the executive outgoing path for speech movements, and a complete lesion of this path will result in inability to exteriorise spoken or written speech with relatively little impairment of comprehension of speech—the so-called "pure motor aphasia" or "pure agraphia". Within the speech area of the brain thus limited, little is known of any localisation of function, but it is generally held that there is a gradual passing over from receptive functions (appreciation of spoken and written language) in the posterior regions, to executive functions (exteriorisation of spoken and written language) in the anterior regions.

In so far as the phenomena of "word-blindness" and "word-deafness" as well as "motor aphasia" and "agraphia" result from lesions of the speech area, they seem to result from lesions of the tracts concerned rather than from damage to the cortex itself. Lesions confined to the cortex and sparing the subcortical white matter, unless they are extensive, do not give rise to permanent disorder of speech.

**PHYSIOLOGICAL CONSIDERATIONS.**—Within a short time after birth the child begins to recognise the nature and uses of some of the objects in the world around it, and to express its simple conscious processes by gestures, and it early appreciates the "gesture language" of those around it. The "mimesis", or gesture language, thus early impressed and expressed, remains throughout life the most stable, the least vulnerable and the longest lasting of the methods of receiving and communicating ideas. Long before it is able to utter any articulate sound, the infant learns to connect certain sounds which it hears with certain objects and with certain events, and the memories of these auditory patterns first implanted serve by far the most important function in the processes and expressions of thought throughout life. Whereas we rely upon our visual memories for our remembrance and intelligence in general matters almost exclusively, yet as regards speech we rely upon auditory memories to a very large extent, and of course those who have never learned to read do so exclusively. The process of recall, both in silent thought and in speaking, is the revival of auditory patterns. From the original connection with hearing, the memories of speech patterns come to be located in that part of the brain associated with the auditory function—in and around the temporal lobe. Later, guided by the auditory memories, the child begins to express himself in articulate speech and he does so by the revival of auditory memories.

All living motion is sense-originated, sense-guided and sense-governed, and a motor process of itself has no proved conscious concomitant. Our consciousness is that of the sensations which accompany the movement, or which result from the movement. The knowledge of correct execution so gained fortifies and increases the functional stability of the speech area, and is of immense importance in the speech function. If it be absent owing to a lesion isolating the speech area on the incoming side, speech degenerates into a jargon and soon becomes impossible, just as in tabes

the walking becomes irregular from loss of the muscular sense conveyed in the posterior columns, and ultimately standing becomes impossible.

When at a considerably later age the child learns to read and to write, certain visual patterns (letters, words, sentences) become connected with certain objects and ideas, and become linked on to the already well-established auditory memories of speech. The meaning of the visual symbols is learned by the child from the meaning of the word or pattern spoken, which he already knows well, and the already developed auditory speech function serves as the instructor of the visual speech function, and throughout life remains the more potent, more dominant and less vulnerable function of the two.

Later still, in learning to write, the child relies upon his visual memories, and as his knowledge of correct execution in writing is largely visual and only in minor degree common sensory from the movements of the hand in writing, it follows that the function of exteriorising speech by writing becomes intimately connected with and a part of the visual speech function, and is usually depressed or lost with the visual speech function as the result of disease. It will thus be seen that there are not separate regions of the speech area in which the auditory memories of language and the execution of spoken speech on the one hand, and the visual memories of language and the execution of written language on the other hand, are represented, but that there are four functions intimately coupled in pairs, which have their seat in the same anatomical substratum. As has already been pointed out, it is a general principle that when the speech area is damaged the speech function becomes depressed as a whole, with the result that function is lost in order of its depth of impression.

**PATHOLOGICAL CONSIDERATIONS.**—By far the most common cause of aphasia, in all its degrees and varieties, is vascular disease. Thrombosis accounts for the majority of these and embolism and hæmorrhage for the minority. Trauma to the speech areas of the left hemisphere may cause a wide range of aphasic disturbances. Cerebral tumour is the usual lesion causing aphasia of gradual onset, and is much the commonest cause of "jargon aphasia" for there are few other lesions which can undercut and, therefore, isolate the temporal convolutions without otherwise interfering with their function.

Left-sided temporal lobe abscesses constantly cause aphasia as one of their early symptoms.

**Symptoms.**—Small lesions of the cortex seldom if ever produce lasting disturbances of speech. This indicates that within the speech area there is no narrow localisation of cortical function and there must be capacity for compensation for such small lesions in the surrounding undamaged cortex. With larger lesions of the cortex, and in proportion to their extent, mutilation of the patterns of speech, slowness of utterance, inability to find the words (inability to recall), especially nominals and above all isolated nominals, occur, in that order.

In the mutilated speech of the aphasic may be sometimes noticed stammering. This condition is at once distinguishable from true jargon aphasia, since the former is slow and halting whereas the latter is facile and voluble. Misplacement of words and the use of wrong words are common and are called "paraphasia". A tendency to repeat a word once pronounced is sometimes present and is designated perseveration of speech. The same faults occur also in writing, as faulty spelling, misplacement of letters and words and the use of wrong words. Much defect of general intelligence always accompanies severe damage to the speech area, especially if comprehension of spoken speech is involved, and this will be readily understood from the very large rôle which speech patterns play in the working of thought. Difficulty in the recall of words and speech patterns, which has been termed "verbal amnesia" or "nominal deficiency", is a characteristic feature of lesions of the speech area. This difficulty is greater with spontaneous revival than with recall, which is brought about by direct sensory stimulation. For example, an aphasic person who is unable

spontaneously to utter a word, may repeat the word at once when it is spoken to him, when he sees it in writing or when the corresponding object is shown to him. It is important in this connection to bear in mind that we do not speak in the letters of the alphabet, nor in the words of our dictionary, but in a running pattern of sound. The pattern or context provides the meaning, while the individual words are negligible and have no meaning. The power of the pattern in aiding revival is very great both from sequence rhythm and musical quality. As an example, an aphasic who has no spontaneous utterance is told to count with his interlocutor. The interlocutor begins counting, the aphasic joins in. The interlocutor then stops, but the aphasic continues counting, carried by the sequence rhythm.

The confusional defects of speech function are met with in extensive damage to the speech area, and are usual as immediate and transient phenomena in all suddenly occurring lesions of the speech area. There is general mental dullness, with varying degrees, usually severe, of depression of speech function and much confusion, both on the acceptive and expressive sides, when any of these functions remain, and the results of the examination of the speech faculty are apt to vary very much from moment to moment, for attention is very difficult to hold and the patient is easily fatigued and bored. Severe degrees of this form of defect may be associated with inability to recognise objects—"object-blindness", and with loss of ability to convey ideas by gesture—"amimia".

**Prognosis.**—In attempting to estimate the degree of recovery which is likely to occur in cases of aphasia, it is necessary first to bear in mind that sudden cerebral injury is apt at first, by the process which has here been described as functional depression or "diaschisis", to cause very wide loss of function, though the lesion may not be very extensive. A total aphasia, for example, is often the immediate result of a lesion of moderate size. Such phenomena last usually not longer than a week, and until they have passed off it is impossible to make a definite statement, either as to the extent of the lesion or the likely degree of recovery. Speech may be regained by two entirely separate processes—either by recovery of function in partly damaged and functionally depressed areas, or by compensatory activity in the undamaged portions of the brain. The possible recovery of function will depend upon the nature of the lesion and upon its extent. It will be greater when a lesion may be judged to be one of pressure rather than of actual destruction, if such pressure be removable, as in subdural hæmorrhage, abscess and gumma, and least when widely spread arterial disease and a failing heart suggest that the lesion is a thrombosis, or when an irremovable tumour is present. The greater the extent of the lesion if it be presumably from vascular occlusion, as judged by the associated signs, paralysis, anæsthesia and hemianopia, the less is the chance for functional restitution, as there is then little hope of any useful restoration of the circulation through collateral vessels. In children under the age of 6 years, unilateral lesions produce no permanent speech defects, provided sufficient intelligence remains, but even to this rule some important striking exceptions have been recorded. When adult life is reached, transference seems to occur but little, yet in a few recorded instances destruction of the posterior half of the speech area has been followed by an almost complete restoration of speech function.

**Treatment.**—The recovery of speech after a lesion causing dysphasia has much in common with the original acquisition of speech in a child. The preservation of a certain degree of intelligence is essential to recovery and the younger the patient the greater the prospect of a successful outcome. It is an unfortunate fact that the majority of cases of dysphasia occur in elderly subjects with arterial disease or in persons with infiltrating tumours in whom a gradual deterioration of cerebral function must be expected. The most hopeful group are the young adults and children suffering from traumatic lesions of the brain or such transient cerebral lesions as subdural hæmatomas, cerebral abscesses, angiomatous malformations and benign tumours. In such

cases spontaneous recovery of speech occurs gradually, but it can be accelerated by a careful and patient system of re-education at the hands of a speech therapist carried out either individually, or in groups.

**METHOD OF EXAMINATION.**—In examining a dysphasic person certain principles must be kept constantly in mind. The patient is always anxious and easily alarmed. He fatigues readily and is abnormally emotional and distractable. It thus follows that he should be examined in a quiet and physically comfortable environment, should be treated with gentleness and should only be examined for short periods such as half an hour at any one time.

It should be remembered that dysphasia, like all manifestations of disordered cortical function, varies in severity and quality from hour to hour and almost from minute to minute in response to such varied factors as attention, fatigue and general bodily well-being.

It follows that the best record of an examination of a dysphasic patient is an objective and factual one, a statement of what the examiner said or did, and what the patient said or did in reply.

Before any detailed investigation is attempted certain facts should be established and, when possible, confirmed from a relative. (1) Is the patient right- or left-handed and, if the latter, did he write with the right hand? (2) What was his state of education as regards reading, writing and knowledge of foreign languages? (3) Is he deaf? If so, to what extent? (4) Is his sight good or bad? Is there hemianopia? (5) Can he understand pantomime or gesture and express his needs thereby? (6) What is his state of consciousness? (7) To what extent is propositional speech preserved and to what extent can he convey a narrative in words? What defects are evident, *e.g.* perseveration, paraphasia or jargon utterances? (8) Can he name objects seen, both simple and familiar and unfamiliar? (9) Can he obey spoken commands? (10) Can he select correctly a test object from a number of them in response to the spoken word? (11) Can he write spontaneously and to dictation and what mistakes does he make? (12) Can he copy printed or written words? (13) Can he obey written commands? (14) Can he write figures and carry out simple arithmetic calculations? (15) Can he understand the significance of pictures? (16) Can he draw such simple objects as a bicycle, a flower or the façade of a house.

Having obtained some insight into the patient's speech defect in a preliminary survey it is essential to assess the degree of mental deterioration (if any) that is present by the battery of tests employed to investigate a case of organic dementia since dysphasia and global mental deterioration each in its way increases and distorts the severity of the other.

**TESTAMENTARY CAPACITY.**—No rule can be laid down as to the capacity of a person suffering from aphasic speech defects to exercise civil rights and to make a will, and each case must be judged upon its merits. The first and all-important consideration is the degree of intelligence, and when this is good it is essential for such capacity that there should be some mode of cognition and of expression left. In cases of uncomplicated executive aphasia either for spoken or written speech there is complete civil capacity, but when, as usually happens, the two conditions coexist, though intelligence and the receptive side of speech may be but little impaired, yet the expressive side of speech is reduced to gesture, and extreme difficulty may be met in ascertaining the patient's wishes. Defects in the comprehension of spoken and written speech interfere seriously with testamentary capacity and with capacity for exercising civil rights. In such cases there is great loss both on the acceptive and on the expressive sides of speech, with confusion of memory and impairment of intelligence. Most satisfactory results have, however, many times been brought about in apparently hopeless cases by careful, sympathetic and repeated procedures, in which the properties to be bequeathed and the likely legatees are assembled before the patient, thus allowing the testator to match the gift with the recipient. The

proceedings should be conducted in the presence and under the direction of a physician thoroughly conversant with the subject of aphasia. All concerned should bear two points in mind, the one being that the wishes of the testator must be paramount, and the other that an obviously just will is most difficult to upset in a court of law.

## DYSARTHRIA

The conversion of mentally formulated speech symbols into spoken language requires the correct use of several mechanisms, concerned respectively with the production of the voice by the passage of a stream of air through the aperture between the vocal cords and the articulation of words by movements of the lips, tongue, palate and jaws. To defects of speech dependant upon disorders of these executive processes the term dysarthria is applied. The neuro-muscular mechanisms responsible for these movements are built upon the same principles as those which control other highly co-ordinated voluntary movements, for example those of the hand. Impulses originating in the appropriate areas of the cerebral cortex are transmitted through the pyramidal tracts to the lower motor neurones (in the case of speech the various bulbar nuclei), and from these a further relay of impulses proceeds through the various peripheral nerves to the muscles concerned. As in other movements the co-ordination of these impulses is dependant upon the simultaneous reception of afferent impulses from the muscles and organs themselves and upon the activity of the cerebellum and other subcortical centres. We thus find that the varieties of dysarthria are strictly comparable with the disturbances of voluntary movement encountered in the limbs.

As we have seen, impulses from the executive areas of the speech cortex are transmitted to the lower centres through both pyramidal tracts, and in consequence speech disturbances do not result from unilateral lesions of the pyramidal tract in the centrum ovale or brain-stem. If, however, both pyramidal tracts are damaged, as commonly occurs in diffuse vascular degeneration, double hemiplegia, degenerative lesions of the pyramidal system, diplegia, tumours of the brain-stem and in advanced cases of disseminated sclerosis, the characteristic disturbance known as *spastic dysarthria* results. Here the speech is slow, stiff and laboured. Words are squeezed out with great effort as if through a rigid mechanism and are poorly formed on account of the stiffness and paucity of movement of the lips, tongue and palate. This condition is often referred to as "pseudo-bulbar palsy" (p. 1443).

When the lower motor neurones subserving the speech mechanisms are bilaterally affected "*flaccid or atrophic dysarthria*" results. The speech is slurred, indistinct and often slightly nasal. Labial and dental sounds are especially affected, but the laboured character of spastic dysarthria is absent. Atrophic dysarthria is met with in lesions of the medulla oblongata of all kinds, in progressive muscular atrophy and in multiple lesions of the bulbar nerves such as peripheral neuritis. Spastic and atrophic dysarthria are characteristically found in combination in those cases of motor neurone disease in which both pyramidal and lower motor neurones are undergoing decay. Primary weakness of the articulatory muscles may result in dysarthria. This is met with in myasthenia gravis where the muscles are subject to excessive fatigability and in some cases of myopathy where there may be great weakness of the muscles of the lips and jaws.

*Ataxic dysarthria* is most characteristically heard in cerebellar disease especially when both sides of the organ, or its afferent and efferent pathways, are damaged as in Friedreich's disease, disseminated sclerosis, cerebellar degeneration and extensive vascular or neoplastic lesions of the cerebellum and pons. In mild cases speech becomes slow, and deliberate with faulty spacing and accentuation of syllables, the

so-called "scanning" or "staccato" speech so common in disseminated sclerosis. When more severe, speech becomes "explosive", some syllables being slurred and almost inaudible, others being produced with a gush of uncontrolled sound. This coarse form of cerebellar dysarthria is most often met with in Friedreich's disease and in acute vascular lesions of the cerebellum and brain-stem. Dysarthria resulting from loss of afferent impulses from the periphery is rare, but is occasionally met with in severe cases of peripheral neuritis and of tabes. Conditions associated with involuntary movements may result in severe speech disturbance. This variety of dysarthria is most commonly met with in cases of chorea and athetosis, but may occur in other varieties of striatal disease, or as a sequela of encephalitis lethargica. In Wilson's disease (p. 1484) dysarthria results from muscular rigidity and goes on to complete anarthria. A very characteristic variety of dysarthria occurs in general paresis; speech is slow and slurred and tremulous and there is a tendency to repeat or reverse the order of the syllables in polysyllabic words. A very similar disorder may be met with in cases of chronic alcoholism and in some varieties of drug intoxication, especially barbiturate poisoning.

## OTHER DEFECTS OF SPEECH

### STAMMERING OR STUTTERING

A spasmodic defect of articulation leading to a sudden check in the utterance of words or to a rapid repetition of the consonantal sounds in connection with which the difficulty arises. To the trouble of articulation are often added spasmodic movements of face and head or indeed of any part of the body.

Except in the rarest instances this condition is not associated with any structural change in the nervous system, or in the organs of articulation, but it has been observed as the end result of a lesion of the speech areas. It occurs with a greater frequency than can be attributed to coincidence in naturally left-handed persons who have been trained to behave as if they were right-handed. It not infrequently occurs in more than one member of a family, but whether this implies a hereditary or environmental influence is uncertain, as it may equally be acquired by a susceptible subject from other members of a child group. The stammerer usually manifests one or other of a number of signs of incipient psychoneurotic instability such as abnormal timidity and excitability, nocturnal enuresis, night terrors and habit spasms, and though these symptoms may recede or disappear with time the stammerer remains more liable than normal individuals to develop neurotic manifestations under circumstances of stress.

The disorder seems to consist of a lowering of the functional stability of the executive mechanism of speech by the effect of embarrassment either at a conscious or unconscious level. It is begotten of shyness and self-consciousness, and probably for this reason is infinitely commoner in boys than in girls, for the latter are much less liable to self-consciousness. It is never present in infancy or very early childhood but arises at the age when shyness and self-consciousness first manifest themselves. Its onset not uncommonly follows a debilitating illness such as measles, diphtheria or whooping cough, and it often appears after a sudden fright, or an experience causing severe emotional strain or embarrassment. Indeed it is the historical utterance of fright and of those who find themselves suddenly "*in flagrante delictu*".

Like other manifestations of anxiety in childhood it is more likely to occur in homes where there are disturbing factors such as parental discord, favouritism and jealousy, over-indulgence or over-strictness and frequent changes of teachers and surroundings.

The stammerer never stammers in the speech of thought nor when talking aloud to himself alone, nor at any time when singing, for in the two former cases the embarrassment of self-consciousness is absent, and in the last case the element of rhythm and music greatly increases the stability and confidence of the function of speech. In rebellious cases this element of self-consciousness, as well as the more overt evidences of psychological instability, may gradually disappear while the stammer remains unaltered as an ineradicable habit.

In articulate speech three muscular mechanisms are concerned: (1) the respiratory mechanism for supplying the blast of air, (2) the larynx for producing the voice and (3) the muscles of the lips, tongue, jaw and palate for articulation. For distinct speech there must be absolute co-ordination of these mechanisms one with another. Consonants are in nearly all cases the source of the difficulty in stammering, and while these are buccal sounds, yet some begin with a laryngeal sound, while others are purely buccal. The former are termed "voiced consonants", and are B, W, V, Zh, Z, Th (as in "thus"), D, L, R, G, Y; and the latter, "voiceless consonants", and are P, F, Th (as in "thin"), S, Sh, T, K; while N, M and Ng terminal are "voiced nasal resonants". If one articulates these consonants it becomes at once clear, and it is the presence of the initial laryngeal element or "voicing" which makes the difference between B, V, Z, D, G, and P, F, S, T, K, respectively.

A careful attention to the manner in which the letter sounds are produced is absolutely essential in the investigation and treatment of stammering. The difficulty occurs most commonly with the explosive consonants, P, B, T, D, G, K, and nearly always where these occur as initial letters—that is, in starting the articulatory mechanism; and to avoid this difficulty which arises after every pause, most stammerers speak in a rapid monotonous fashion. The fault chiefly lies in the direction of energy to articulation rather than to phonation. The patient held up by his stammer usually remains silent, but occasionally having produced the first sound, he continues to repeat it—the reduplication stammer, which has been the origin for the names "stammer" or "stutter" by which the malady is known. Often the patient uses a trick or contortion to prevent the stutter or to relieve the feeling of nervous tension and embarrassment in consciousness which the defect causes, and these tend to become engrafted on him, as (1) associated sounds—whooping, grunting, crowing, etc.; (2) habit spasms—contortions of the face, limbs or body, which sometimes take a complicated form and exactly resemble the co-ordinated form of tic.

**Prognosis.**—The majority of the cases tend to a spontaneous cure, and recovery is hastened in all cases by systematic treatment. In every class of case the results of treatment may come slowly at first, but perseverance will in almost every case bring success.

**Treatment.**—Attention should be paid to conditions of general health, and to the mental well-being and satisfaction of the child, with plenty of scope for pleasure and for satisfying occupation. When possible, defects in the home and school environment should be eliminated. Speech training at the hands of a trained speech therapist either individually or preferably in special classes is invaluable. It is well for the patient to speak, read or recite in a large room alone, loudly, slowly and distinctly. The following system for such exercises is useful: (1) The chest must be kept well filled with air. This most important point is often most difficult to the patient. (2) He must speak slowly, with a full resonant voice. (3) When he comes to the word on which he tends to stutter, he should raise his voice and direct his energies to vocalisation, and not to articulation. If the difficulty be over a voiced consonant, he must be directed to voice it firmly. If the consonant over which he stumbles be a voiceless one, attention must be directed to the vocalisation of the subsequent vowel sound; for instance, in "pat" he must attempt to vocalise the "a", and he will find little difficulty in prefixing "p" as the syllable is uttered. (4) Gymnastic and singing exercises are valuable additions to treatment. Should associated movements be



present, the speaking exercises may be carried on in front of a mirror, so that the patient may see these himself, and endeavour to suppress them.

The development of confidence and self-reliance is everything in the treatment of stammering. The skilled teacher first gains the liking, respect and submission of his patient. He then assures him that his defect will disappear, and that he can cure himself, and demonstrates to him by correcting the faults that he can speak normally. In adult stammerers also first place in treatment is to be given to speech re-education. Even prolonged psychotherapy is seldom effective, although the stammer may become less pronounced by the lessening of the patient's state of anxiety and the general improvement in mental health.

## APRAXIA

**Definition.**—A disorder of cerebral function, characterised by inability to perform certain familiar purposive movements, in the absence of motor and sensory paralysis and ataxia (Kinnier Wilson). This disorder does not depend upon defective perception (agnosia) nor upon general reduction of intelligence.

**Ætiology.**—Apraxia may result from both general and local diseases of the brain. It may be met with in general paralysis of the insane, in cerebral arteriosclerosis and in several forms of dementia, and in certain cases of cerebral tumour. It occurs in its purest form from local lesions of the brain, and may then be confined to one region of the body. It may result from lesions of the posterior part of the prefrontal area of the left side, the so-called "motor or verbal" aphasia and agraphia being good examples of apraxia of speech and writing respectively, and lesions in this region may also cause apraxia of the limbs on one or both sides. Lesions of the anterior half of the corpus callosum have been associated with conspicuous apraxia, as have also bilateral lesions in the posterior parts of the hemispheres. In the latter cases, the apraxia is likely to be associated with some degree of lack of recognition of an object, and of its uses (agnosia), and this causes apraxia from a loss of correct comprehension of the act required. Apraxia is sometimes met with in cases of hemiplegia in which, notwithstanding the complete recovery of motor and sensory paralysis, the performance of familiar acts—from the highest skilled movements, such as the fingering of the pianoforte or of the violin, or the use of his tools by a craftsman, to the simplest act—may be no longer possible.

**Symptoms.**—The features of the condition may be well demonstrated by the consideration of left-sided hemiapraxia. There is neither loss of power nor loss of sensibility in the left upper extremity, but in many of these cases there is a diminished awareness of the left side of the body. When such a patient is asked to perform some familiar act with the right hand, he at once does so correctly, but when ordered to perform the same act with the left hand he is unable to do so. Either he makes aimless wandering movements with the left hand, or he may succeed in making movements somewhat resembling those required of him, with much slowness and clumsiness. Sometimes he may perform some act which is entirely different from that required of him, and this phenomenon is called *parapraxia*. When the apraxia is partial, the patient may be able to perform some acts and not others, his inability usually, but not always, increasing with the complexity of the act required. Or he may be able sometimes to perform an act in which he commonly fails. Not infrequently such a patient, wearied with the unsuccessful attempts of his left hand, will abruptly perform the act correctly with his right hand, to get rid of it. And he will define his defect by saying, "I know quite well what you want me to do, but I cannot do it". Spontaneous volitional movement is similarly affected, and this leads invariably to a marked loss of initiative in the use of the affected limb—the patient will not try to use it. The apraxic patient is often to an astonishing degree unaware

of his disability, and frequently becomes conscious of it for the first time when it is pointed out to him by another person.

**Diagnosis.**—Apraxia may be confused with astereognosis, with agnosia and with cortical ataxia. A correct conception of the nature of the two former conditions will exclude the possibility of error. In cortical ataxia the patient obeys the word of command at once and succeeds more or less with the act required, the defect being clumsiness of execution. The clinical examination of patients for apraxia must include—(1) the general psychological condition as regards attention, memory and reasoning; (2) an inspection of sensory appreciation for defects of simple perception in the regions of smell, sight, hearing, taste, cutaneous sensibility and muscular sense; defects of recognition of sensory impressions in these regions (agnosia); defects of memory and (3) an examination of executive power for any defects in the movements determined by visual, auditory, tactile and kinæsthetic stimuli. What response does the patient make to objects held in front of him or to gestures made to him? Can he imitate movements? Can he, when requested, make simple and purposive movements, with and without the objects in his hands? When given an object, how does he hold it and use it?

## AGNOSIA

In certain conditions of cerebral disease, it is found that each and all of the sensory organs, when called into play, may fail to arouse an intelligent perception of the object exciting them. This inability to recognise the import of a sensory stimulus is called agnosia. Those patients who present apraxia and agnosia, often show other interesting phenomena which are of importance; these are (1) inattention, (2) defective capacity for retaining recent impressions, (3) lack of initiative and (4) perseveration. Agnosia is most commonly associated with lesions involving one or both parietal lobes.

## THE CEREBROSPINAL FLUID

The cerebrospinal fluid is the liquid which fills the cerebral ventricles, the sub-arachnoid cisterns and the general subarachnoid space. It is formed by the choroid plexuses of the lateral, third and fourth ventricles and, escaping through the foramina of Magendie and Luschka, passes over the convexities of the brain and through the whole extent of the spinal subarachnoid space to be reabsorbed into the venous blood-stream through the arachnoid villi, particularly those contained in the Pacchionian bodies in relation to the sagittal sinus. The precise method of its formation remains undecided; the bulk of available evidence indicates that it is produced by a process of dialysis, but certain facts suggest that a process of active secretion may also play a part. As regards the great majority of its crystalloid contents, the fluid corresponds accurately to a protein-free filtrate of the plasma and varies in composition with changes in the circulating blood. Certain crystalloid contents, however, are present in a concentration difficult to explain on a theory of pure dialysis.

The total quantity of the cerebrospinal fluid in a healthy adult varies from 90 to 150 ml. Its rate of production under natural conditions is unknown, and is influenced by the composition of the blood plasma, the capillary pressure in the choroid plexus and the permeability of the cells of the plexus, as well as by the pressure of the fluid in the ventricles. Although the cerebrospinal fluid does not circulate in the sense that the blood circulates, there is a steady flow in health from its site of origin in the ventricles to that of its absorption in the arachnoid villi, but the rate of this flow under normal circumstances remains unknown.

The normal cerebrospinal fluid is a clear, colourless fluid indistinguishable in appearance from water and it has a remarkably constant composition. As obtained by lumbar puncture it contains from 0 to 5 cells (endothelial cells and lymphocytes) per c.mm. Its chemical composition is as follows :

Protein (mainly albumin) .	0.02 to 0.04 per cent.	(20 to 40 mg. per 100 ml.).
Glucose . . . . .	0.05 to 0.09     "	(50 to 90 mg. per 100 ml.).
Chlorides (as NaCl). .	0.72 to 0.75     "	(720 to 750 mg. per 100 ml.).

In health the globulin content is insufficient to give a positive Nonne-Apel or Pandy test.

#### LUMBAR PUNCTURE

The method by which the cerebrospinal fluid is best withdrawn for diagnostic or therapeutic purposes is by lumbar puncture. The patient should lie in the left lateral position, with the head supported by one pillow and at the same level as the lumbar spine. A firm couch or operating table is to be preferred, and if the operation is performed on the patient's bed the introduction of fracture boards under the mattress is advisable. The patient's back must be in a vertical plane. The knees are drawn well up to produce the maximum convexity of the spine, but the neck should not be sharply flexed, or pressure measurements will be inaccurate. The site of lumbar puncture is the midline in the interspace between the third and fourth or the fourth and fifth lumbar spines. The skin should be anaesthetised with local anaesthetic, and the lumbar puncture needle should be introduced accurately at right angles both to the longitudinal and transverse axes. Pointing the needle even slightly upwards, downwards or towards the side is likely to result in contamination of the fluid with traces of blood. The whole procedure must be carried out with the utmost attention to asepsis, and the precautions taken should not be less than those necessary for a major surgical operation. The needle thus introduced will be felt to penetrate in turn the spinous ligament and the dura mater, and on withdrawing the stylette the fluid will flow freely in the normal subject at the rate of about 3 drops a second. In the rare cases where lumbar puncture is impossible or inadvisable, cerebrospinal fluid may be obtained either by cisternal puncture or by direct tapping of the cerebral ventricles.

**PRESSURE OF THE CEREBROSPINAL FLUID.**—This can only be ascertained by actual measurement with a manometer; estimates based upon the rate of flow are fallacious. When it is necessary to measure the pressure, a three-way needle with manometer attachment should be employed, and before the readings are taken the patient must be lying relaxed and comfortable, with easy respirations. The normal pressure of cerebrospinal fluid varies from 60 to 150 mm., and will be seen to rise and fall over a distance of 5 to 10 mm. with the respiratory movements. Coughing and straining give rise to an abrupt increase in the pressure of from 30 to 50 mm. A pressure of over 150 mm. is evidence of increased intracranial pressure, and readings of over 300 mm. are common in the presence of intracranial tumours, meningitis and other conditions characterised by raised intracranial pressure. When the cerebrospinal pressure is found to be 300 mm. or more, fluid should be withdrawn slowly and in the minimum quantity necessary for pathological investigation (5 ml.), as the rapid withdrawal of a large quantity of fluid may result in sudden death from the formation of a medullary pressure-cone or from uncinate herniation.

**QUECKENSTEDT'S PHENOMENON.**—In the normal subject the pressure of the fluid in the lumbar sac directly reflects the pressure within the cerebral subarachnoid spaces and the ventricles, and any change in the intracranial pressure is immediately transmitted through the patent subarachnoid space and causes a change in the level of the fluid in the manometer. This forms the basis of the valuable test for patency of the subarachnoid space known as Queckenstedt's test.

If, with the lumbar puncture needle and manometer in position, the right jugular vein is firmly compressed, an immediate rise in the level of the fluid in the manometer will be noted in the normal person, the pressure rising rapidly from the normal 80 to 120 mm. to 300 mm. or more. On releasing the compression of the jugular the pressure rapidly returns to its former level. If there is any block in the spinal subarachnoid space, such as may be caused by extradural compression, or a spinal tumour, or if there is interference with the escape of fluid from the cranial cavity, there will be no rise in the pressure of the lumbar fluid on jugular compression (complete block), or a rise of only a few cms. (incomplete block). In the latter case release of the jugular compression will be followed by a very slow return of the meniscus to the former level or the level may remain unaltered, indicating a ball-valve type of obstruction. Again, if the withdrawal of a small quantity (4 to 8 ml.) of fluid is followed by a persistent fall in the pressure of about 50 per cent., there is probably obstruction to the normal flow of cerebrospinal fluid. These two tests afford valuable evidence of any occlusion of the spinal subarachnoid space.

**APPEARANCE OF THE CEREBROSPINAL FLUID.**—Any departure from the normal watery appearance of the cerebrospinal fluid is readily detected. The fluid may be freely blood-stained in cases of recent subarachnoid or cerebral hæmorrhage, or of trauma to the brain. In such cases the blood is usually present in large amounts, and is intimately mixed with the cerebrospinal fluid in all specimens removed. Blood contamination resulting from faulty technique in withdrawing the fluid can usually be recognised, as it is usually scanty in amount and varies in intensity in different specimens. If the blood has been mixed with the fluid for more than a few hours before withdrawal, it assumes a slightly orange tint on account of the breakdown of the blood pigment. Such a specimen if centrifuged or allowed to stand will give a bright canary-yellow supernatant fluid, a condition known as *Xanthochromia*. In cases punctured several days after a severe subarachnoid hæmorrhage, the fluid may be thick and brownish-orange in colour. In addition to cases of resolving subarachnoid hæmorrhage, xanthochromia may be present in cases of long-standing spinal blockage, subdural hæmorrhage, some cases of polyneuritis, and occasionally in cases of cerebral tumour. It is often associated with a great increase in protein content of the fluid, which may thus undergo spontaneous clotting on withdrawal.

The combination of xanthochromia with greatly increased protein content of the cerebrospinal fluid, and evidence of spinal block is known as *Froin's syndrome (loculation syndrome)*, and is very characteristic of severe spinal compression.

**Turbidity** of the cerebrospinal fluid is caused by the presence of a great excess of cells, and is thus characteristic of meningitis. It may vary in degree from slight opalescence to a frankly purulent fluid.

**INCREASE OF PROTEIN CONTENT.**—This is of great importance, and occurs in many pathological conditions of the central nervous system. As has already been stated, it may result from occlusion of the subarachnoid space from any form of spinal block. It occurs in all cases of meningitis, whether pyogenic, tuberculous or syphilitic. It is one of the earliest changes in the fluid in cases of cerebral abscess. It may be found in acute poliomyelitis and most virus diseases of the nervous system, but it is slight or absent in encephalitis lethargica. An isolated increase in protein content occurs in many cases of intracranial tumour, particularly where the tumour impinges upon the surface of the brain or the walls of the ventricles. It may be met with after vascular lesions of the brain, even though there has been no escape of blood into the subarachnoid space, and also in cases of acute infective polyneuritis.

**INCREASE IN CELL CONTENT.**—An increase in the cell count of the cerebrospinal fluid is found in almost all inflammatory diseases of the nervous system. In pyogenic meningitis an enormous excess of cells is the rule, and the vast proportion of the cells are polymorphonuclear leucocytes. A small number of lymphocytes may also be present, and the proportion of these gradually increases as recovery takes place. A

lymphocytosis is characteristic of tuberculous and syphilitic meningitis, and of most virus infections of the nervous system. In tuberculous meningitis a mixed cytosis often occurs, at first with as high a proportion as 40 per cent. of polymorphonuclear cells, but as the disease progresses the proportion of lymphocytes steadily rises until they represent 90 per cent. or more of the total cell count. A mixed pleocytosis is also seen in cases of cerebral and extradural abscess, in sinus thrombosis, and after extensive cerebral softenings.

**DECREASE IN GLUCOSE CONTENT.**—The glucose content of the cerebro-spinal fluid is decreased in varieties of meningitis, particularly in those due to pyogenic organisms, in which case the fluid commonly fails to reduce Fehling's solution on boiling. It is almost invariably reduced in tuberculous meningitis but only rarely in meningitis due to viruses (see p. 1396). It is also reduced in some cases of neurosyphilis.

**ALTERATION OF CHLORIDE CONTENT.**—The chloride content of the cerebrospinal fluid is lowered in all cases of purulent or tuberculous meningitis, largely as a result of the diminution of the plasma chlorides, which occurs in these as in other acute febrile illnesses. This change is of particular value in the diagnosis of tuberculous meningitis, in which affection levels as low as 600 to 650 mg. per cent. may be found early in the disease, in contrast to the relatively normal chloride content in the case of other diseases causing a lymphocytic pleocytosis.

An increase in the chloride content as well as that of non-protein nitrogen is found in uræmia and other conditions of salt retention.

**LANGE'S COLLOIDAL GOLD REACTION.**—In neurosyphilis and in some cases of disseminated sclerosis, the globulin fraction of the total protein of the cerebrospinal fluid increases and may almost equal the albumin fraction. The high globulin content gives the fluid a power of precipitating colloids from suspension. The estimation of this power in relation to colloidal gold is the basis of Lange's test. To 10 dilutions of cerebrospinal fluid (from 1 in 10 to 1 in 10,000) constant amounts of colloidal gold are added, and the mixtures allowed to stand for 24 hours. The form of the precipitation curves has a differentiating value. Thus in general paralysis the first 6 dilutions are precipitated (paretic curve), in tabes dorsalis, the third and fourth dilutions show the maximal precipitation (luetic curve); in meningitis, the sixth to eighth dilutions are precipitated (meningitic curve). In disseminated sclerosis the combination of negative Wassermann reactions in blood and fluid and a paretic curve in the fluid is frequently found.

**ORGANISMS.**—The nature of the organismal content is determined (1) by the direct examination of films made from the centrifugalised fluid, (2) by cultures from the fluid and (3) by the inoculation of animals with the fluid.

**THE WASSERMANN REACTION.**—This is positive in all conditions of recent syphilitic disease impinging upon the meninges, and always in general paralysis. Though often positive in tabes, it may be found negative.

## INTRACRANIAL TUMOURS

Under this heading are grouped all new formations which encroach upon the intracranial space and which produce the familiar pressure symptoms and local symptoms of tumour, though some of them are not, strictly speaking, neoplasms.

**Ætiology.**—The brain is one of the commonest seats of new-growth in the body. Further, new-growth is one of the commonest forms of structural disease of the brain—second only in incidence to lesions of vascular origin.

Cerebral tumour may occur at any age, but it is relatively rare in the very young and in the very old. There is no significant difference in its incidence in the two sexes. The relation between head injury and the first symptoms of cerebral tumour is one that has often been pointed out, though it is likely that in most cases where

this relation exists, the blow on the head has simply served to bring a pre-existing tumour into symptomatic prominence, by causing either œdema or hæmorrhage in its substance or vicinity. It must be remembered in this connection that a cerebral tumour may exist for a long period without definite symptoms.

**Pathology.**—The pathological classification of intracranial tumours has a practical importance, for when the nature of a new growth can be determined clinically, some idea of its future behaviour can be formed and the surgeon can make his plans to meet the problems which each variety of tumour presents.

The chief varieties of intracranial tumour are as follows :

*Tumour of the brain substance—Glioma.*

*Tumour arising in the meninges or nerve sheaths* {Meningioma.  
Neurofibroma.

*Secondary carcinoma and sarcoma.*

*Blood vessel tumours.*

*Tumour of the pituitary body and stalk.*

*Infective granuloma—Tuberculoma, Syphiloma.*

*Parasitic and other cysts.*

It is not possible to indicate with precision the relative incidence of these different types of tumour, for the figures available from different institutions must reflect their particular circumstances and are not representative of the population as a whole. But it is possible to state that glioma constitutes about 40 per cent. of all intracranial tumours and meningeal and pituitary tumours together from 20 to 30 per cent. Formerly, the incidence of secondary carcinoma was said to be about 6 per cent., but recent evidence has indicated that it is much higher and may well be as high as 20 per cent. of the total. There can be no doubt that as greater precision in diagnosis is reached, the frequency of this complication of visceral carcinoma becomes more fully recognised.

**GLIOMA.**—As its name implies, the glioma is a tumour arising in the glial or supporting tissue of the brain, but within the limits of this term are included growths of *very varied cytological type and modes of growth*. Some are richly cellular, highly vascular and rapidly growing, others are relatively acellular and may be exceedingly slow in growth. But they have certain important characteristics in common. They originate within the substance of the nervous system and all infiltrate to a greater or less extent the surrounding nerve tissue. They are thus invariably locally malignant. They do not invade tissue outside the nervous system or cause metastases in other parts of the body, though in some, fragments may become detached and be carried in the cerebrospinal fluid to distant parts of the subarachnoid space and there continue their growth as distinct implantation tumours. Gliomas are prone to undergo degeneration and necrosis. If this is rapid it may lead to cyst formation; if it is slow it may lead to calcification within the tumour. Hæmorrhages into the substance of a glioma are common and the surrounding brain tissue is often œdematous. Occasionally gliomas are multiple.

Many types of glioma have been described, but these classifications are ephemeral and largely artificial, for more than one pathological type may be represented within a single tumour and the same tumour may present different features at successive periods of its course. But with this reservation it is useful to recognise certain common and relatively well-defined clinical and pathological types.

*Astrocytoma* is the commonest of all gliomas and is a diffusely infiltrative tumour of the white matter which occurs at all ages and in any part of the brain. Its structure is relatively uniform and its growth often very slow. The survival period after local removal may be long, especially when, as in the cerebellum, a satisfactory excision of the surrounding tissue can be achieved.

*Glioblastoma multiforme* is a tumour only slightly less common than the astrocytoma but is far more cellular, rapidly growing and varied in its histological appearance. It is a tumour of the cerebral hemispheres, and although it may occur at any age, is commonest in middle age or later and usually terminates life within a year of its first symptoms. Because of its invasive nature it is, of all gliomas, the least amenable to surgical removal.

*Medulloblastoma* is a highly cellular and rapidly growing tumour almost confined to the roof of the fourth ventricle and cerebellum. It is commonly found in children and is in the form of glioma most often spread by implantation across the subarachnoid space.

Other varieties of glioma are described in relation to the ependyma, choroid plexus and oligodendroglia.

**MENINGIOMA OR ENDOTHELIOMA.**—This is a connective tissue tumour which grows from the endothelial cells of the arachnoid villi particularly where these penetrate the walls of the dural venous sinuses. Meningiomas are therefore found in the neighbourhood of the venous sinuses, especially the superior longitudinal, the sphenoparietal, the petrosal and circular sinuses. They do not invade the brain but compress and displace it, and may become deeply embedded in it. They may infiltrate the overlying bone which may become so thickened that a visible or palpable boss is present on the surface of the skull. Meningiomas are highly vascular tumours, and large nutrient vessels may be present in the neighbouring skull and scalp. Calcification in the substance of these tumours is common.

**NEUROFIBROMA.**—This also is a connective tissue tumour arising from the sheaths of the cranial nerves. The vast majority grow from the sheath of the auditory nerve and constitute the common tumour of the lateral recess—the acoustic neurofibroma. Occasionally they grow from the fifth or other cranial nerves. The neurofibroma may be solitary or may appear as part of a generalised neurofibromatosis when it is often bilateral on the acoustic nerves. It is a firm, nodular tumour which gradually buries itself in the side of the brain-stem and often erodes the bones of the internal auditory meatus. It is usually of very slow growth but may undergo necrosis and cyst formation.

**SECONDARY CARCINOMA.**—As has already been indicated secondary carcinoma is probably more common than is generally realised. It is a frequent event in lung cancer, which forms the most important source of brain metastases, and it is not uncommon for symptoms of secondary involvement of the brain to precede those of the primary growth in the lung.

Indeed in all adult cases presenting the signs and symptoms of intracranial tumour the possibility of carcinomatous metastasis should be explored, particularly in a patient who is losing weight or deteriorating rapidly.

Other common sources of metastatic tumours are the breast, prostate and gastrointestinal tract.

Carcinomatous deposits are commonly blood-borne and multiple, and are liable to undergo necrosis and cyst formation and hæmorrhage.

Rarely they may reach the brain by direct invasion from the naso-pharynx. In exceptional cases there may be a diffuse infiltration of the subarachnoid space with carcinoma, and when it occurs alone this "meningitis carcinomatosa" may be very difficult to diagnose.

**BLOOD-VESSEL TUMOURS.**—Tumours and congenital anomalies of the blood-vessels are relatively common in the brain compared with other organs. They take two principal forms: (1) angiomatous malformations consisting either of arterio-venous varices or telangiectases. These are most often found in the hemispheres but may occur in the brain-stem or cerebellum. They involve the brain diffusely, particularly on its surface, and may present themselves as tumours or as cases of cerebral hæmorrhage. (2) True angiomatous neoplasms or hæmangioblastomas which commonly

occur in the cerebellum and give rise to blood-cysts. They may be associated with similar tumours in the retina and may be familial—a combination often known as Lindau's disease.

**PITUITARY TUMOURS.**—These arise from the glandular elements of the pars anterior. They usually take the form of an adenoma and may be composed of any of the three types of cell found in this body.

The commonest is the chromophobe (neutrophil) adenoma, consisting of a mass of neutrophil cells with clear vesicular nuclei lying in masses in a fine connective tissue stroma, or occasionally arranged in columns or in a primitive alveolar formation. This type of tumour is associated with symptoms of hypopituitarism. The less common variety is composed chiefly of cells of acidophil type whose cytoplasm contains acidophil granules of varying size. This type is associated with the clinical picture of acromegaly. Both the foregoing varieties of adenoma commonly attain a sufficient size to expand the sella turcica, and to escape from it to cause neighbourhood symptoms by involving the optic chiasma or the oculomotor nerves. The rarest type of adenoma is that composed of cells containing coarse or fine basophil granules—the basophil adenoma associated with Cushing's syndrome. This is a tumour of small size which may only be detected by making serial sections and never causes expansion of the sella or symptoms of involvement of neighbouring structures. Very rarely pituitary adenomata may undergo malignant degeneration, and occasional examples of tumours of mixed cell type are met with.

Another tumour arising in association with the pituitary body is the Rathke pouch, or supra-sellar cyst (adamantinoma). This arises from cell rests derived from the buccal outgrowth (Rathke's pouch) from which the anterior lobe of the pituitary is developed. Such tumours are commonly situated above the sella turcica but may be partially or wholly intra-sellar. They are partially solid, partially cystic, tumours composed of masses of transitional epithelium lying in a fine connective tissue stroma and containing cystic spaces. They frequently undergo degeneration and subsequent calcification, and may reach the size of a golf-ball and so come to protrude far into the floor of the third ventricle and obstruct its cavity, so producing a severe degree of hydrocephalus.

**CHOLESTEATOMATA.**—These, sometimes called "mother-of-pearl" tumours, on account of their glistening appearance, are found in connection with the basal meninges. Their origin is uncertain. They are of slow growth, and may run a symptomless course. They consist of a greasy, greyish, friable and more or less laminated mass, made up of layers of a closely packed mosaic of flat, polygonal cells. The tissue is necrotic, and contains no blood-vessels.

Among the rarer tumours of the brain may be mentioned dermoid tumours, teratomata, chordomata, which arise from rests of the anterior end of the primitive notochord and are found below the base of the brain, lipomata, fibromata, neuromata, neuroblastomata, consisting actually of undifferentiated nerve cells, and enchondromata.

**CYSTS.**—Cysts of the following varieties may be met with on the surface or in the substance of the brain: (1) Serous cysts of the arachnoid. These may occur as part of a diffuse arachnoiditis or may occur alone without any known cause. (2) Porencephalic cysts. These commonly result from softening after embolism or thrombosis or severe brain injury in early childhood. They may lose all trace of their origin and form thin-walled cavities, containing colourless fluid which often extend from the ependyma to the pia-mater and involve the whole thickness of the pallium. (3) Cysts derived from tumours—especially gliomata and secondary carcinomata. The tumour giving rise to such a cyst may be extremely small and may appear as a small nodule in one part of the circumference. Such cysts contain a highly albuminous fluid which is often yellow in colour. (4) Blood cysts, which are usually derived from highly vascular tumours but may follow trauma or intracerebral hæmorrhage from



any cause. (5) Cysts following the breakdown of areas of the brain which have become necrotic from vascular occlusion. (6) Cysts of the septum pellucidum. (7) Colloid cysts of the third ventricle. (8) Cysts derived from remnants of the developing pituitary body and described in connection with pituitary tumours. (9) Dermoid cysts. (10) Parasitic cysts, of which the more common is the bladder worm of the tapeworm, *tania solium*, which is called, on account of the thickness of its wall, *cysticercus cellulosæ*. These are usually multiple, and grow in the folds of the pia mater in the depths of the sulci and occasionally in the fourth ventricle. It is usual for these cysts to shrink and become calcified in from 3 to 6 years. Less commonly the hydatid, or cyst of *tania echinococcus*, is found. It is usually single, may reach a large size and present the signs of a slowly growing tumour with eosinophilia.

**INFECTIOUS GRANULOMATA.**—Tuberculomata are more common in the young, but they may occur at any age. They are secondary to tuberculosis elsewhere in the body. They vary in size from that of a grain of wheat to that of a pigeon's egg, and are more often found in the cerebellum and brain-stem than in the cerebral hemispheres. They may be solitary or multiple. When large, caseation occurs in the centre and on section the tumour presents a dry, yellowish crumbling or even diffuent centre, with a greyish-red peripheral growing zone, where are located living tubercle bacilli and actively growing tubercles. In old tuberculomata very dense calcification may take place with the formation of so-called "brain-stones". Before the advent of antibiotics the surgical removal of tuberculomata, although readily carried out, was associated with so great a risk of fatal tuberculous meningitis that it was best avoided. Now this risk can to a great extent be controlled, and surgical removal is often the treatment of choice of chronic tuberculomata.

Syphiloma is to-day a very rare intracranial tumour. It grows most often from the meninges and is thus a surface tumour, though it may burrow deeply into the brain tissue. It is most commonly found above the tentorium. It is occasionally very hard in consistency, and tends in many cases to scar and become obsolete. It is sometimes impossible to distinguish this tumour from a tuberculoma without the aid of a microscope and the serum reaction. Actinomycetoma and tumours from other streptothrix infections are also rare.

**Symptoms.**—The rates of growth of the different kinds of tumour vary widely. Some cases run their course from onset of symptoms to fatal termination within a few weeks, while in others there is evidence of gradual growth over a period of years. In the latter group it may be only in the final stage that the true nature of the illness becomes apparent, and only in retrospect that earlier symptoms assume their real significance. This is especially so in the case of those tumours which for months or years have manifested their presence only by generalised epileptiform fits. In yet other cases, an intracranial tumour may remain latent during life, being revealed unexpectedly at post-mortem examination.

Between these two extremes a great variety of symptom-complexes may be presented by an intracranial tumour. Thus, it may first show itself by producing signs of raised intracranial tension alone—that is, by general signs, or by signs of a gradually progressive local lesion alone—that is, by focal signs. Whichever of these two elements is initially lacking will probably appear later. A third manner in which a tumour may first signal its existence is—as has been mentioned—by the occurrence of generalised epileptiform fits in the absence of any other symptoms and signs. In this instance, also, general and focal signs will probably ultimately make their appearance. Again, a sudden onset of symptoms from hæmorrhage into a glioma, or from œdema of surrounding brain, may usher in the clinical course of a tumour within the skull.

The age of the patient is not without influence in determining the symptomatology and clinical course of a tumour. Thus, in childhood the early appearance of greatly raised intracranial tension—that is, of general symptoms, is the rule. This is mainly due to the fact that at this age the tumour is commonly in the fourth ventricle, and

is thus favourably placed to produce internal hydrocephalus. In elderly persons, on the other hand, the picture of a tumour is apt to be blurred, general signs are late in development, and focal signs are indistinct. Possibly the presence of a background of cerebral arterial degeneration and its associated cerebral changes are responsible for this blurring of clinical outline. It may be supposed that the tumour does not write its mark upon a clean slate when arterial and cerebral degeneration are already present.

**GENERAL MANIFESTATIONS.**—These symptoms are the result of an increase in intracranial pressure and are therefore absent in cases of tumour where the pressure remains normal. The degree to which a cerebral tumour causes an increase in intracranial tension is very variable and depends upon a number of factors. The growing tumour by its bulk occupies a portion of the available intracranial space, which is a constant, and, therefore, after displacing cerebrospinal fluid, the tumour causes directly a rise in pressure. Many tumours, from their position, interfere with the free flow of fluid through the ventricular system and thus produce an obstructive hydrocephalus. This accounts for the rapid increase of pressure seen in tumours of the cerebellum, mid-brain and third and fourth ventricles. Other tumours may interfere with the normal venous return from the hemispheres and so produce œdema of the brain tissue with a proportionate increase in its bulk. These different factors often reinforce one another and thus set up a complex vicious circle. This in large measure explains the undoubted fact that a given tumour of rapid growth gives rise to much greater increase in intracranial pressure than does one of similar size and position which has developed slowly.

The general manifestations of increased intracranial pressure consist of the following: papillœdema, headache, vomiting, mental drowsiness and loss of vivacity, double vision, alterations in the pulse-rate, blood pressure and respiration, giddiness nasal irritation and occasionally generalised convulsion.

**Papillœdema.**—This is by far the most constantly present of all the general manifestations. Papillœdema appears to be a stasis œdema of the nerve-head owing to the increased intracranial pressure forcing the cerebro-spinal fluid into the meningeal sheath which invests the optic nerve, and into the perivascular spaces which accompany the central vessels of the nerve. The nerve sheath becomes distended, and venous stasis occurs. On ophthalmoscopic examination the earliest changes are increased redness of the disk, with disappearance of the physiological pit. As the process increases the whole margin of the disk becomes lost. It enlarges in area, and becomes visibly swollen and presents the appearance of a mole-hill as seen from above. The point of emergence of the vessels, at the centre of the disk, becomes buried by white exudation, which occurs also all over the disk, and taking a form determined by the radiating nerve fibrils, gives the disk the appearance of being striated in a radial fashion, like a chrysanthemum. A similar exudate may rupture the membrana limitans interna in little droplets at the macula, and coagulating as it comes in contact with the vitreous humour, produces the characteristic radially arranged macular figure or "macular fan", exactly similar to that seen in renal disease. The venous congestion of the retina leads to multiple hæmorrhages, which infiltrate along the radially arranged nerve fibres, and for this reason are flame-shaped. With the outpouring of much exudation, the disk becomes white. In the course of time the hæmorrhages become white flame-shaped scars, the whole disk contracts, the swelling disappears, and the disk becomes white, flat and atrophic, and distinguished only from that of primary optic atrophy by the scarred remains of the exudate at its edge, producing a fluffy outline like that of torn cotton-wool, along the vessels and at the centre. In the early stages of papillœdema, even though there be considerable swelling of the disk, vision is little impaired. As the process increases, however, in proportion to the degree of the swelling, to the amount of exudate and to the length of time the papillœdema has lasted, consecutive optic atrophy sets in,

vision becomes impaired and blindness results. Peripheral constriction of the visual fields, large pupil and dimness of vision are the signs that, if the papillœdema be not speedily relieved, blindness will certainly result. Perfect vision may be retained for a time, even with a high degree of papillœdema. So important is papillœdema in the diagnosis of tumour of the brain, that it is necessary to bear constantly in mind all other causes which may give rise to it.

Papillœdema may occur in certain general intracranial conditions other than tumour. (1) In meningitis, as a late sign, rarely before the tenth day, and as many cases of meningitis do not last so long, it is chiefly met with in the less acute forms, such as tuberculous meningitis. (2) States of arterial hypertension from whatever cause but particularly in malignant hypertension in young subjects. (3) Renal disease may give a retinal picture of intense papillœdema, macular figure and hæmorrhages, sometimes quite indistinguishable from that due to tumour. This is often seen in the small white kidney of young subjects, and sometimes in small red kidney, but there is no form of renal disease in which papillœdema has not been observed. (4) Anæmic states of various kinds sometimes give rise to papillœdema. As regards groups (3) and (4) it is essential to emphasise the facts that papillœdema, headache and vomiting may occur as a symptom-complex, both in renal disease and in anæmic states. (5) Septicæmic conditions, especially infective endocarditis, may cause papillœdema. (6) Lastly, papillœdema has been noted in connection with compression of the uppermost part of the cervical cord, and with acute myelitis.

The retinal changes in diabetes are always, and those in renal disease often, distinguishable from papillœdema resulting from increased intracranial pressure. In diabetes the change is essentially a hæmorrhagic retinitis due to degeneration of vessels, sometimes with waxy-looking exudation in circinate patches; and in renal disease it is often a general œdema of papilla and retina, with hæmorrhages and white patches far away from the disk. The papillœdema resulting from increased intracranial pressure is always bilateral, though it may appear in one eye before the other, unless there be local pressure upon one optic nerve, which always delays or prevents papillœdema appearing in that eye. Otherwise, an earlier commencement upon one side is of no localising value.

*Headache.*—The sensation may vary from a mere feeling of fullness of the head to the most agonising pain. It is more often remittent than continuous, and may be absent for long periods together; it often occurs on first waking in the morning or after a period of recumbency or stooping. It is rarely localised to any definite region, except when the growth actually involves the bone, or when pressure has caused local thinning of the bone, when local pain and tenderness on pressure may occur. Usually it is referred indefinitely to the frontal or to the occipital or to the vertical region. When occipital it may be associated with pain and stiffness of the neck, and head retraction. This is due to a general pressure effect, and does not indicate any localisation. Headache may be entirely absent, even in the presence of severe papillœdema. It may precede the development of papillœdema even by a long period, or may be later in its appearance.

*Vomiting.*—Only two-thirds of all cases of intracranial tumour present vomiting as a symptom. It rarely occurs in the absence of the two chief signs of increased intracranial pressure, papillœdema and headache. When the headaches are severe, it may be associated with much nausea, and the attacks are often referred to by the patient as "bilious attacks". Usually a result of increased pressure, it may be directly produced by lesions of the cerebellum, irritation of the vestibular nerve and the visual disorientation resulting from diplopia. As a symptom of intracranial tumour it hardly deserves the cardinal importance which has been assigned to it in most descriptions of this disease.

*Loss of vivacity and mental drowsiness.*—Even when intellectual capacity shows not the slightest impairment, there is from the first onset of symptoms a loss of vivacity,

slight heaviness and an absence of restlessness which is of value in diagnosis. It is almost unheard of for a tumour patient to suffer from insomnia. As the symptoms increase, so do heaviness and drowsiness, though a perfect but slow cerebration may persist until the latest stages of the disease.

**DIFFERENTIAL DIAGNOSIS OF TUMOURS IN THE PITUITARY REGION**  
(WALSHE) (MODIFIED)

	ADENOMA.			PITUITARY STALK TUMOUR.	MENINGIOMA.	GLIOMA OF OPTIC CHIASMA (rare).
	Chromophobe.	Chromophil.	Mixed Cell.			
Age Incidence.	From adolescence onwards.			From 10 years to early adult life.	From 30 years onwards.	Usually in childhood.
Fundus Oculi.	Primary optic atrophy.			Papilloedema in children; usually primary optic atrophy in adults.	Primary optic atrophy.	Primary optic atrophy.
Visual Fields.	Bitemporal hemianopia.  (—Occasionally homonymous hemianopia—)			Bitemporal hemianopia, or central scotomata.	Bitemporal hemianopia.	Bitemporal hemianopia, proceeding to early blindness.
Pressure Symptoms.	Absent, or late.			Early and severe, except in adults.	Absent, or late.	Absent, or late.
Glandular Symptoms.	Hypopituitarism.	Hyperpituit. or Hypopituit.	Mixed.	Hypopituitarism.	Nil.	Nil.
Situation.	Sellar.			Suprasellar.	Suprasellar.	Suprasellar.
Radiological.	General enlargement and deepening of sella.			Shadows above and in sella. Sella shallow, and with uneven floor.	Commonly no change.	Enlargement of sella forwards beneath ant. clinoid processes.

**Double vision.**—Diplopia is a common symptom and is usually at first intermittent and experienced on looking to one or both sides. It is due to weakness of one or both external rectus muscles, and may be associated with an obvious convergent squint.

*Blood pressure, pulse-rate and respiration.*—In many cases of intracranial tumour of slow growth these functions remain unaltered until the terminal stage of the disease, but in cases where there has been an excessive and rapid rise in intracranial pressure, e.g. rapidly growing or degenerating tumours, abscess, or extradural and subdural hæmorrhages, they may be considerably altered. Fall in the pulse-rate is the most constant change and may reach figures around 40 per minute in a person with a normal rhythm of 70 to 80 per min. Less common is a rise in blood pressure occurring *pari passu* with the fall in pulse-rate. It is most often seen in cases of rapid cerebral compression and is characteristic of extradural hæmorrhage. Respiration tends to be slow and shallow, and when cerebral compression is severe it is often irregular and may become grouped and may show the wax and wane of movements which bears the name of Cheyne-Stokes respiration. When the respiratory function is depressed the lips and extremities may be cyanosed—a sign of ill-omen in tumour cases.

*Giddiness.*—This symptom is not infrequently reported by patients with intracranial tumour, particularly if it is situated below the tentorium. It usually consists of a feeling of faintness and general unsteadiness, particularly on stooping, but may amount to true vertigo.

*Nasal irritation.*—This curious symptom is seen sufficiently often to make it worthy of mention. The cause is quite unknown.

*Convulsions.*—As will be stressed later, epileptic fits of all types, indistinguishable from those of idiopathic epilepsy, are among the commonest early symptoms of tumours originating above the tentorium. Much more rarely they may occur as a symptom of general increase in intracranial pressure, particularly in young children and in cases where the increase of pressure has been very abrupt.

*FOCAL SIGNS.*—These have been fully described in the section upon the localisation of lesions of the brain, but certain points require further emphasis. Of all the early symptoms of tumours above the tentorium the most common is the occurrence of epileptic fits. These may take the form of focal fits of any kind or may be generalised, and may precede any other manifestation of intracranial tumour by many years. Any person developing fits for the first time after the age of 25 should be looked upon as a tumour suspect. Although in all cases of intracranial tumour the symptoms and signs of raised intracranial pressure ultimately make their appearance, they may be late in doing so, and in such cases the clinical picture is that of a progressive local destruction of brain-tissue.

In examining cases of intracranial tumour signs may be observed which appear to be conflicting or mutually contradictory. In such, it should be remembered that symptoms and signs which appear early in the clinical course are of greater localising value than those which appear late, and that signs which only make their appearance in the presence of a severe rise in intracranial pressure should be treated with great reserve. Of these so-called "false localising signs" the most notorious is the abducens paresis seen in most cases of raised intracranial pressure. It probably results from shifting of the brain-stem and stretching of the nerve in its course through the subarachnoid space, and should always be disregarded as a localising sign. To a less extent the same is true of the third, fifth and seventh pairs of cranial nerves, whose functions may show slight impairment in the presence of greatly increased pressure without any direct involvement of their fibres in the tumour. On the other hand, cranial nerve palsies occurring early in the course of the disease, before there is any increase in intracranial tension, may be valuable evidence of direct involvement of these nerves, either in the brain-stem or in their courses through the subarachnoid space or foramina of exit.

The presence of papilloedema may considerably modify the localising information to be obtained through the function of vision. Blindness will naturally destroy all information which might have been obtained from an examination of the visual

fields, and will, in addition, give rise to dilated pupils, inactive to light. Less severe degrees of papilloedema may give rise to irregular constrictions of the fields of vision, which may easily be mistaken for an incomplete bitemporal or homonymous hemianopia. When intracranial hypertension is severe, particularly in the case of posterior fossa tumours, a considerable degree of deafness may be present due to congestion of the structures of the internal ear on one or both sides.

Proptosis is by no means uncommon in tumours of rapid growth or in the presence of rapidly developing internal hydrocephalus. It is caused by venous congestion of the orbital contents, and may be more marked on one side than on the other. In women, amenorrhœa may occur in cases with tumours elsewhere than in the neighbourhood of the pituitary body. It is particularly common in mid-cerebellar tumours causing severe hydrocephalus.

Especial mention may be made of tumours of the pituitary body and stalk. Their signs consist of a combination of endocrine disturbance and symptoms due to damage of surrounding nerve structures, and have been described in a previous section, but since the tumours in this neighbourhood have their own typical symptom-complexes, the table, as shown on p. 1387, may be useful in differentiating them.

**Diagnosis.**—The differential diagnosis of intracranial tumour has to be made from (1) other conditions causing papilloedema, (2) other conditions causing headache and (3) other local lesions causing symptoms and signs of local diseases of the brain.

Renal disease, arterial hypertension, cerebral syphilis and rarely encephalitis may be characterised by all three groups of symptoms, and so present peculiar difficulty and should be considered in every case of suspected cerebral tumour. Cerebral abscess is in a special category, since it is a tumour in the wider sense of an expanding intracranial lesion, and so shares all the general and local features of tumour. Abscesses nearly always follow obvious suppuration elsewhere, especially in the middle ear or nasal sinuses or in the thorax, but they may be latent for long periods. Their onset is insidious but usually more rapid than in the case of tumour, and general signs, such as low fever, a toxic appearance and changes in the cerebro-spinal fluid, are present (see p. 1405). Other causes of obstructive internal hydrocephalus may closely simulate tumour; of these chronic arachnoiditis, stenosis of the aqueduct of Sylvius, and syphilitic or other forms of chronic basal meningitis may be mentioned. Saccular aneurysms of the larger cerebral blood vessels may be mistaken for tumours with disastrous results.

The diagnosis of intracranial tumour is not complete when a decision is reached that such a lesion is present within the skull; it is necessary to localise its position and if possible to determine its nature. This topographical and pathological diagnosis calls for a skilful evaluation of the various symptoms and signs against the background of the patient's history. Careful examination of the skull should never be omitted. This may reveal asymmetry of contour, thickening of bone, dilated blood vessels or areas of tenderness or altered percussion note, which may give valuable information. Auscultation may reveal an audible bruit. In experienced hands this purely clinical approach gives results of considerable precision in many cases, but there will always be a number of cases in which a complete diagnosis cannot be reached by purely clinical methods. In the majority of these it will be evident that a tumour is present, but the evidence will be insufficient to determine its position and nature. In a minority a local lesion may be diagnosed with certainty, but there may be doubt whether it is a tumour or some other destructive lesion. In either case recourse has to be made to instrumental aid. Radiographs of the skull may give valuable assistance. These may show changes indicative of long-standing increased intracranial pressure, areas of local absorption of bone, abnormal vascular channels or areas of abnormal calcification. Examination of the cerebro-spinal fluid may give valuable information but it should be practised with caution if there is reason to suspect much increase in intracranial pressure, and should be avoided in the presence

of more than a trace of papilloedema. Manometry may establish the presence or absence of raised intracranial pressure and analysis of the fluid may throw important light upon the nature of the pathological process in the brain. But the most important accessory methods of diagnosis are ventriculography and angiography. Ventriculography is a purely surgical procedure and should only be carried out by an experienced neuro-surgeon under circumstances in which it is possible to proceed forthwith to a major cerebral operation, if this should prove necessary. By ventriculography, not only can the localisation of a tumour, in many cases, be established with accuracy, but its extent can be defined, thus enabling the surgeon to plan his operation to the best advantage. Further, a number of cases can be demonstrated to be inoperable, thus sparing the patient the discomfort of a fruitless exploration. As experience and skill in ventriculography increase it becomes increasingly obvious that in very few cases can this investigation be wisely omitted before an attempt is made to remove a brain tumour. Cerebral angiography, by which radiographs of the cerebral blood vessels are taken while they are filled with an opaque substance, has a more limited but increasing value in the investigation of tumours of the cerebral hemispheres, and is now almost essential in cases of vascular tumours and suspected aneurysms. In some cases the electro-encephalogram may afford evidence of localising value.

**Course and Prognosis.**—An intracranial tumour usually causes increasing symptoms, which progress with exacerbations and remissions until papilloedema ends in blindness and until the pathological intracranial condition becomes incompatible with even a vegetative existence. Death usually comes in one of two ways. More commonly the patient sinks gradually into stupor and from this into deepening coma, in which he dies from hypostatic broncho-pneumonia. In a minority of cases death occurs suddenly by an abrupt cessation of respiration. The patient becomes deeply cyanosed, for the heart continues to beat for many minutes after respiration has failed, and in such a condition the patient may be kept alive for hours by artificial respiration. This mode of death is most common when the increase of intracranial pressure has been great and of rapid development, as occurs in many posterior fossa tumours. It is attributable to the failure of the medullary centres from the forcing of the cerebellum and brain-stem down into the foramen magnum, or from pressure exerted on the mid-brain by herniation of the uncus through the incisura of the tentorium. This accident may readily be precipitated by withdrawal of cerebro-spinal fluid by the lumbar route, and it is for this reason that great caution should be exercised in performing this operation on patients with high intracranial pressure. Occasionally a tumour may become obsolete. A tuberculoma may heal, and ultimately become calcified and a glioma may degenerate or cease to grow, but these events are too rare to be considered within the bounds of practical perspective. The average duration of cases not operated upon rarely exceeds a year after diagnosis has become certain.

**Treatment.**—The natural termination of a case of intracranial tumour is death, and the ideal of treatment must be the successful removal of the growth by surgical operation. Failing this, and it is frequently impossible, all that can be hoped for is the relief of headache and sickness, and delaying of blindness.

In respect of the radical, surgical treatment of tumours, it will be remembered that probably more than half of the cases (if we include glioma and secondary carcinoma) are infiltrative tumours in the brain-substance and thus not amenable to complete removal. In such, it is clearly improper to carry out mutilating operations which can at best only serve to prolong for a time a life which is a burden both to the patient and his relatives. On the other hand, signal successes can be obtained in the case of meningiomas, tumours of the auditory nerve and the pituitary body and some cystic astrocytomas, particularly of the cerebellum. It will therefore be seen how important it is to be able to determine with some precision the nature of the tumour present in any given case. When this is not possible, an exploratory operation

is often justified. But it would be a mistake to suppose that surgical intervention is a matter of routine in every case in which intracranial tumour is diagnosed. Each case must be considered on its merits.

Failing the possibility of a successful removal, the palliative operation of decompression may be needed to relieve the symptoms caused by raised intracranial tension. This consists of the free removal of bone, and the incising of the dura mater over the region of the tumour. For brain-stem tumours decompression is not only useless but also dangerous.

In cases in which complete removal has proved impossible deep X-ray therapy may be employed. The results are very variable. Some types of tumour, notably the medullablastoma, respond very favourably at the time, but usually recur after an interval which grows longer decade by decade as radiotherapeutic technique improves. A survival period of 10 years or more is now not uncommon. The response in the case of astrocytomas and glioblastomas is much less predictable but, on the whole, is disappointing, and when improvement occurs it is short-lived.

*Relief of pressure by dehydration.*—There are circumstances in which it may be desirable and necessary to reduce the brain volume and the intracranial pressure; for example, to relieve pressure headache, to avert impending coma or death, to render the patient capable of co-operating in his examination and thus facilitating a localising diagnosis, and finally to make surgical procedures more easy. This may be achieved by administering hypertonic solutions. In the ordinary case, the rectal injection of from 2 to 3 oz. of magnesium sulphate dissolved in 8 oz. of water may be tried. But for a very rapid effect, intravenous injection of from 50 to 75 ml. of a 50 per cent. solution of dextrose or sucrose or of a 15 per cent. solution of sodium chloride, is effective. It should be remembered that when the effect of such "medical decompression" has worn off the symptoms of raised intracranial pressure are apt to reassert themselves with increased severity. These methods should therefore only be employed with restraint when there is only a short time to be tided over before surgical relief is available. Pain and vomiting may be relieved with the various analgesics of the coal-tar series. Morphine should not be used as it is followed by grave depression of respiration. Codeine phosphate is a valuable analgesic which is relatively free from this disadvantage.

## MENINGITIS

**Definition.**—The inflammatory processes to which we apply the name of meningitis are infective in origin, and usually have their seat in the leptomeninges—the pia-arachnoid. A true inflammatory lesion of the dura mater, that is, pachymeningitis, is much less common, and is usually a localised process due to the direct spread of infection from adjacent bone.

Acute leptomeningitis, on the other hand, is usually generalised, and even when it arises from a local focus of infection it spreads rapidly throughout the subarachnoid space, this spread being facilitated by the cerebro-spinal fluid and also by the negligible bactericidal potency of this fluid. Further, the inflammation not only produces its characteristic changes in the pia-arachnoid, but also greatly changes the composition of the cerebro-spinal fluid. These changes may be said to reflect with considerable accuracy the nature and cause of the meningitis, and thus it is that the examination of this fluid has so great a diagnostic value. Acute leptomeningitis may result from invasion of the leptomeninges by organisms carried in the blood-stream, as occurs in septicæmic conditions, meningococcal meningitis, tuberculous meningitis and many cases of pneumococcal meningitis. Alternatively the organism may reach the meninges by direct spread from a neighbouring focus of infection, of which suppuration in the middle ear and nasal sinuses, infections of the scalp, skull, face and eye, and cerebral



abscesses are the most common. It may also gain direct access by penetrating wounds of the head and as a complication of fracture of the base of the skull.

Pachymeningitis may be cranial or spinal, and is usually secondary to either syphilis, tuberculous disease of bone, or middle-ear suppuration. The condition formerly known as "pachymeningitis hæmorrhagica interna" is now regarded as traumatic and not inflammatory in origin, and is described under the heading of chronic subdural hæmatoma (see p. 1450).

The fine infiltration of the pia-arachnoid by the cells of secondary carcinoma, of glioma, or sarcoma has been spoken of as a meningitis, but although such an infiltration may give rise to symptoms resembling those of a true meningitis, the term is not strictly accurate, though it is well to bear in mind that this form of new-growth does occur and give a picture of meningeal irritation.

The most useful classification of the varieties of meningitis is according to the nature of the micro-organism producing the inflammation, namely; (1) Meningococcal Meningitis; (2) Pneumococcal Meningitis; (3) Pyogenic Meningitis; (4) Tuberculous Meningitis; (5) Benign Lymphocytic Meningitis; (6) Syphilitic Meningitis and (7) Other Forms of Meningitis.

### (1) MENINGOCOCCAL MENINGITIS (see p. 54)

#### (2) PNEUMOCOCCAL MENINGITIS

**Ætiology.**—Pneumococcal infection of the meninges most commonly follows upon a similar infection elsewhere in the body, empyema and pneumococcal otitis being the commonest lesions, while pneumonia, abdominal infection, abscess and joint infection are less common. In one-third of the cases, however, the meningeal infection is primary. The characteristics of the cerebro-spinal fluid are that it is purulent and sometimes so thick that it will not flow through the needle. It is greenish-yellow in colour, contains a large amount of albumin and multitudinous polymorphonuclear cells, among which the characteristic pneumococcus is found. In fulminant, rapidly fatal cases the fluid may be turbid from the presence of pneumococci alone, no reaction in the form of pleocytosis being present. The disease may occur at any age. It is sometimes a terminal event of a pneumococcal infection elsewhere, and passes almost unnoticed, or is discovered only at the autopsy. Meningitis which follows operations upon the nose and disease of the nasal bones is usually of the pneumococcal variety.

**Pathology.**—The surface of the brain and spinal cord is highly characteristic. Usually the whole surface of the vertex and of the base is covered with a thick, tenacious, greenish-yellow pus, which is contained in the meshes of the arachnoid, and between this and the dura. The ventricles often contain pus. A similar exudation is found upon the spinal cord, more especially upon the dorsal aspect, and in the cervical and lumbo-sacral regions. The major affection of the vertex of the brain is the peculiarity of this disease, and only in the rarest cases is the base alone affected. The exudation is characterised by a greater amount of fibrin than in other forms of meningitis.

**Symptoms.**—The symptoms are those which are common to all forms of meningitis. Some of the cases are indistinguishable symptomatically from those of tuberculous meningitis. Others run a very rapid course, and present few features other than headache, vomiting and pyrexia, with a rapidly oncoming and quickly fatal coma. In others again, the meningeal symptoms are concealed in the terminal asthenia of a previously existing pneumococcal infection elsewhere, such as empyema, purulent pericarditis or peritonitis.

**Diagnosis.**—This rests upon the presence of signs of meningitis, or the existence of coma alone, together with a cerebrospinal fluid which is purulent from the presence of polymorphonuclear leucocytes, and the finding of pneumococci in the fluid.

**Prognosis and Treatment.**—In the past, pneumococcal meningitis was uniformly fatal. Occasional recovery was later reported as a result of treatment with pneumococcal antisera.

The introduction of sulphonamide therapy led to a marked improvement in the outlook, and the use of penicillin has completely changed the prognosis in this grave disorder in which the mortality should not now be more than 10 to 20 per cent. if treatment is initiated immediately. According to Honor Smith and her co-workers, penicillin should be administered intrathecally by the lumbar route in doses of 8000 to 16,000 units 12-hourly for the first 2 days and thereafter 24-hourly for a further 3 days. This should be combined with intramuscular administration of 120,000 units of penicillin daily and with sulphadiazine by mouth, an initial dose of 4 g. being followed by 2 g. 4-hourly for several days after the fever has settled. Adverse reactions have been reported in cases where more than 20,000 units of penicillin were administered intrathecally in one dose. Blockage of the cerebral or spinal subarachnoid space by the accumulation of organising purulent lymph may necessitate the giving of penicillin by the cisternal or ventricular routes.

More recently, favourable results have followed the use of penicillin alone, in massive doses intramuscularly, 2,000,000 units every 2 hours, none being given intrathecally.

### (3) PYOGENIC MENINGITIS

Apart from meningococcal and pneumococcal infections, suppurative meningitis may result from the invasion of the meninges by staphylococci, streptococci, gonococci, *H. influenzae*, coliform bacilli, *B. anthracis* and streptothrix.

Staphylococcal and streptococcal infections are by far the most common. They may result in young children from septic conditions of the umbilicus and from infections of the skin. Usually they are due to extension of an infection from structures adjacent to the meninges, and follow disease of cranial and spinal bones, especially caries in the middle ear, erysipelas and other infections of the scalp, wounds of the meninges, especially bullet wounds, rupture of intracranial abscess and they may occur in the course of a general septicæmia.

**Pathology.**—The pathology of these conditions does not materially differ from that of pneumococcal meningitis. In all cases the exudation is purulent, and in the meningitis due to *B. anthracis* it is of a red colour, due to concomitant blood effusion. The cerebro-spinal fluid contains large numbers of polymorphonuclear leucocytes, together with the micro-organism responsible for each variety. Suppurative meningitis resulting from bone disease and from wounds of the meninges may be localised by the formation of meningeal adhesions, and an intrameningeal abscess may result. Such an abscess situated upon the upper surface of the temporal bone is not an uncommon result of caries of the middle ear.

The clinical aspect is that common to all forms of acute meningitis, high pyrexia, rigors and delirium being conspicuous. The course is rapid, and, before the introduction of modern chemotherapy, led to an almost invariably fatal termination. In the localised form where drainage can be ensured and extension of the infection prevented, recovery should take place.

**Diagnosis.**—This depends upon the presence of the clinical signs of meningitis and of a cerebro-spinal fluid containing polymorphonuclear leucocytes in large quantities, and upon the recognition in this fluid of the several micro-organisms responsible, by microscopic examination and culture. The recognition of *H. influenzae* requires that cultures should be made upon a blood medium, for otherwise the organism may be easily overlooked and the fluid reported as sterile. Further, the presence of some well-known cause for suppurative meningitis, such as ear disease, staphylococcal infection, etc., suggests the diagnosis.

Acute otitis media may give rise to symptoms closely resembling those of meningitis, such as headache, pyrexia, vomiting, head retraction and delirium. In such cases examination of the ear, which should be made a routine in all cases where meningitis is suspected, will reveal tympanic distension, the relief of which is followed by a speedy disappearance of the symptoms. In this connection it must be borne in mind that meningitis and intracranial abscess seldom follow directly upon acute otitis, but are usually the sequelæ of chronic otitis, which has resulted in caries of the temporal bone. When evidences of caries of the middle ear are present in a case presenting cerebral symptoms, distinction has to be made between meningitis and abscess of the brain. Here the presence of localising symptoms, either temporal or cerebellar, and the presence of papillædema and any tendency to a temporary abatement of the symptoms point to the existence of an abscess, and further lumbar puncture will in all but the rarest cases settle the point. In cases of abscess in which cells and organisms are found in the cerebrospinal fluid, these exist in small numbers only, as compared with the copious cells and organisms present in the fluid of suppurative meningitis (see p. 1409).

**Treatment.**—In cases of meningitis secondary to mastoid disease, the source of infection should be at once cleared out by surgical procedure. As in the case of pneumococcal meningitis the prognosis and treatment of all forms of pyogenic meningitis have been profoundly altered by the introduction of sulphanilamide and its derivatives and of antibiotics, and the treatment in general is the same as that which has already been described in the case of pneumococcal meningitis. Meningitis due to *H. influenza*, *Ps. pyocyanea* and to some strains of coliform bacilli has been shown to respond favourably to treatment with streptomycin and other antibiotics (see pp. 10 and 13).

#### (4) TUBERCULOUS MENINGITIS

This disease results from the general invasion of the cerebro-spinal leptomeninges by the tubercle bacillus, and this organism invariably arrives in the meninges by the blood-stream from some previously existing focus of tuberculous infection elsewhere, and most commonly from caseous tracheo-bronchial and mesenteric glands and tuberculous bone disease. Occurring at all ages, it is the form by far the most frequently met with in the second and third years of life.

**Ætiology.**—Tuberculous meningitis is rare during the first year of life, and especially during the first 6 months. Its greatest incidence is during the second and third years. It is common throughout childhood and early adult life, after which it becomes increasingly rare, though cases may be met with even in the elderly. The sexes are equally affected. The primary focus from which the organisms are carried to the meninges is most often a tuberculous bronchial or mesenteric lymph gland. In consequence the most potent causes of the disease are exposure of the young child to cases of open tuberculosis and the drinking of infected milk.

Sometimes the source of infection is tuberculous disease of the lungs, of the urogenital tract, of the abdomen, of the ear, of the joints or of bone. Operations upon the sites of tuberculous disease may directly cause the dissemination of the tubercle bacilli, and especially surgical procedures upon tuberculous intracranial tumours, upon spinal caries and upon tuberculous disease of bones and joints. The acute specific fevers, and especially measles, are sometimes the exciting causes of the disease. Injury to the head sometimes determines the attack.

**Pathology.**—The essential change in tuberculous meningitis is the presence of an inflammatory exudate studded with discrete miliary tubercles in the pia-arachnoid membranes, particularly in the interpeduncular space and over the base of the brain.

On removing the skull-cap the dura is found to be so tense that it can only with difficulty be indented by the pressure of a finger. When the dura is incised the cerebral convolutions are seen to be flattened and pressed firmly against the inner

surface of the dura. No cerebrospinal fluid escapes from over the surface of the hemispheres. In extracting the brain from the skull it is commonly ruptured and fluid escapes with a gush from the dilated ventricular system, allowing the hemispheres to collapse. The base of the brain, especially the interpeduncular space, is seen to be covered with a gelatinous greenish-yellow exudate which surrounds the optic chiasma, the emerging cranial nerves and infundibulum and the vessels of the circle of Willis, and spreads out to the tips of the temporal lobes and to the stems of the Sylvian fissures. Only rarely does this exudate spread on to the convex surfaces of the brain. In cases of relatively long duration the exudate acquires a greyish colour, and is tough in consistency and firmly adherent to the brain. Close inspection of this inflammatory exudate shows it to be studded with innumerable, small, grey tubercles. These are particularly numerous in relation to the blood vessels, and they can be seen in large numbers along the course of the middle and anterior cerebral arteries. The whole ventricular system is uniformly and greatly dilated, and flakes of green gelatinous lymph may be found mixed with the cerebrospinal fluid contained in the distended ventricles. Frequently small tubercles can be seen scattered over the walls of the ventricles and over the surface of the choroid plexuses. Not infrequently discrete tuberculous foci may be found scattered through the substance of the hemispheres, cerebellum and brain-stem. These vary in size from the pin-point tubercles characteristic of the basal meninges to caseating masses the size of a marble. Rarely thrombosis may be seen in one or other of the venous sinuses, and occasionally areas of softening are found in the brain substances.

The meninges of the spinal cord are usually also involved, and tubercles may be seen upon the surface of the cord or the inner aspect of the dura mater.

Examination of the rest of the body almost invariably shows the changes of generalised miliary tuberculosis, the exception being those rare cases in which tuberculous meningitis has resulted from a tuberculoma in the substance of the brain.

**Symptoms.**—The onset is usually gradual, with signs of vague and slight illness. In children, general apathy and neglect of amusements and play, headache, loss of appetite, obstinate constipation, dullness, fretfulness, restlessness at night with grinding of the teeth during sleep, headache, vomiting and pyrexia are common symptoms. In older subjects, lassitude, depression, mental alteration, perversity and hysterical manifestations are frequent. Constipation is usually present, and the breath has a peculiar fetor. The facial expression is one of illness and frowning discomfort, and there is disinclination to talk. Young children may be speechless for days together. As a rule, in this stage of the disease young children complain of nothing, and delirium is rare; but as age advances, delirium increases in frequency, and headache, usually frontal, is increasingly complained of. These slight and vague symptoms may last from a few days to several weeks, and constitute what has been called the prodromal stage of the malady. An early disappearance of the knee and ankle jerks, and the occurrence of retention of urine are often early signs and should be looked for in suspected cases. In those cases which are said to begin acutely, careful enquiry will generally reveal that some symptoms such as the above have preceded the acute onset. The further development of the disease is marked by the appearance of a lethargy, which soon deepens into a stupor, from which it is difficult or impossible to arouse the patient. Vomiting is of frequent occurrence, and headache may be severe. The child lies upon its side in a "cramped" position, resenting any disturbance. The expression becomes vacant, with wide-open eyes and dilated pupils, as if the gaze were fixed upon some distant object. There is often some retraction of the angles of the mouth, and there is frequently a bright malar flush. In the later stages the limbs are generally extended and rigid. Stiffness of the neck is the rule, and head retraction may occur, but this is never so marked as in pyogenic meningitis. The abdomen is always markedly retracted and a *tâche cérébrale* is often conspicuous. A single sharp cry, apparently causeless, called the hydrocephalic cry, which is common in all

forms of meningitis and also in other infantile intracranial affections, is sometimes heard.

Ocular phenomena make their appearance towards the end of the first week of the developed disease. All varieties of varying and persistent strabismus and ptosis are met with, paralysis of the external rectus being the most common. Rolling movements and independent movements of the eyeballs may occur. None of these signs is constantly present. The pupils may be contracted at first, and may show varying inequality, but in the later stages they are dilated. Papilloedema is often present towards the end of the second week, if the patient survives so long. It is of moderate intensity, the height of the swelling rarely exceeding two dioptries. Choroidal tubercles sometimes occur.

Convulsions are common in every stage of the disease in children, but rare in adult cases. They may be the first symptom of the onset, but are more often met with in the later stages of the disease. They may be local or general. Repeated rhythmic movements are frequent, and are specially noticeable in connection with the mouth, where sucking and champing movements and grinding of the teeth are common. Rhythmic movements of the limbs may also occur. Coarse tremor upon movement of the limbs is the rule, and spasmodic twitching of the muscles is frequent. In rare cases, movements exactly like those of chorea occur. Kernig's sign is usually present.

The temperature is usually raised one or two degrees, but it presents no characteristic features. Irregularity of the pulse is the rule, and is of considerable diagnostic importance. Rapid in the early stages, it tends to become unduly slow in the stage of coma, and again rapid as death nears. Cheyne-Stokes breathing and grouped breathing are common. Constipation is usually a marked and persistent feature.

**Diagnosis.**—The early symptoms of the disease may give rise to difficulty in diagnosis, but this is relatively simple when the disease is advanced. The diseases liable to be confused with tuberculous meningitis at its commencement are other forms of meningitis, virus diseases of the nervous system, especially acute poliomyelitis, cerebral abscess, the exanthemata—especially enteric fever—and pneumonia. It must be borne in mind that in children convulsion, strabismus, head retraction and stiffness of the neck, with pyrexia, may be symptomatic of many maladies apart from meningitis, especially of apical pneumonia. When signs of meningeal irritation are unmistakable the condition has to be distinguished from the various forms of pyogenic meningitis. In the latter the degree of meningism is usually more intense and the cerebrospinal fluid reveals a turbid or purulent fluid with a predominantly polymorph pleocytosis and the causative organism can usually be cultured.

Poliomyelitis and other virus infections of the nervous system can at their commencement closely simulate tuberculous meningitis and it is in such cases that the retention of the cerebrospinal fluid chlorides and glucose at their normal level can be such a valuable aid to diagnosis.

The meningeal reaction apt to arise from time to time in cases of cerebral abscess may closely resemble tuberculous meningitis and may be associated with a mixed pleocytosis and a sterile fluid.

In any case suspected of being one of tuberculous meningitis a diagnostic lumbar puncture should be carried out without delay as the success of modern treatment is much influenced by the time of its commencement. The characteristic features of the fluid are, that it is usually under considerable pressure, it is clear or only slightly turbid, has no visible deposit before centrifugalisation, but it often forms a fine flocculent clot. It contains an excess of albumin. The normal sugar is reduced or absent, and a value over 50 mg. per 100 ml. practically excludes the diagnosis. It is sometimes between 40 and 50 mg. per 100 ml., but in the majority values under 30 mg. are obtained. In other forms of non-purulent meningitis such as poliomyelitis and benign lymphocytic meningitis the glucose content of the cerebrospinal fluid is

almost invariably normal. Early reduction of the chloride content below 700 or even 650 mg. per cent. is of value in distinguishing tuberculous meningitis, especially from virus diseases of the nervous system. There is a pleocytosis with a high proportion of lymphocytes, 70 to 80 per cent. being of this nature, and the rest being polymorphonuclears. Careful examination will reveal the presence of the tubercle bacillus in more than half the cases, and their presence can be readily demonstrated by injecting the fluid into the subcutaneous tissue of guinea-pigs, when the characteristic lesion of tubercle results and also by culture. It must be remembered that in some cases the polymorphonuclear leucocytes may be in excess, but these cases are at once distinguished from other forms of meningitis by the presence of numerous lymphocytes, by the absence of the meningococcus and of the other pyogenic organisms and by the presence of the tubercle bacillus.

**Course and Treatment.**—Before the advent of streptomycin, tuberculous meningitis was invariably fatal and usually ended in the patient's death in from 3 to 8 weeks of the onset of symptoms.

To-day, provided that early diagnosis is achieved, the vigorous use of streptomycin together with sodium aminosalicylate (P.A.S.) and isoniazid (I.N.H.) should result in recovery in at least 50 per cent. of cases.

Streptomycin is administered both intrathecally and intramuscularly and either sodium aminosalicylate or isoniazid by mouth continuously for the initial period of 8 to 12 weeks. If general improvement as measured by appetite, weight, subsidence of fever and loss of drowsiness is satisfactory and is confirmed by a gradual return of the cerebrospinal fluid towards normal, a rest of 1 month in intrathecal treatment alone should be given. At the end of this period a further course should be given and thereafter a gradual withdrawal of treatment may be achieved provided always that improvement is maintained. Good results are now being obtained using isoniazid (e.g. 100 mg. t.d.s.) combined with streptomycin administered only by the intramuscular route (e.g. 1 g. daily), thereby avoiding the need for daily intrathecal injections. The addition of cortisone to this régime is still *sub judice*.

Careful observation at increasing intervals must be maintained over a period of 5 years.

Prominent among the complications which may arise are chronic hydrocephalus from the development of a plastic meningeal fibrosis around the base of the brain and leading in its turn to double hemiplegia, convulsions, blindness and imbecility and deafness from the degeneration in the cochlear nerves resulting from the use of intrathecal streptomycin.

#### (5) BENIGN LYMPHOCYTIC MENINGITIS (CHORIO-MENINGITIS)

**Synonyms.**—Epidemic Serous Meningitis; Benign Aseptic Meningitis.

**Ætiology.**—The causative agent is unknown, but there is evidence that one or more neurotropic viruses are responsible. No organisms have been found in the cerebro-spinal fluid. The disease has been transmitted to animals by injection of cerebro-spinal fluid obtained in the acute stage of the affection. The malady so named appears to be of wide distribution.

**Pathology.**—Since recovery is the rule, nothing much is known of this, but lymphocytic infiltration of the lepto-meninges has been found in one fatal case.

**Symptoms.**—Children are mostly affected, but no age appears exempt. The onset is abrupt, with headache, sickness and fever. The typical signs of meningeal irritation are present, neck and spine rigidity, Kernig's sign, irritability and restlessness and sometimes delirium. Somnolence is unusual. In young children convulsions may occur. The fever mounts to 102 or 103°F. and fluctuates. It may disappear in 2 or 3 days, or persist for 3 weeks. Lumbar puncture yields a cerebrospinal fluid under pressure, usually clear but sometimes opalescent. The cell count ranges from

50 to 1500 per c.mm. After the first 2 or 3 days these cells are almost wholly lymphocytes. The sugar and chloride contents remain at normal height, thus differing from the findings in other forms of acute lepto-meningitis, and resembling the findings in acute poliomyelitis.

**Diagnosis.**—This depends upon the cerebrospinal fluid findings and upon the benign course of the illness. For a few days differentiation from poliomyelitis may be impossible.

**Prognosis.**—Recovery is the rule.

**Treatment.**—Repeated lumbar puncture reduces the intracranial tension. Beyond this, only general nursing care is needed.

#### (6) SYPHILITIC MENINGITIS

Meningitis due to infection by *Treponema pallidum* is one of the characteristic lesions met with in practically all cases of syphilitic disease of the central nervous system, and plays its part in the production of the symptom complexes of these maladies, from acute cerebral syphilis and acute myelitis to general paralysis and locomotor ataxy. It may occur at any period after infection, but one-half of the cases occur during the first 4 years. In a few cases the symptoms have been noticed coincidentally with the syphilitic roseola.

**Pathology.**—The morbid process consists essentially in an infiltration of the meninges with lymphocytes and plasma cells, spreading from the perivascular spaces where the spirochaetes multiply freely, and it may lead to scarring and opacity of the membranes, with consequent strangling of the nerves and vessels and occlusion of the arachnoid space, or to massive gummatous formation in the meninges. It is essentially a chronic form of meningitis though it may result in the production of acute symptoms. A marked feature is that the meningeal changes may be found actively progressive in one spot, and equally regressive in another. The disease may be local or diffuse, and it may attack the dura (pachymeningitis) and involve the overlying bone, or it may spread from the pia-arachnoid into the sublying nervous tissue (meningo-encephalitis).

The cerebrospinal fluid is characteristic. It is usually under increased pressure, is clear and colourless, and contains lymphocytes and no other cell forms. The number of the lymphocytes present is in direct proportion to the activity of the meningeal syphilis. The spirochaete has rarely been found in the fluid, yet inoculation of apes with the fluid has proved successful.

**Symptoms.**—Apart from those conditions of nervous syphilis in which meningitis is associated with arterial disease, the formation of massive gummata and neuronie degeneration, syphilitic meningitis may be described as giving rise clinically to the following conditions:

##### 1. Headache.

2. *Hydrocephalus.*—In those acute cases of cerebral syphilis characterised by rapidly oncoming headache, vomiting and papilloedema, mental reduction and somnolence without localising symptoms, and which respond readily to treatment, it seems certain that ventricular distension, consequent upon adhesive meningitis and ependymitis, is responsible. A more slowly oncoming ventricular occlusion may give rise to symptoms which cannot be distinguished from those caused by a non-localisable intracranial tumour. Syphilitic meningeal occlusion may give rise to typical hydrocephalus, and a considerable proportion of the cases of infantile hydrocephalus are of this nature and are due to congenital syphilis. A few cases are recorded in which chronic hydrocephalus of this nature has occurred in adult life.

3. *Infantile syphilitic meningitis.*—This is a chronic malady which commences insidiously during the first few months of life, with signs of general nervous deterioration. The appearance of the brain is very characteristic. The membrane over the

vertex is opaque and thickened and adherent to the cortex. The gyri are shrunken, the sulci wide and the surface of the brain has in parts the appearance of wash-leather. The child does not get on, and takes an ever-decreasing notice of its surroundings. Power of movement lessens, the limbs become rigid and the clinical aspect comes to resemble exactly that of a severe cerebral diplegia. Convulsions are of frequent occurrence. The diagnosis is not difficult, for the signs of meningitis are obvious and those of congenital syphilis may be present. There is an excess of lymphocytes in the cerebrospinal fluid, both in which and in the blood there is a positive Wassermann reaction. The prognosis in any case where the symptoms have become marked is most unfavourable.

4. *Adult syphilitic meningitis*, with a symptom-complex closely resembling that of tuberculous meningitis, has been reported on many occasions (see pp. 1395, 1461).

5. *Paralysis of cranial nerves*.—This common and often isolated symptom of nervous syphilis may result from sclerosing basal meningitis or from the presence of a gumma in the course of the nerve. Several of the nerves may be involved together in one patch of meningitis. Any of the cranial nerves may be affected from the olfactory to the hypoglossal, but the third or oculo-motor nerve is by far the most frequently attacked.

**Treatment.**—The treatment of the above conditions is that appropriate for nervous syphilis in general (pp. 223, 1461). Penicillin is now the treatment of choice, but a diminishing number of physicians still prefer to follow it up with courses of bismuth and organic arsenic by injection. Iodide of potassium is also of value and should be administered over a long period.

#### MENINGISM

The term "meningism" is used for a group of cases which present symptoms of meningitis and in which no pathological change can be found either in the cerebrospinal fluid, or, if death occur, in the meninges or cerebral tissue. It is met with in children in association with acute febrile diseases, and is presumably due to the toxin present. Recovery is usually rapid and complete.

### HYDROCEPHALUS

**Definition.**—The term "hydrocephalus" denotes an abnormal accumulation of cerebrospinal fluid within the skull. This may be confined to the ventricular cavities, giving rise to the variety known as internal hydrocephalus; or it may involve both the ventricular and the general subarachnoid spaces, a condition referred to as communicating hydrocephalus. This distension is associated in many cases with an expansion of the cranial bones and enlargement of the skull.

**General Considerations.**—Theoretically this abnormal increase of fluid may result from one or more of three causes, viz.: (1) excessive production of fluid; (2) interference in the normal flow of fluid and (3) defective absorption. The fluid is normally produced by the choroid plexuses of the ventricles, and flows through the ventricular system into the general subarachnoid space by way of the foramina of Luschka and Magendie in the roof of the fourth ventricle. It then fills the basal cisterns and, passing forward between the tentorium cerebelli and the brain-stem, flows up over the cerebral hemispheres to be absorbed by the arachnoid villi, which project into the walls of the venous sinuses and discharge their contents into the venous blood-stream. Some of the fluid passes downwards into the spinal subarachnoid space but it is estimated that only one-tenth of the fluid is absorbed from arachnoid villi in the spinal spaces.

Of the causes of hydrocephalus the most important and the one of which we have the most precise knowledge is obstruction of the normal cerebrospinal flow, and it



is evident that this obstruction may occur at several different points and be produced by a great variety of pathological causes. Some of these are known and some remain obscure. It will thus be seen that hydrocephalus is the end result of a variety of causes and until our knowledge is more complete, it is most satisfactorily classified on a clinical basis and described as a number of clinical pictures which recur with some frequency.

The following principal varieties of hydrocephalus are met with: (1) congenital hydrocephalus; (2) chronic acquired hydrocephalus and (3) acute acquired hydrocephalus.

In the majority of cases in which general atrophy of the cerebral tissues occurs, fluid accumulates both in the ventricles and in the subarachnoid space; but such compensating enlargement is not to be regarded as, in any sense, of the same nature as true hydrocephalus. Such accumulation of fluid is found in cases of cerebral diplegia, general paralysis of the insane, cerebral arteriosclerosis, and chronic alcoholism, and it also occurs in the brains of old people. It is merely the result of wasting and shrinkage of the brain tissue, and the accumulation of fluid takes place in order to fill the space within the rigid skull which is thus vacated.

### (1) CONGENITAL HYDROCEPHALUS

**Ætiology.**—Hereditary influences are of importance in the causation of congenital hydrocephalus. This disease frequently affects several children of the same parents, and it may even appear as a striking familial disease, affecting members of several generations of the same stock. Spina bifida, meningocele and hydromyelia are of frequent occurrence in association with this condition, and irregular or arrested development of the brain-stem and cerebellum, particularly the Arnold-Chiari malformation, are common. Among other bodily abnormalities not infrequently associated with the affection may be mentioned hare-lip, cleft-palate, talipes, rectal and testicular ectopia and imperforate anus. In a few cases definite syphilitic lesions of the ependyma of the brain-stem in the region of the aqueduct or fourth ventricle have been found. In many cases the ætiology remains completely unknown.

**Pathology.**—The quantity of fluid which is found in the ventricles after death varies greatly, usually being 15 to 20 oz. In long-standing cases with great cranial enlargement, very large quantities have been met with. The character of the fluid does not usually greatly differ from that of normal cerebrospinal fluid. Its specific gravity varies from 1.008 to 1.010. It is clear and colourless, or occasionally slightly yellow. It contains a very small quantity of albumin and a normal quantity of chlorides. The dilatation of the lateral ventricles is more extensive than that of the third and fourth ventricles, and is usually symmetrical upon the two sides. It affects the body more than the cornua of the ventricles, so that the central cortex is most thinned. The foramina of Monro are greatly enlarged and the anterior pillars wasted. The convolutions are flattened and the sulci indistinct. The thickness of the cerebral substance is much reduced. In advanced cases the cerebral hemispheres have the appearance of thin-walled sacs, which collapse entirely when the contained fluid is allowed to escape. In a few cases the aqueduct has been found closed as if by an antecedent ependymitis.

**Symptoms.**—In congenital hydrocephalus the enlargement of the head is the first noticeable feature. It may take place during intra-uterine life, and it may be so great as to make delivery impossible without destruction of the head. More frequently the cranial enlargement, not noted at the time of birth, becomes evident during the first weeks of life. The increase usually affects all the diameters of the cranial cavity, and is most marked at the vertex and least at the base. Trousseau compared the opening out of the cranial bones, which occurs as the head enlarges, to the falling back of the petals of an opening flower. The forehead is large, rounded,

and projects forward, the temporal fossæ are obliterated and the parietal eminences carried backwards. The vertex is often somewhat flattened, as also may be the occipital region. The direction of the external auditory meatus alters with the increasing size of the head; normally directed obliquely forwards it comes to look directly inwards or even obliquely backwards in severe cases. The head is frequently asymmetrical. The sutures may be widely open, and then there is marked bulging along these lines and at the fontanelles. The skull may attain enormous dimensions, and it may be beyond the child's power to lift or even move the head. Many examples are recorded in which the circumference has been from 60 to 80 cm. The face is characteristically triangular, contrasting markedly with the forehead. Wasting of the facial subcutaneous tissues and retarded development of the maxilla and mandible often render the contrast still more striking. Bulging of the orbital plates of the frontal bones presses down the eyeballs, so that the pupils become more or less covered by the lower lids, and a band of the sclerotic may be visible between the iris and the upper lid. The hydrocephalic child often uses his hands to depress the cheeks, and so draws down the lower lids out of the position which they impair the line of vision. The hair of the head becomes scanty, the subcutaneous veins of the scalp are often greatly developed and distended, and sometimes a vortex of distended veins radiates from the region of the anterior fontanelle. Percussion of the skull gives a characteristic, hollow, "cracked-pot" note.

The general nutrition is poor, and bodily development retarded in proportion to the severity of the effect of the hydrocephalus upon the nervous system. The nervous symptoms which appear during the course of congenital hydrocephalus are both variable and inconstant, depending upon the severity of the condition and the rate at which it progresses. They may be summed up in the following list in order of frequency: convulsions, mental failure, spastic paralysis of the limbs, optic atrophy, deafness, nystagmus, headache, papillædema and vomiting. There is no constancy regarding these symptoms. Convulsions may be absent, and mental acuity may be unimpaired. Spastic weakness occurs in less than half the cases, optic atrophy still more rarely and papillædema is distinctly unusual.

*Convulsion.*—While it is to be borne in mind that the whole course of hydrocephalus in children may run without the occurrence of convulsion, yet in the majority of cases this symptom is conspicuous. In some of the post-natal cases the symptoms of cerebral disorder are ushered in by convulsion, and it is probable that in many cases such convulsions are the immediate expressions of the morbid process, of which the primary hydrocephalus is the final result. The convulsions which recur at intervals throughout the course of the majority of cases of hydrocephalus result from a condition of functional instability of the cerebral cortex, which long-continued increased intracranial pressure brings about. The convulsions are usually general, with loss of consciousness.

*Mental impairment.*—All degrees of mental reduction occur, from the least noticeable to complete idiocy. The more severe forms are met with in cases when cerebral agenesis and porencephaly are associated. The psychical reduction is less prominent the greater the age at which the symptoms commence, and, as a rule, the intelligence is far greater than the severity of symptoms (cranial enlargement, paresis, etc.) might lead one to expect. Cerebration is usually slow and the disposition placid, and periods of somnolence are of common occurrence.

*Paralysis.*—The effect of long-continued ventricular distension in many cases is to cause degeneration of the pyramidal system, and, according to its degree, the latter entails bilateral spastic paralysis with contracture. The first signs of the onset of this event are exaggeration of the deep reflexes, and the change in type of the planar reflexes from the flexor to the extensor response. The lower extremities are affected earlier and to a greater extent than are the upper, and at one period of the disease a case may present the picture of cerebral diplegic rigidity comparable with that of

**Little's disease.** The upper extremities are affected later. The paresis of the limbs is almost always symmetrical and equal upon the two sides. Sensibility is generally normal.

Vision is interfered with in a considerable proportion of the cases. The enlargement of the infundibular portion of the third ventricle, by pressure upon the inner borders of the converging optic tracts, may cause bitemporal hemianopia with atrophy of the nasal portions of both optic discs, this condition subsequently progressing to complete blindness and complete optic atrophy.

In rare cases, optic atrophy is the result of papilloedema. Strabismus is commonly present and it is most frequently convergent. Nystagmus is met with in the subjects of hydrocephalus who are blind from optic atrophy, and it is of frequent occurrence in long-standing cases in which spastic paresis is well marked.

Headache is rarely complained of, and never dominates the clinical picture in children, and is never so severe and persistent as that arising from the presence of an intracranial growth. Cerebral vomiting is of comparatively rare occurrence.

When one considers the profound anatomical alterations which take place in the advanced stages of the disease, the occurrence in some cases of unusual symptoms indicative of interference with the functions of the cerebellum, brain-stem and cranial nerves is easily explicable. Unilateral or bilateral ataxy, vertigo, deafness, anosmia and paralysis of cranial nerves, are the most important of such unusual symptoms.

The signs of failure of the nervous system as a whole usher in the fatal result in severe cases. For some days or perhaps weeks before death, hebetude may become profound; spastic paresis gives place to flaccid paralysis with muscular wasting, the deep reflexes disappear, and the sphincter mechanism loses its control and subsequently its tone.

**Diagnosis.**—On account of the characteristic appearances of the skull this seldom presents any difficulty, though in childhood only a careful history will serve to differentiate the congenital from the chronic acquired type of hydrocephalus. The enlarged skull of rickets is recognised by its different conformation, by the absence of nervous signs, with the possible exception of convulsions, by the absence of the characteristic change in the percussion note and by the presence of other rachitic signs. The rare condition of macrocephaly is not associated with any distortion of the relative proportions of the skull. It should be remembered that an abnormally large head is hereditary in some families.

**Prognosis.**—In all severe and progressive cases the prognosis is hopeless. In some of the milder cases the process becomes arrested, and the patient may attain to adult life with the possession of all his faculties. In cases in which the disease becomes stationary, the prognosis as regards mental capacity and the continuance of recurring convulsions has to be considered. If the mental capacity at the time of the arrest is fair, it is not likely to deteriorate further, unless epilepsy is established. When mental reduction is marked at the time of arrest, any appreciable degree of improvement cannot reasonably be expected. A certain number of cases of mild congenital hydrocephalus cease to progress and the symptoms retrogress and disappear permanently.

**Treatment.**—In those cases in which there is evidence of congenital syphilis the employment of antisiphilic treatment is indicated.

The results of surgical interference for the relief of pressure or to attempt the re-establishment of a way of escape for the cerebrospinal fluid have been, up to the present, so unsatisfactory, that many writers and authorities consider such measures unjustifiable. It should be remembered, however, that in severe and progressive cases one is dealing with a necessarily fatal malady, and a few encouraging results have been published, which appear to justify further investigation. Ventricular paracentesis is useless, as any relief which results is only temporary and it is not without danger if the intraventricular pressure is raised.

## (2) CHRONIC ACQUIRED HYDROCEPHALUS

**Ætiology.**—Hydrocephalus, usually of the internal type secondary to obstruction in the cerebrospinal fluid pathway, may result from a variety of causes. Foremost among these is meningitis, especially the posterior basic meningitis of infancy and early childhood, but it may result from any type of meningitis, including tuberculous meningitis, in which recovery from the initial disease takes place. It is caused by occlusion of the foramina of Luschka and Magendie, and results in a uniform distension of the entire ventricular system. Another group of cases depends upon a primary, non-neoplastic stenosis of the aqueduct of Sylvius, as described by Stookey and others. Some of these cases show a proliferation of the sub-ependymal glia with constriction of the lumen of the aqueduct. In others the ependyma may undergo proliferation with the development of tufts which project into the lumen of the canal and form valve-like obstructions to the flow of fluid. Again, in others the lumen itself may be split up into a number of minute channels hardly visible to the naked eye. The ultimate cause of this aqueductal atresia is unknown. In a third group acquired hydrocephalus results from the presence of neoplasms of slow growth which obstruct the cerebrospinal fluid channels; of these the slowly growing cerebellar astrocytomas of early childhood are the most important. Other causes are cysts and slowly growing tumours of the third and fourth ventricles, supra-sellar (Rathke pouch) cysts, and pineal or other tumours of the mid-brain.

**Symptoms.**—The symptoms of chronic acquired hydrocephalus depend largely upon the age at which the process starts. If the malady begins in early infancy the picture is in all respects similar to that of congenital hydrocephalus. If it occurs in early childhood before the sutures of the skull have become fused and the bones of the vault indistensible, the picture is that of moderate hydrocephalus combined with the symptoms and signs of raised intracranial pressure.

Pressure symptoms often begin abruptly after the signs of hydrocephalus have been present for a considerable time. Prominent among these are headache, usually paroxysmal in character, vomiting, strabismus and double vision. In such cases papilloedema is common and if left unrelieved leads to failure of vision from consecutive optic atrophy, which may come on with very great rapidity. In long-standing cases mental failure may occur, and weakness and inco-ordination of movement from a combination of disturbances of the pyramidal and cerebellar systems. There may be considerable arrest of physical development, and in cases extending into later childhood puberty is commonly delayed or complete infantilism may persist.

**Treatment.**—In some cases of acquired hydrocephalus the cause can be removed by surgical operation and cure may result. To this category belong those due to tumour or cyst formation. Various methods of re-establishing the cerebrospinal fluid flow have been devised in cases of stenosis of the aqueduct or occlusion of the meningeal foramina. The most successful of these is Torkildsen's operation, in which the aqueduct is by-passed by means of a plastic or rubber catheter introduced into the posterior horn of one of the lateral ventricles and passing under the scalp to enter the spinal subarachnoid space through the atlanto-occipital membrane. As in congenital hydrocephalus, the different forms of ventriculostomy have proved disappointing and external decompressions usually only afford temporary relief, quickly followed by the added complications of cerebral herniation.

## (3) ACUTE ACQUIRED HYDROCEPHALUS

This condition results from rapid and severe obstruction to the flow of cerebrospinal fluid in subjects whose skulls are no longer capable of expansion, or in the case of children when the expansion of the skull cannot keep pace with the ventricular distension. Therefore, unlike the congenital and the chronic forms of hydrocephalus

there is little or no enlargement of the head and the clinical picture is that of raised intracranial pressure, usually without localising signs.

**Ætiology.**—In former times the term acute hydrocephalus was applied to tuberculous meningitis, and ventricular distension indeed plays an important part in the evolution of this malady. The use of the term in this connection has, however, fallen into disuse. The common cause of the condition is new formation within the skull in such a position as to obstruct the flow of cerebrospinal fluid. It is thus most often met with in tumours of the third and fourth ventricles, and of the posterior cranial fossa.

**Symptoms.**—These are the general symptoms of increased intracranial pressure of rapid onset and great severity. The majority of cases present themselves with the symptom-complex of headache, vomiting and papilloedema without signs of any local lesion of the hemispheres or cerebellum. In severe cases proptosis may be present; distension of the veins of the scalp may be seen; and the skull commonly has a characteristic "cracked-pot" percussion note. Radiological examination may reveal a mottled appearance of the vault resembling that of beaten silver, and there may be some decalcification of the posterior clinoid processes and general flattening of the cavity of the sella turcica. The diagnosis is confirmed by ventriculography.

**Treatment.**—This is essentially that of the underlying cause.

#### (4) OTITIC HYDROCEPHALUS

This term has been used to describe certain cases of raised intracranial pressure occurring in the course of middle-ear suppuration, which appear to be due to an abnormal accumulation of cerebrospinal fluid.

The condition usually occurs in children, and has to be distinguished from cerebral abscess. Headache, vomiting, papilloedema and squint are common but, unlike cases of abscess, there is little, if any, toxæmia and the cerebrospinal fluid remains normal except for an increase in its pressure.

There is evidence that the condition is caused by a non-suppurative thrombosis of the cortical veins or venous sinuses, and similar cases have been described as a complication of other localised infective processes, *e.g.* tonsillar infections (see p. 1410).

The illness runs a benign course, and complete recovery normally ensues. The intracranial hypertension may be controlled by repeated lumbar puncture.

### ENCEPHALITIS

Inflammation of the brain may be met with under widely different clinical associations. It may occur as a primary disease or as a complication of known infective processes, affecting the system locally or generally, and it may occur as an associated event in diseases of the meninges. As a primary condition it is met with in a variety of virus diseases of the nervous system, pre-eminent amongst which is encephalitis lethargica. These are described in a later section. It is found as the result of infection of the brain with pyogenic organisms, derived either from local sources of infection in the neighbourhood of the brain or from pyæmia, and it may then be either suppurative (brain abscess) or non-suppurative. It may occur as a complication of many of the acute specific fevers, especially measles, vaccinia and mumps. In these the encephalitis may only be a part of a general inflammation of the nervous system—an encephalo-myelitis. Acute encephalitis may be found in rare cases as the sole manifestation of cerebral syphilis.

In all forms of meningitis there is some degree of extension of the inflammation into the brain tissue, and this assumes an important degree in tuberculous meningitis and in some cases of epidemic cerebrospinal meningitis.

The symptoms common to all forms of encephalitis are the general symptoms of severe intracranial disease—headache, somnolence, coma, irritability, delirium, convulsions and vomiting; and, in addition, local symptoms of irritation and paralysis, the precise nature of which is determined by the position and extent of the lesions.

### (1) CEREBRAL ABSCESS

**Synonym.**—Suppurative Encephalitis.

**Ætiology.**—Suppuration within the brain is never primary, but is the result of extension of infection from neighbouring tissues or through the blood-stream from foci of infection in distant organs. In rare cases, the original focus of infection is undiscoverable.

The following are the important causal factors :

1. *Direct infection* from infected regions in the immediate vicinity (*adjacent abscess*).—The important cause of infection is any form of infective disease in the bones or soft tissues of the head and neck. From 60 to 70 per cent. of all cerebral abscesses arise in this way. By far the most common cause is chronic suppuration in the middle ear and petrous temporal bone, particularly when this is complicated by a superimposed acute infection. Infection of the frontal or other accessory nasal sinuses is second only in importance to middle-ear disease, and chronic infections of the bones of the skull, suppuration of the scalp, orbital cellulitis, carbuncles of the neck and face are other causes.

Adjacent abscesses are usually solitary and commonly occur in the part of the brain in closest proximity to the primary focus of disease. Thus, abscesses secondary to ear disease are usually situated in the corresponding temporal lobe or cerebellar hemisphere, those resulting from disease of the nasal sinuses in the frontal lobes and so on. Exceptions to this generalisation are, however, met with.

The exact manner in which the infection spreads to the brain probably varies in different cases. In some it occurs by a septic thrombosis of a vein communicating between the infected region and the underlying brain. In others the organisms gain access to the brain substance by spreading along the perivascular spaces from a localised area of meningitis evoked by the primary disease. In others still there may be direct spread by continuity through the process of "ulceration" of the surface of the brain described by MacEwen. When the primary disease affects the upper surface of the petrous bone the abscess is commonly situated in the temporal lobe which may be adherent to the tegmen tympani, while if the posterior surface of the petrous bone is affected, the abscess is usually in the cerebellum. In cases both of direct extension and spread through the perivascular spaces, the cerebrospinal fluid shows the presence of leucocytes, predominantly polymorphonuclear, during the stage of invasion, indicating that the meninges have been involved even though no symptoms of meningitis are present. The organisms responsible are commonly streptococcus, pneumococcus or staphylococcus. The infection may be mixed. Other pyogenic organisms may be found, and rare cases are caused by streptothrix infection.

2. *Pyæmic states.*—Abscesses resulting from infection through the blood-stream are termed "*metastatic or hæmatogenous abscesses*" and comprise from 20 to 25 per cent. of the total. They commonly arise as a complication of chronic suppuration in the chest, such as bronchiectasis, empyema or lung abscess. Less commonly they occur as a complication of chronic bone disease, puerperal septicæmia, acute infective endocarditis or other septicæmic conditions. Subacute bacterial endocarditis may lead to multiple embolic foci of encephalitis but not to actual abscess formation. Rarely metastatic abscesses may arise from localised suppuration in remote parts, such as the liver and appendix, where there has been no evidence of a pyæmic state. It is probable that the 10 per cent. of cases of cerebral abscess in which no primary

cause can be found fall into this category, the original focus of disease having undergone complete resolution.

Metastatic abscesses are commonly multiple but may be solitary. They are usually situated in the cerebral hemispheres and originate at the junction of the cortex and subcortical white matter or in the central grey masses. They are rare in the cerebellum and brain-stem. The organisms responsible are streptococcus, staphylococcus and pneumococcus and mixed infections may occur.

3. *Trauma*.—Traumatic abscesses may result from penetrating wounds of the skull, particularly when fragments of metal, clothing, bone and scalp are carried into the brain. Such cases are extremely rare in peace but assume considerable importance in times of war. Fracture of the base of the skull may permit infection to gain access to the brain from the middle ear or naso-pharynx. Fractures involving the inner wall of the frontal sinuses or cribriform plate may be followed by the development of a cerebral abscess after a long latent interval.

*Pathology*.—Cerebral abscess—whether adjacent or metastatic in origin—usually commences at the junction of the cortex and the subcortical white matter. As it increases in size the surrounding brain tissue is displaced and severe distortion of the brain and ventricular system results. The commonest site is the temporal lobe, and approximately half of all cerebral abscesses are found in this region, a reflection of the importance of middle-ear disease as an ætiological factor. The frontal lobes and the lateral lobes of the cerebellum are other areas frequently affected. Abscess in the parietal or occipital lobes or brain-stem is rare.

If it has been left unmolested until the patient's death a cerebral abscess may attain the size of a hen's egg or even of a large orange, but many lead to a fatal outcome before they attain such dimensions. The cavity contains thick greenish-yellow pus, which is often extremely fetid. Commonly the abscess cavity is multilocular, and its interior is usually of a greyish-green colour and covered with adherent purulent debris. The abscess wall varies greatly in character with the age of the abscess. In cases of recent origin there may be only a slight line of demarcation between the ragged, irregular cavity and the surrounding brain. If the abscess has been present for a few weeks a well-defined capsule can be seen and this can often be felt by the exploring cannula at operation. In chronic cases the capsule may become so thick that the whole abscess can be shelled out of the brain without rupture. The pus in such an abscess may become inspissated and sterile. The white matter for a wide area surrounding an abscess is very cedematous, and may contain areas of softening and fresh abscess formation. The more acute the abscess the more marked is the surrounding œdema. The surface of the brain overlying an abscess often shows a localised area of meningitis with flakes of purulent lymph adherent to the pia mater.

The earliest stages of the development of a cerebral abscess seldom come under direct observation but there is every reason to suppose that the initial process is the development of an area of encephalitis around the nidus of invading organisms. In this area there is a mobilisation of inflammatory cells, with dilatation of capillaries and œdema. Gradually liquefaction and pus formation take place in the centre, while a fibroblastic reaction at the periphery gives rise to the abscess wall. Outside this again is a neuroglial proliferation together with a diffuse inflammatory infiltration of the brain substance and perivascular spaces.

Many cases of abscess are associated with a terminal spreading meningitis and in a proportion of cases rupture may have occurred either into the ventricles or the general subarachnoid space, a complication which is invariably fatal within a few hours. In adjacent abscesses it is not uncommon to find an associated subdural or extradural abscess, which is invariably in direct contact with the primary focus of disease.

*Symptoms*.—A cerebral abscess has its origin in inflammation, and constitutes, when developed, a foreign body within the skull. Death may result from the effects

of continually increasing intracranial pressure and wide interference with cerebral function, or from the spread of the infection from the abscess to the meninges and general subarachnoid space. The symptoms may be grouped in four classes: (1) Those of local suppuration; (2) those of increased intracranial pressure; (3) localising signs dependent upon the position of the abscess and (4) those of the terminal extension of the infective process.

The onset of symptoms is usually extremely insidious and is apt to be overshadowed by those of the preceding disease. The usual sequence of events is that a case of mastoid suppuration or frontal sinusitis does not progress quite as well as it should do as judged by the local condition, and gradually the picture of cerebral abscess makes its appearance without it ever being possible to state with certainty where the original illness ended and the complication began. Similarly with blood-borne infections it is seldom possible to determine with precision the time at which an abscess began to form, although occasionally a rigor may mark the time of onset.

The earliest and most constant symptom is headache. This is characteristically intermittent in the early stages, felt across the forehead and in the occipital region irrespective of the site of the abscess, especially on rising in the morning and accentuated by coughing, sneezing or stooping. The pain attains to an agonising degree of intensity and gradually becomes more prolonged, frequent and severe until drowsiness begins to dim its severity. In some cases a considerable degree of local pain and hyperæsthesia to touch or pressure may be felt over the site of an abscess. Occasionally during the months in which a slowly developing abscess is forming there may be periods lasting a day or two of intense occipital pain, nuchal rigidity, vomiting and fever. These disturbances may pass as "bilious attacks" or "influenza", but are in reality due to meningeal irritation set up by a deeply seated infection. Vomiting is a common early symptom. It usually occurs with the headaches but, especially in cases of cerebellar abscess, it may arise suddenly and with great violence in the absence of any other symptoms. Mental changes are common. These vary from slight lassitude and a vague feeling of unwellness to drowsiness and ultimately coma. Delirium is common during periods of meningismus. Double vision is often complained of, and is usually an intermittent uncrossed diplopia on lateral deviation of the eyes which results from weakness of one or both external recti.

Symptoms of focal disturbance of the nervous system are less constant and usually later in occurrence than the symptoms of general intracranial disorder. Epileptic disturbances of any kind may occur with abscesses in the cerebral hemispheres, taking the form of generalised convulsions, focal fits or petit mal attacks according to the site of the lesion. There may be weakness on one side of the body or in one limb, or sensory disturbances of a similar distribution. Disorders of vision due to the presence of hemianopia may be encountered and disturbances of speech are common in abscesses of the left temporal lobe. Where the cerebellum is involved the patient may be aware of awkwardness of voluntary movement, particularly with regard to standing and walking, and giddiness may be complained of.

The patient usually has a strikingly sallow, earthy complexion with a slightly cyanotic tint about the lips and nose. The tongue is thickly coated, the breath extremely offensive, the lips dry and cracked and often bleeding from being picked. The temperature chart is usually characteristic. Fever is present but of a very low degree, seldom rising above 100° F. and often being subnormal for a day or 2 days at a stretch. When it rises above 101° F. it will usually be found that this rise is coincident with symptoms of meningism. In chronic cases the patient may appear to be completely afebrile but careful recording will usually demonstrate an occasional rise to 99° or 100° F., sometimes at intervals of many days. Equally valuable is a record of the pulse-rate. This is almost always unnaturally slow and in no intracranial condition with the possible exceptions of extradural and subdural hæmorrhage is this depression of the pulse-rate so constant as in cerebral abscess. In persons with a



normal rhythm of 70 to 80 per minute the pulse may often be found to fall progressively over days or weeks to 50 or fewer beats per minute. With the bradycardia is associated a similar but less striking fall in the respiration rate.

The mental state is often characteristic. It is best defined as one of irritable drowsiness. Left alone the patient will remain quiet for hours together with eyes closed, only rousing occasionally to cry out with intense paroxysms of headache. Any attempt at examination is met by a fretful opposition and lack of attention which in the early stages are only too often thought to be due to sheer bad temper. Mental slowness is more often met with in this than in any other intracranial disorder. A question put to the patient may remain unanswered, as if unheard, for a minute or more and then, just when it is about to be repeated, a perfectly appropriate answer will be given in a petulant voice. The patient may often be seen tentatively covering first one eye and then the other on account of double vision and in such cases an obvious internal strabismus may be present.

The optic fundi in cases of cerebral abscess commonly show papilloedema if the condition lasts for more than a few weeks. The swelling of the disks may come on with great rapidity and attain 3 to 4 dioptries of swelling with numerous hemorrhages during the course of a few days. It not infrequently continues to increase in severity for some days after the abscess has been drained and may even appear for the first time during this period. Some degree of neck rigidity and a weakly positive Kernig's sign are not uncommonly met with, particularly when the abscess is situated in the cerebellum or when an appreciable degree of meningeal reaction is present. Local tenderness of the skull to firm pressure or percussion is a common finding and may afford valuable help in localising the abscess in doubtful cases. The patient may rapidly become emaciated to a remarkable degree, especially when the abscess is in the cerebellum.

Localising signs will naturally vary with the position of the abscess. Temporal abscess usually begins in the inferior portion of the lobe and extends upwards and forwards. When situated on the left side in a right-handed person one of the earliest focal disturbances to occur is disorder of speech. At first this takes the form of difficulty, then of inability to name objects correctly; later, difficulty in understanding spoken and written language and paraphasia make their appearance. Naturally speech disturbances are not met with in right-sided temporal lobe abscesses except in strongly left-handed persons. Another early sign of temporal abscess is disturbance of the contralateral fields of vision. This nearly always takes the form of a congruous upper quadrantic hemianopia which gradually spreads to involve the lower quadrants until a complete hemianopia is present. As the abscess extends forward towards the motor projection fibres weakness of the opposite side of the face of a supranuclear type develops, to be followed by similar weakness of the contralateral arm and then of the leg until a complete hemiparesis may be present with characteristic increase in the tendon reflexes, diminution or loss of the abdominal reflexes and an extensor plantar response. Contralateral sensory disturbances may be met with but they are late to appear and by no means common. Epileptic disturbances may occur in temporal lobe abscesses *and when these are deeply situated the fits may assume a characteristically uncinate form.*

Abscesses in the frontal lobes are, on the whole, more silent than those in the temporal lobes. Whether adjacent or metastatic in origin they usually originate well forward in the prefrontal areas and may attain a very large size without producing any localising signs whatever. Mental change of the kind already mentioned may be an unduly conspicuous feature. Apathy and forgetfulness may be marked and an early loss of sphincter control may be noted. As the abscess extends backwards towards the motor area a contralateral hemiparesis develops involving face and arm before the leg, and if the lesion is on the left side, an increasing degree of executive aphasia may be in evidence in normal persons. Epileptic fits are not uncommon.

Abscesses situated in the parietal and occipital lobes are rare. Except as a complication of osteomyelitis of the skull they are almost invariably metastatic in origin. The most important local signs that they give rise to are contralateral sensory loss of a cortical type in the case of parietal lobe abscesses and defects in the contralateral fields of vision in those situated in the occipital region. In either case epileptic attacks may occur.

Cerebellar abscesses often present great difficulties in localisation. The general symptomatology is much the same as in cases where the abscess is situated above the tentorium, though on the whole the mental alteration is less and the vomiting and occipital pain more marked in cerebellar cases. Nystagmus is a valuable sign which is seldom completely absent and some degree of weakness of a lower motor neurone type on the same side of the face is often present. Both these signs, however, may be found in cases with a localised area of meningitis in the posterior fossa without any abscess within the cerebellum itself. The most reliable sign is the presence of hypotonia and inco-ordination of movement of the limbs on the same side of the body. In bed these changes are most readily detected in the arms but, if the patient is well enough to walk, the inco-ordination may be very evident in the gait. It is by no means unusual for a cerebellar abscess to be present for many weeks without producing any detectable localising signs while the general condition of the patient leaves little room for doubt as to the presence of an abscess somewhere.

The cerebrospinal fluid is very seldom completely normal in cases of cerebral abscess and examination of the fluid can afford very valuable aid in the diagnosis of doubtful cases. Withdrawal of fluid is, however, by no means devoid of risk and may lead to a rapidly fatal result, either by precipitating medullary failure or by causing the abscess to rupture into the ventricle. For this reason when the diagnosis is not in doubt lumbar puncture should be avoided, and when there is a suspicion that an abscess is present the smallest necessary quantity of fluid only should be withdrawn through a very fine needle. The pressure of the fluid is raised and may reach a very high figure. The first change to take place in the composition of the fluid is an increase in the amount of total protein from the normal 40 mg. per cent. to 60 or even 80 mg. per cent. With this is found a gradual increase in the number of cells to 10 or 20, and rarely more than 100 per c.mm. At first the cells are almost entirely lymphocytes, though an occasional polymorph may be identified in a long search. As the number of cells increases the proportion of polymorphs increases until they may constitute 10 per cent. or even 20 per cent. of the total. Finally, as the abscess approaches close either to the ventricle or to the convex surface of the brain such a brisk pleocytosis may be caused that the fluid becomes turbid in appearance but is still sterile with a normal or only very slightly reduced content of chlorides and sugar. The finding of a turbid cerebrospinal fluid in which no organisms are seen and which remains sterile on culture is always extremely suggestive of a cerebral abscess.

**Diagnosis.**—The diagnosis of cerebral abscess has to be made from other complications of suppuration in the vicinity of the brain, and from other expanding intracranial lesions, particularly cerebral tumour.

The varieties of intracranial complication of neighbourhood suppuration most likely to be confused with cerebral abscess are :

1. Acute spreading meningitis.
2. Localised meningitis, with or without an extradural abscess.
3. Infective venous sinus thrombosis.
4. " Otitic " hydrocephalus.

1. *Acute spreading meningitis.*—The differential diagnosis here seldom presents serious difficulty. The high, sustained fever, rapid pulse, delirium and marked neck rigidity all make the recognition of acute meningitis easy. Difficulty does, however,

arise when a cerebral abscess is causing a brisk meningeal reaction and actual infection of the subarachnoid space is imminent. In such cases the symptoms and signs of the two diseases are likely to be superimposed on one another. The finding in such cases of a turbid fluid without visible organisms, which is sterile on culture, with normal salt and sugar content is very suggestive of an abscess with an acute meningeal reaction.

2. *Localised meningitis*.—This condition often affords the most difficult problem in the differential diagnosis of cerebral abscess. In the presence of an acute infection on the outer aspect of the dura, especially if there is an extradural abscess as is so often the case in mastoid disease, it is not surprising that there should be a brisk local inflammatory reaction of the leptomeninges on the inner aspect of the dura. This local area of meningitis may produce the same local symptoms and signs as an abscess in the same locality and if it involves the base of the brain may also give rise to all the signs of raised intracranial pressure by obstructing the normal circulation of cerebrospinal fluid. In otitic cases this is particularly likely to occur in the posterior fossa, thus simulating a cerebellar abscess. On the whole, such cases come on more rapidly than abscesses and the symptoms and signs are more fluctuant. The temperature is usually higher and the pulse-rate more rapid than in abscess and the signs of meningeal irritation more marked. The central nervous signs are those which might be expected to result from a lesion on the surface rather than in the substance of the brain, for example, cranial nerve palsies. There seems every reason to suppose that in some cases this localised meningitis is capable of undergoing complete resolution, especially since the introduction of antibiotics. On the other hand, it may be but the prelude of a general meningeal spread.

3. *Infective venous sinus thrombosis*.—This condition seldom resembles cerebral abscess sufficiently closely to present serious difficulty in diagnosis. It is characterised by high, swinging fever with frequent rigors, intense toxæmia and the other evidences of a pyæmic state. There are no signs indicative of raised intracranial pressure or of local disturbance of brain function.

4. *Otitic hydrocephalus* (see Hydrocephalus, pp. 1399 and 1404).—Otitic hydrocephalus is a condition almost confined to children and adolescents. It is characterised by the symptoms and signs of raised intracranial pressure, including papilloedema, without signs of focal damage to the brain. Its onset is more acute and the symptoms more violent than in cerebral abscess and the patient's general condition between paroxysms of headache remains remarkably good. Apart from an increase in its pressure and quantity the cerebrospinal fluid is quite normal.

Cerebral abscess may be distinguished from cerebral tumour by its association with suppurative conditions elsewhere in the body, the rapid increase in symptoms, the general reaction of the patient and the changes in the cerebrospinal fluid. In spite of these criteria, chronic cerebral abscesses are not infrequently operated upon in the belief that they are true neoplasms.

*Course and Prognosis*.—The natural termination of a cerebral abscess which is not drained is in the vast majority of cases the death of the patient. Cases of spontaneous evacuation of the pus through the ear or nose are recorded in the literature, and in a small number of cases the pus becomes inspissated and the capsule so enormously thick that the abscess may lie dormant in the brain for many years and become calcified. Such abscesses may later be removed bodily as encapsulated "tumours", the nature of which is only discovered after section. Death takes place from the results of raised intracranial pressure, from acute meningitis from spread of the infection to the general subarachnoid space, or from rupture into the ventricle.

*Treatment*.—The treatment of cerebral abscess is surgical. The condition is one of the greatest urgency, as death may occur at any moment. Surgical treatment should only be entrusted to an experienced neuro-surgeon, and direct drainage through the portal of entry, e.g. the middle ear or frontal sinus carries a high mortality. In

the past the recovery rate has been low, but with modern neuro-surgical technique a high proportion of recoveries can be obtained. Unfortunately epileptic fits subsequently occur in approximately 50 per cent. of cases recovering from cerebral abscess.

## (2) ENCEPHALITIS LETHARGICA (see p. 1414)

### (3) ENCEPHALITIS ASSOCIATED WITH ACUTE SPECIFIC FEVERS

**Ætiology.**—Acute encephalitis may occur as a rare complication of a number of acute specific fevers, especially of the exanthemata. In some cases the brain alone may be involved but in others the nervous system may be more widely affected and the picture is rather that of an encephalomyelitis. The fevers most commonly associated with this complication are measles and vaccinia but it occurs also with variola, scarlatina, mumps and varicella and many other acute febrile disorders. The incidence of encephalic complications of these diseases varies noticeably from time to time.

The exact relationship of the encephalitis to the preceding infection is by no means clear, nor is it certain that the cerebral complications of the different exanthemata are identical. The hypothesis that the exanthem merely serves to activate some unknown causative agent, such as a latent virus, is without confirmation. It must also be borne in mind that all cerebral complications of acute fevers are not necessarily encephalitic but may result from vascular occlusion by thrombosis or embolism, or from hæmorrhage, or from meningitis.

**Pathology.**—In a great many cases recovery ensues, and the pathology of the condition remains unknown. A considerable number of cases of measles and vaccinia encephalitis have, however, been subjected to full pathological examination and have shown a fairly constant condition of the nervous system, and the much rarer examples following other fevers have generally conformed to this picture. The brain and spinal cord show diffuse congestion, particularly of the white matter, sometimes causing petechial hæmorrhages. Numerous areas of acute demyelination occur, particularly in the perivascular zones. These are so constant as to have suggested the title "*perivascular myelinoclasia*" (Hurst) for this group of disorders. In addition there is a *marked perivascular infiltration with round cells, and a more diffuse cellular reaction* in the nervous tissue with mobilisation of microglia and proliferation of the astrocytes.

**Symptoms.**—The time of onset of encephalic symptoms is fairly constant in each exanthem. In measles it is commonest towards the end of the first week, in vaccinia from 10 to 14 days after the vaccination, and in variola during the second week of the eruption. Common symptoms are drowsiness, increasing in severe cases to coma, headache, convulsions, cranial nerve palsies, dysarthria and dysphagia, and in some cases myoclonic or choreiform movements. Slight signs of meningeal irritation, such as neck rigidity, irritability and photophobia, may occur and there may be an increase in the fever. Papillædema may develop. In cases associated with myelitis marked weakness in the lower limbs with retention of urine is common. Loss of the abdominal reflexes and extensor plantar responses are frequent. The cerebrospinal fluid is commonly under increased pressure, and shows an increase in protein content with a mild lymphocyte pleocytosis (10 to 50 per c.mm.). The Lange colloidal gold reaction may be strongly positive and sometimes paretic in character. The content of sugar and chlorides is normal.

**Diagnosis.**—The occurrence of symptoms of this order at the significant period of the different diseases makes the diagnosis, in most cases, clear. It should be remembered, however, that acute fevers in children may determine the moment of onset of tuberculous meningitis, and that vascular disorders may occur in a similar setting.

**Prognosis.**—In cases which do not succumb to coma or convulsions during the first week, recovery is the rule and is usually remarkably complete. Residual paralyses

are exceptional. In a small number of cases some residual intellectual impairment may result and in other cases a liability to fits. The mortality in vaccinal cases is from 25 to 40 per cent.; that in measles and the other common exanthemata very much lower.

**Treatment.**—This is symptomatic. There is no evidence that specific antisera, when available, affect the course of the nervous complications.

#### (4) SCHILDER'S DISEASE

**Synonym.**—Encephalitis Periaxialis.

**Definition.**—A malady characterised anatomically by a progressive and massive demyelination of the white centres of the cerebral hemispheres, proceeding from a single focus or from two symmetrical foci, and producing the clinical picture of progressively increasing failure of cerebral function, local at first, but advancing in terms of the functions of the contiguous regions which are next affected, by the spread of the disease from its starting-point.

**Ætiology.**—Nothing is known of the essential nature of the disease, nor is it certain that all cases included under this heading form a homogeneous group. Originally regarded as an inflammatory, probably an infective, disease, the increasing evidence of its familial incidence suggests that it may be primarily degenerative. It has also been suggested that those cases in which an inflammatory reaction is present may be infective, and those in which it is absent—as it may be—degenerative. Many of the reported cases have occurred in childhood, even as early as the second year. The latest case was in the fifth decade of life. The sexes are equally affected.

**Pathology.**—The characteristic lesion consists of: (1) A primary demyelination and, later, destruction of the axis cylinders of the central white substances of the cerebral hemispheres, which till very late spares the subcortical zone of white fibres and the radial cortical fibres, and produces a translucent jelly-like appearance of the oval centres. (2) A very early and perhaps primary overgrowth of the neuroglia, forming a feltwork, which is particularly intense round the vessels. (3) A general infiltration of the white matter of the brain with round cells, most of which are engaged in the removal of altered myelin or in the formation of neuroglial fibres.

The process commences most commonly as symmetrical patches of demyelination, in either occipital white centre, less frequently in both temporal white centres or in both prefrontal white centres, and spreads directly thence until the whole of the oval white centres becomes demyelinated. The corpus callosum is involved, and the demyelination spreads downwards through the crura into the brain-stem. Sometimes, especially in the central regions, the disease starts on one side, and, after playing havoc with the white centre of one hemisphere, spreads across the corpus callosum into the other. The resulting picture of a brain, normal on the surface, and on section with apparently normal cortex and intact subcortical white bands, but with the oval centre completely changed and translucent, is peculiar to this disease. Not infrequently other patches of the disease may be scattered throughout the central nervous system. This scattered distribution and the prominence of demyelination bring Schilder's disease very close to disseminated sclerosis, and it has actually been described as "disseminate sclerosis in childhood"; but the massiveness and mode of spread of the lesions, together with their distribution, with predilection for the brain and avoidance of the spinal cord, its incidence in childhood and its entirely different symptomatology, separate Schilder's disease sharply from disseminated sclerosis. It is largely to Collier that we owe the clinical recognition of this malady.

**Symptoms.**—The clinical aspect is precisely that which might be expected from a progressive destruction of cerebral function, spreading by contiguity from the initial seat of the disease. In many of the cases blindness—by which is meant blindness without any change in the optic disks and with pupils reacting normally to light—

has been the first symptom, and is the result of the symmetrical demyelination of the occipital white matter. As the disease spreads forwards into the temporal regions, bilateral deafness appears; and, later, bilateral ataxy and astereognosis—due to parietal involvement, bilateral spastic paralysis—the result of central involvement, and complete amentia—due to callosal and prefrontal involvement, develop.

In those cases in which the initial seat of the disease is in the temporal, central or frontal regions, the first symptom to appear is obviously determined by the location, and the order of development of symptoms will be changed, but the mode of progress is the same in all. Where the disease starts on one side only, hemianopia or hemiplegia is the first symptom, and these are followed by the train of added signs produced by the extension of the disease into other regions. Complete mindlessness and paralysis always dominate the clinical picture in the end. The disease-process within the brain sometimes causes swelling with increase of intracranial pressure, and signs of the latter may appear in the form of headache, vomiting and papillœdema. Such cases are not common, and most of them have been regarded in life as cases of intracranial tumour. Fits are by no means uncommon. Sometimes they constitute the initial manifestation of the disease, and they may occur at any time during its course, and may be local or general. Fever is usually absent, but there may be irregular pyrexia and some of the more acute cases have been pyrexial throughout. The cerebrospinal fluid is normal in the majority of the cases, but sometimes there is an increased protein content and a small excess of lymphocytes.

**Diagnosis.**—The onset with cerebral blindness or with bilateral deafness, followed by signs of progressive cerebral destruction, is so rare in any other disorder as at once to suggest the diagnosis of Schilder's disease, indeed no less than two-thirds of the reported cases have shown this picture. When the disease begins unilaterally, and more particularly when headache, vomiting and papillœdema are present, the distinction from intracranial tumour is difficult or even impossible, for in both diseases the local commencement and the progressive destruction occur. In Schilder's disease, however, high-grade papillœdema is not met with, and consecutive optic atrophy does not occur. It should be borne in mind that any locally commencing progressive destruction of the brain may be an example of this malady.

**Course and Prognosis.**—In most cases Schilder's disease is regularly progressive to a fatal termination. In some, however, periods of standstill have been noted, while in a few others marked improvement for a time has occurred. The duration has varied from 7 days to 36 months, with an average of 9 months.

**Treatment.**—No treatment is at present known that will influence the course of this disease.

#### (5) SUBACUTE INCLUSION BODY ENCEPHALITIS

In recent years a type of subacute encephalitis at present only observed in children and adolescents has been reported by Dawson, Van Bogaert, Greenfield and others.

Pathologically it is characterised by the presence of inclusion bodies in the nerve cells, generally regarded as the hallmark of virus diseases together with polioclasia and neuronophagia.

Together with this is a degree of demyelination and sclerosis of the white matter reminiscent of the leuco-encephalitides of the Schilder type.

Clinically the disorder runs a progressive subacute course towards a fatal termination. The earliest symptom is usually mental deterioration often associated with epileptic manifestations. Later involuntary movements of various kinds occur and the child gradually develops the picture of bilateral rigidity of extrapyramidal type with relatively few pyramidal signs until death occurs at a stage of profound dementia with akinesia and contractures.

## VIRUS DISEASES OF THE NERVOUS SYSTEM

Certain viruses have a selective affinity for the nervous system and are therefore spoken of as "neurotropic". They act upon the nerve cell, and to a less degree upon glia cells, but not upon the white matter. They are capable of multiplication and of exerting their pathogenic action only within the nerve cell, where their life and activity are short-lived.

The essential lesion resulting from their presence is an acute necrosis of the nerve cell, leading to the death and destruction or to the damage of the cell. A secondary glial and vascular reaction ensues as a result of which lymphocytes pass into the cerebrospinal fluid from the perivascular spaces in the affected regions of the nervous system.

The so-called post-infective encephalitis that may follow the acute exanthemata has not the pathological characters common to the proved virus infections of the nervous system, since the lesion is one of demyelination and not an attack upon the nerve cell. The nature of this form of encephalitis remains obscure (see p. 1411).

### ENCEPHALITIS LETHARGICA

**Synonym.**—Epidemic Encephalitis.

**Definition.**—An acute febrile disease, occurring sporadically and epidemically, due to the infection of the nervous system by a virus which has not yet been identified but which can be inoculated into the nervous system of monkeys, reproducing the disease. The malady has its principal incidence upon the upper parts of the nervous system, the cerebrum, basal ganglia and brain-stem. Though very definite, it is remarkably polymorphic, and it is sometimes mono-symptomatic, and its type has changed greatly during the passage of an epidemic. The absence of evidence of case to case infection has necessitated the assumption that infection is transferred by carriers, or by those in the pre-symptomatic stage of infection only.

**History.**—When we read of the influenza epidemic which swept over Europe in 1580 and which was accompanied by a malady so peculiar as to gain the title of "schlafkrankheit", and afterwards of the epidemic described by Sydenham in 1675 as "febris comatosa", the "sleeping sickness" of Tübingen in 1712 and Dubini's epidemic of the fatal "electrical chorea" in Northern Italy in 1846, we cannot but agree with von Economo's conclusion that these epidemics were epidemics of lethargic encephalitis. The subsequent epidemics of Mauthner's "Nona" in Piedmont in 1891, and also Pfuhl-Leichtenstern's "haemorrhagic encephalitis" in 1905 have been shown to be similar to lethargic encephalitis, both clinically and pathologically. The malady last became pandemic in Britain and Northern Europe from 1917, reaching a maximum in 1920, and then declined almost to vanishing point over the next 15 years.

In this country sporadic cases of sufficiently definite characteristics to stand up to both clinical and pathological criteria of diagnosis have continued to make their appearance, but they are rare. It should be remembered that many cases thought to be of this nature prove at autopsy to be due to tumours or other causes. On the other hand, the continued appearance of cases of Parkinsonism in young people, not infrequently associated with other post-encephalitic sequelæ, makes it seem likely that instances of the infection, so mild as not to produce clinically recognisable symptoms, are not infrequent.

**Ætiology.**—During the period of its frequent incidence, the disease occurred both sporadically and epidemically, with no centre of spread. It was more prevalent in the cold season of the year. No age was exempt from the malady, and cases occurred

in the seventh decade of life, but it was rare in young children and seemed to be most incident in the first half of adult life. The mode of infection is unknown. According to von Economo, when once the virus obtains access to the nervous system it spreads, as in other cases of virus diseases of the nervous system, by axonal routes. Its effect remains confined to the nervous system, but the occurrence of progressive nervous sequelæ long after the acute illness, which is such a marked characteristic of the disease, suggests that the virus may survive in the nervous system for long periods of time.

The height of the epidemic incidence of lethargic encephalitis has many times coincided with a severe epidemic of influenza, but no further connection between the two conditions is known. Claimed at one time as an aberrant form of poliomyelitis infection, von Economo's disease has proved quite distinct, both in its age incidence, seasonal prevalence, morbid anatomy and symptomatology. Economo first succeeded in transferring the disease to the monkey by intracerebral inoculation in 1916. Subsequent smaller epidemics in Japan and St. Louis, though conforming in general to the features of the pandemic of 1917-1920 have shown sufficiently constant variation in age incidence and death-rate as well as clinical feature to make it seem likely that there exist more than one strain of the virus.

**Pathology.**—The pressure and quantity of the cerebrospinal fluid are always increased, and in a few of the cases blood or the products of hæmorrhage are present. In about one-third of cases the cell count has been normal. In the rest there has been a moderate lymphocytic pleocytosis, with little or no protein increase, the titre of the sugar tending to a high normal and that of the chlorides being normal. No prognostic indications can be derived from the nature of the fluid. The vessels of the brain are markedly congested and full of blood, and the colour shows a characteristic change from the normal throughout the whole of the grey matter, varying from a rosy flush to a deep salmon-pink, giving rise to the term "the rose-coloured brain". When hardened in formalin, this colour becomes a heavy purple grey. Both subdural and deeply seated hæmorrhages are occasionally found. Economo describes the anatomical picture as one of unvarying constancy. It is that of an œdematous and congested brain, with all the grey matter conspicuously reddened in contrast to the white matter, which is of normal colour. There is a non-purulent and, properly speaking, a non-hæmorrhagic inflammation of the whole grey matter exclusively, the white matter being uninvolved. There is most conspicuous perivascular lymphocytic cuffing remarkable for the absence of any polymorphs, with an intense cellular infiltration of the grey matter with elements of the microglia, while the neuroglia is unaltered and demyelination does not occur. Accompanying and succeeding these inflammatory changes is a certain measure of neuronophagia, with primary loss of the ganglion cells.

**Symptoms.**—In the acute forms of the malady the onset is often ushered in by general symptoms, such as shivering, malaise, headache, and fever and bodily pains, a thickly coated white tongue and constipation, and sometimes vomiting and persistent hiccough. This train of symptoms usually appears in the story as an attack of "influenza". The pyrexia does not usually last longer than a week. Countless such attacks of "influenza", distinguishable only by the occurrence of transient diplopia, or of slight somnolence, and often even without any such distinguishing features, have been completely recovered from at the time, but have been followed, after long intervals, by the slow onset of the Parkinsonism of lethargic encephalitis. Again, the epoch of infection may apparently give rise to no symptoms at all, and long afterwards an insidious onset of Parkinsonism ensues.

**The Nervous Signs.**—*Mental symptoms.*—An increasing lethargy, which often becomes very deep, is present in many of the cases. In this condition the patient will lie for days without stirring a muscle, taking no heed of his surroundings and passing the dejecta under him unheeding. Yet when roused by command and



vigorous bodily stirring, he will wake up and hold a very intelligent conversation, lapsing back at once when he is left alone, even though his mouth be half full of unswallowed food. In this condition, *flexibilitas cerea* may often be demonstrated in the limbs. The lethargy may last for 3 weeks or longer even in patients who completely recover. It passes away gradually. Unrousable coma is invariably a sign of impending dissolution. Subsequent memory of events during the early days of the lethargy may be remarkably retained. Insomnia may be a troublesome early symptom, and even when the patients are markedly lethargic they will complain that they cannot sleep. Occasionally reversal of sleep rhythm may occur, the patient sleeping soundly all day only to become restless and overactive at night. Lethargy, however, may be completely absent and the early mental state be that of vivacious excitement and talkativeness. Irritability and restlessness may be present. In some cases the first nervous sign may be delirium or mental aberration, which may rapidly develop into acute and violent mania; such cases are rapidly fatal. In cases which recover after severe symptoms, considerable mental reduction and self-obvious mental change may persist. Indeed, it has been said that no sufferer from this disease ever regains his original mentality, and it is a common experience to find the personality very seriously changed in the way of mental reduction. Complete incapacity for any sustained work, entire change of character, anti-social tendencies, moral perversion and depressed neurasthenic states are not uncommon sequels of the disease, particularly when it occurs in children or adolescents (see also p. 1634).

*Convulsions* are very rare, but they may undoubtedly occur as in other forms of encephalitis. Indeed, the initial clinical picture may be dominated by convulsion, and closely resemble "status epilepticus" from other causes.

*Ophthalmoplegia* and other paralyses in the region of the cranial nerves are most often nuclear in type, but peripheral paralysis of any cranial nerve may be met with, most commonly unilateral paralysis of the facial nerve. The pupils may show every abnormality which a lesion of the nervous system can produce. Inequality, unroundness, eccentricity and loss of light reflex and ciliary paralysis may occur. The loss of light reflex may be unilateral. The external ophthalmoplegia, being nuclear in origin, involves both eyes in terms of their conjugate movements, and the upward and downward movements are, as a rule, more severely impaired than are the lateral movements. Bilateral ptosis is very usual, and is a most important and valuable early indication of the disease. The common error is to consider it part of the sleepy state. The nuclear ophthalmoplegia is often irregular, giving rise to strabismus and diplopia. Either in addition to the above or existing alone, there may be peripheral paralysis of any of the oculo-motor nerve trunks. The degree of the ophthalmoplegia varies in different cases from slight diplopia with hardly noticeable strabismus to complete paralysis of both eyes. It may be rapidly transient or permanently severe. In severe cases which survive there is always some improvement in the degree of paralysis in the course of time.

*Vision.*—The diplopia and loss of accommodation cause much defect of vision, but many of the patients complain of a loss of vision in each eye, which is too great for any such explanation, the cause of which is not yet explicable. Papilloedema has been reported in a few cases. It is transient and never reaches a high degree.

Bilateral nuclear facial paralysis and bulbar paralysis are not uncommon. Paralysis of any individual cranial nerve may occur, and also of any individual spinal root. Such paralyses always completely recover in the course of time.

Symptoms indicative of lesion of the basal ganglia are among the most common features of the disease, and they are often the most persistent. These consist of weakness of movement, rigidity with slowness of movement and spontaneous involuntary movements. The weakness, rigidity and slowness of movement give rise to a peculiar immobility of facial and bodily expression and movement. The face is mask-like, the neck stiff and the head moves little and slowly, the trunk bent forward and

stiff, the arms held away from the trunk, the whole appearance of the patient closely resembling that of paralysis agitans. Rapid fluttering of the eyelids when gently closed is characteristic of this condition. The spontaneous involuntary movements may be of a rhythmic tremulous nature, as in paralysis agitans, or there may be slow rhythmic, choreiform, athetoid, myoclonic, irregular or highly complicated movements: these may be met with at any stage of the malady, but most commonly appear some little time after the acute stage has passed away. Fibrillation and fascicular twitching of the muscles is very common in the acute stage. In cases where bulbar symptoms, either of a spastic or flaccid kind, are present, hypersalivation of the nature of a true sialorrhœa is often a most troublesome symptom.

In addition to the above common symptoms and signs, other indications of involvement of the cerebral hemispheres may occur. Bilateral spasticity with signs of involvement of the pyramidal systems, increased jerks, lost abdominal reflexes and extensor plantar responses are common. Hemiplegia, aphasia and hemianopia may occur. Meningeal symptoms may be very marked in the early stages, such as suboccipital headache, painful stiffness of the neck, head retraction, vomiting and Kernig's sign. Indeed, rapidly fatal cases have occurred in which the clinical picture throughout was hardly distinguishable from that of acute meningitis, but without any leucocytosis in the cerebrospinal fluid. A major incidence of the lesions upon the cerebellum gives rise to the picture of acute cerebellar ataxy following a lethargic onset, and the end-result may be a condition closely resembling a usual type of disseminate sclerosis. Such cases make a good recovery in the course of time.

Peripheral pains are sometimes very severe and are usually quite local. They may be the first signs of the illness, and may persist for months after recovery. They are presumably due to the lesions around the nerve roots which have been already referred to.

*Spinal symptoms.*—Since lesions have been found in the spinal cord, it is only to be expected that focal spinal symptoms should be met with in rare cases. These are usually acute atrophic paralyses similar to those of poliomyelitis and recover completely. It has been argued, however, that this atrophic palsy is due to a lesion of the spinal roots. More severe lesions may apparently give rise to a condition resembling acute transverse myelitis.

The incontinence which is almost constantly present, even when the lethargy is far from deep, is the result of the lethargy. Transient conscious dysuria is, however, not infrequent in the early stages of the disease. The deep reflexes may be lost in severe cases during the acute stages, and they are usually absent in premortal conditions. Otherwise they tend to be exaggerated, especially if involvement of the pyramidal system be present. The condition of the abdominal and plantar reflexes depends upon the presence or absence of lesions affecting the pyramidal tracts. In the former case, the abdominal reflexes will be absent and the plantar reflexes of the extensor type.

Attention must be drawn to a group of cases in which the initial manifestations of the disease are so slight as not even to interfere with the daily work or to call for medical attention, and yet in the course of months, or it may be even years, the most serious and completely incapacitating paralysis appears. Such a patient may notice that he sees double, and does not feel very well for a few weeks. He recovers, but after a few years begins to manifest the signs of a slowly oncoming Parkinsonism. A similar result in the slow and late development of grievous symptoms may follow any attack of lethargic encephalitis and make the prognosis in this malady very difficult.

*Sequelæ.*—The disabilities which this malady may leave in its wake are numerous and varied. The mental, paralytic and Parkinsonian end-results have already been referred to, but special mention must be made of the so-called oculogyric crises, and of involuntary spontaneous movements, having the general features of habit spasms or tics.

**Oculogyric crises.**—This term is applied to recurring attacks of tonic conjugate deviation of the eyes. This is almost always upwards and is accompanied by wrinkling of the forehead, extension of the neck and in fact all the muscular activity associated with the act of looking upwards. Deviation of the eyes to one side is exceedingly rare. The attacks may occur several times a day or only at an interval of months. They are often very specific in their times of occurrence and may be precipitated by a variety of stimuli such as emotion, fatigue or watching a moving picture. The attack may last from a few minutes to many hours and often passes off only after sleep. It is commonly associated with an intense degree of mental depression and while it lasts the patient may experience recurring obsessional thoughts, be impelled to carry out stereotyped movements or develop ideas of reference, particularly feelings of persecution.

Patients suffering from oculogyric crises always show some signs of Parkinsonism. The attacks often gradually grow less frequent over a period of years and may cease completely. Their frequency and duration is in many cases considerably reduced by the regular administration of amphetamine sulphate 5 to 10 mg. twice daily.

**Post-encephalitic tics.**—A great variety of stereotyped involuntary movements are met with in post-encephalitic subjects usually in association with some degree of Parkinsonism. Rhythmic movements of the jaws, tongue and face are common. Alterations in respiratory rhythm with sighing, gasping inspirations may occur. Torticollis, indistinguishable from the variety met with in elderly subjects, is not rare and there may be hideous recurring contortions of the face and trunk and most grotesque mannerisms of gait and speech.

**Diagnosis.**—A diagnosis of lethargic encephalitis is not infrequently made, but must be received with the very greatest reserve at the present time. Under this title most neurologists have encountered a great variety of nervous disease, including intracranial tumour, cerebral abscess, subdural hæmatoma, tuberculous meningitis and the like. In typical cases the diagnosis presents no difficulty, the rousable lethargy, incontinence, ophthalmoplegia and negative, lymphocytic or blood-containing cerebrospinal fluid being so characteristic as to preclude possibility of error. The less usual forms of the malady, and especially those with very gradual onset and slight symptoms, often present great difficulty and require much care and full knowledge of the possible symptomatology of the disease for their recognition. There is no specific laboratory test for the malady, and the diagnosis must be based upon clinical grounds. Where meningeal symptoms are prominent, distinction has to be made from other forms of meningitis and from poliomyelitis. Here, the cerebrospinal fluid is of the highest importance, as polymorphonuclear leucocytes occur very rarely in lethargic encephalitis. In cases commencing with peripheral pains, excitement, maniacal symptoms or convulsions, careful lookout should be kept for the advent of ptosis, ophthalmoplegia or lethargy, the appearance of which, following such symptoms, should at once suggest the diagnosis. It must be borne in mind that the clinical picture of the disease may be dominated by a hemiplegic condition, and that an apoplexy may occur during the acute stage of the disease. Slight cases of the disease are frequently unrecognised, or are indeed unrecognisable in the early stages, but here the diagnosis can often be made with certainty from the end-results; the peculiar ophthalmoplegia, the spontaneous involuntary movements and the paralysis agitans-like syndrome being almost pathognomonic of the malady.

**Course.**—The course of the disease is extremely variable. It may be a slight transient illness lasting but a few days, and leaving no sequelæ after a few weeks; or a most malignant disease, fatal in a few days. In others, symptoms indicative of fresh lesions may occur repeatedly weeks and even months after the onset.

**Prognosis.**—A rapid onset and quick development of severe symptoms, marked pyrexia, delirium and maniacal excitement are bad prognostic signs and indicate a rapidly fatal issue. After the third week of the disease, the probabilities are all in

favour of survival. The prognosis, however, as to how much permanent damage to the nervous system will eventually remain is hardly possible, since slow improvement may go on for months and even years. Of the acute cases occurring at the height of an epidemic, 40 per cent. are quickly fatal, 30 per cent. are reduced to chronic invalidism and 30 per cent. appear to recover completely (Economo). In most of these latter the syndrome of Parkinsonism subsequently appears after an interval which may be a few months or many years, and the weakness, rigidity and tremors, which form this paralysis agitans-like picture persist indefinitely.

**Treatment.**—Nothing being known of the infectivity and mode of spread of the disease, isolation and disinfection are not usually employed. Each case must in England be immediately notified to the public health authorities. No treatment is known which has any specific influence upon the disease. Intravenous injection of colloidal iodine solution (150 ml. for a dose), repeated on the second and fourth days, has been advocated, and is certainly without harmful effects, but there is little evidence that it is of value. There has as yet been little opportunity to investigate the effects of antibiotics. It remains therefore to use those measures which will help to keep the patient alive and those which relieve symptoms. Nasal feeding may be necessary. Relief of the constipation is most important and is often followed by striking improvement in the symptoms. After the acute stage, treatment is concerned with combating the physical and mental listlessness and depression which so often persist and with the restoration of normal mobility and function to the limb. In these, physical and occupational therapy can play a useful part.

## HERPES ZOSTER

**Synonym.**—Zoster; Shingles.

**Definition.**—An acute infection of the posterior root ganglion by a neurotropic virus, leading to severe pain in the distribution of the corresponding posterior root, and to the appearance of a crop of vesicles in the cutaneous distribution of the root.

**Ætiology.**—The virus of zoster stands in some as yet undetermined relation to that of chicken-pox, and the appearance of the latter malady in a susceptible subject some 14 days after contact with a case of zoster has been too frequently recorded to be of the nature of coincidence.

The disease is seen at all ages, but according to Head is perhaps most common in adolescents. In elderly patients it is frequently a more serious as well as a more painful affection than in young persons. It may arise without discoverable cause and with a febrile reaction and considerable malaise. It may also occur apparently "symptomatically" during the course of arsenical medication, or during such illnesses as pneumonia, tabes dorsalis and tuberculosis.

**Pathology.**—The essential lesion is an acute inflammation of the dorsal root ganglion of the same histological character as the lesion of acute anterior poliomyelitis. There are degenerative nerve cell changes, with accompanying microglial reaction and perivascular infiltration with round cells. Later, degenerative changes occur in the fibres of the dorsal roots and of the peripheral sensory nerves. The Gasserian ganglion and the thoracic and upper two or three lumbar ganglia are most often affected. There is an increased protein and lymphocyte count in the cerebrospinal fluid.

**Symptoms.**—There may be an onset with fever which persists for 2, 3 or even 4 days. There is from the first pain at the place at which later the herpetic eruption is to appear. This occurs on the third or fourth day of the illness. At first the rash is a patchy erythema, upon which appear small vesicles filled with clear fluid. From the fifth to the tenth day the vesicles dry up and shrink progressively until a scab is formed. This finally drops off, sometimes leaving considerable scarring. These

scars may be anæsthetic to touch, pinprick and temperature sense. The pain before and during the evolution of the cutaneous lesion may be intense. It is of a burning and itching quality, and in frail and elderly persons it may persist as a most intractable post-herpetic neuralgia for months or even years.

Herpes of the ophthalmic division of the fifth nerve is most commonly found in elderly persons. Corneal vesicles may form and burst, giving rise to ulcers, which may spread and end in residual scarring (nebulæ), which impairs vision.

Herpes of the geniculate ganglion occasionally occurs. The vesicles are found in the pinna, and there is pain in this region, over the mastoid, and sometimes in the fauces (see pp. 1248, 1346).

Localised paralysis may accompany herpes. Thus, in ophthalmic herpes there is occasionally third-nerve palsy, with ptosis and squint. In geniculate herpes, facial palsy with loss of taste over the anterior two-thirds of the tongue is the rule. In herpes of the lower thoracic ganglia there may be paralysis of the oblique abdominal muscles on the affected side. The marked local bulging of the abdominal wall which ensues resembles at first sight the presence of an abdominal tumour. These paralysees do not invariably clear up, though the facial palsy of geniculate herpes does so more frequently than the paralysis of the abdominal muscles.

**Treatment.**—The course of the cutaneous lesions is not influenced by treatment, which is directed to keeping the vesicles dry and free from infection. For this purpose a dusting-powder of starch or zinc oxide, or a collodion dressing may be used.

During the acute stage, pain may be relieved by aspirin or phenacetin, but the post-herpetic neuralgia so often met with in elderly patients may prove intractable, and so severe as to render life scarcely tolerable. It consists of a persistent, burning soreness often associated with numbness and dysæsthesia over the area previously effected by the eruption.

This pain is aggravated by fatigue, worry and physical debility and often induces a neurotic reaction on the part of the patient or a state of depression in which suicide may be contemplated.

Both analgesics and hypnotics are commonly needed over a period of many months. The former may profitably take the form of some such mixture as the following: tinct. gelsemi min. 10, phenazone gr. 10, phenobarb. sod. gr.  $\frac{1}{2}$ , Aq. chlorof. ad fl. oz. 1 t.d.s. For the latter one of the short-acting barbiturates is to be preferred. A word of caution should be given against the dangers of excessive sedation in elderly subjects, especially with bromides, as a toxic confusional state is easily produced.

A great variety of local applications have been used without avail. Surgical measures such as division of peripheral nerves, posterior spinal roots or the spino-thalamic tract in the cord are equally ineffective. As a last resort in the elderly depressed subject frontal leucotomy may be justified and while it does not remove the unpleasant sensation it allays tension and depression and frees the patient's mind from perpetual preoccupation with the pain which is one of the most noticeable features of this distressing malady.

## RABIES

**Synonyms.**—Hydrophobia; Lyssa.

**Definition.**—This is an infective disease due to a filtrable virus which is located in the salivary glands and central nervous system. It is transmitted to man and most warm-blooded animals through infective saliva of canines or blood-lapping bats. There is a long and variable incubation period, and a short pyrexial illness of sudden onset characterised by fever, nervous exaltation and violent muscular spasms involving the œsophagus and respiratory system. Once symptoms have supervened, the patient invariably succumbs.

**Ætiology.**—The disease is generally transmitted either by the licking of a freshly abraded surface of skin or the bite of an infected dog. In Eastern Europe and the Orient, wolves not uncommonly transmit the disease and, owing to extensive laceration of the tissues, a greater proportion of people bitten by them develop the disease than with either dogs or jackals. It has been estimated that wolf bites entail a mortality of 80 per cent. In Trinidad, in 1925 an epidemic of paralytic rabies in man was attributed to the bites of vampire bats, cattle being the original source of infection.

**The virus of rabies.**—This belongs to the class of neurotropic viruses that have a special affinity for attacking the grey matter of the nervous system.

Pasteur, in 1881, discovered that rabies could be transferred in series from animal to animal by subdural inoculation of emulsions of central nervous tissue derived from an infected dog. In rabbits, after some twenty passages, the virus became modified; firstly, the incubation period of ordinary street virus which varied from 8 to 60 days was reduced to 7 days; and, secondly, it lost its capacity to reproduce the disease on subcutaneous inoculation. Such a virus is known as fixed virus or virus fixé. Street virus, on the other hand, is transmitted from the local wound via the peripheral nerves to the central nervous system, and if the sciatic nerve be inoculated the lumbar cord becomes infectious several days before the virus can be demonstrated in the brain (di Vestea and Zagari). This accounts for the fact that cases bitten about the face, head and neck have such a short incubation period. The virus is destroyed at 50° C. and is attenuated by drying—a fact made use of in the preparation of antirabic vaccine by the Pasteur method.

**Pathology.**—Excess of cerebrospinal fluid, petechial hæmorrhages of the pia-arachnoid and injection of its vessels may be found at autopsy. Histological examination reveals cellular infiltration of the perivascular lymph spaces as well as Negri bodies within the cytoplasm of the nerve cells and their processes. These bodies were described by Negri in 1903. They are globular or ovoid structures, of variable diameter (0.5 to 25.0 microns), and are especially common in the Purkinje cells of the cerebellum and the hippocampus. These inclusion bodies are present in the brain of 97 per cent. of dogs infected with street virus.

**Symptoms.**—The period intervening between the bite and the clinical manifestations varies from 1 to 2 months, as a rule, the limits being 11 days to over a year. Face, head and neck bites have a shorter incubation period than those on the upper extremity, and arm bites a shorter incubation than those implicating the leg. The onset is generally sudden, but prodromal symptoms are sometimes noted for a day or two before a hydrophobic syndrome appears. For convenience, three stages are described.

1. *The invasion stage.*—This includes prodromal features such as pain in the scar, fever, headache, rapid pulse, anxiety, restlessness, insomnia, irregular and sighing respirations and phases of rushed speaking.

2. *The stage of excitation.*—This supervenes in 24 to 48 hours. There is intense restlessness, mental excitement, hyperæsthesia and hydrophobia which consists of a sudden spasmodic spasm of the muscles of the mouth, pharynx and larynx and, to a greater or lesser degree, the whole respiratory musculature. A typical attack may be induced by offering the patient water. As the glass approaches the mouth, the head retracts in a series of spasmodic jerks associated with gasping respirations, while any water reaching the mouth is immediately ejected. The shoulders are elevated, the chest expanded, and the sterno-mastoid and platysma muscles contracted. Later, the synaptic resistance in the reflex arcs become so lowered that a variety of sensory stimuli such as a sudden sound, cold air, strong light, a strange smell and even the suggestion of water may suffice to induce the attack. The voice is altered. Frothy saliva collects in the throat and mouth and is flung off the lips during the attacks which may be characterised by intense fury or the most profound terror. Lastly, opisthotonus and general respiratory spasm are superadded. In the interval the mind

is clear, the patient remaining quietly at rest in bed. Examination of the central nervous system reveals, as a rule, nothing more than increased deep reflexes. Glycosuria is not uncommon and vomiting, exhaustion and emaciation characterise the final stage of the illness. Death during the paroxysm may occur from dilatation of the right heart, though sometimes near the end the spasms ameliorate or cease altogether.

3. *Stage of paralysis*.—If the patient survives long enough, paralysis of various types, including ascending spinal paralysis, paraplegia and hemiplegia, may supervene. The patient lies helpless and exhausted, and generally dies in coma. In man this stage is rarely seen in canine-transmitted rabies, but paralytic rabies is commonly encountered in the bat-transmitted variety in Trinidad.

In the Trinidad outbreak all the cases were of this variety, and all proved fatal. The onset is acute, with fever and headache. Numbness and burning sensations in one or both legs, paresis of the legs and retention of urine follow. After 2 or 3 days the paraplegia becomes more complete, and the plantar and tendon reflexes disappear. One limb is commonly affected before the other. In a few days the paralysis begins to ascend, involving the muscles of respiration, articulation and deglutition. There is dyspnoea and restlessness. The sufferer remains conscious, but may be delirious. Sensory changes are of variable intensity. A final brief coma precedes the fatal issue. During this time the temperature swings round 103° F., and there is profuse sweating. Hydrophobic symptoms are exceptional, and when present slight. The cerebrospinal fluid yields an increased globulin content, but is otherwise normal. The duration of the illness is from 4 to 8 days.

*Rabies in the dog*.—These animals never show the hydrophobic syndrome observed in man. The earliest manifestation appears to be a change in temperament, followed by irritation and exacerbations of vicious fury in which the animal runs amok, biting wildly anything in its path. Later, swallowing becomes difficult, the bark is altered, the jaw drops and general paralysis ensues. Death invariably follows some 2 to 5 days after the first symptoms appear. In dumb rabies the stage of excitation is absent.

*Diagnosis*.—As a rule, little difficulty is experienced in diagnosis, but occasionally tetanus, the cerebral type of typhus fever, bulbar paralysis from any cause, and datura and other poisonings encountered in Oriental countries may need differentiation. Lyssophobia or hysteroid counterfeiting of the disease generally manifests itself within the first 10 days, and is unaccompanied by fever or other serious features.

*Prognosis*.—By no means all patients bitten by rabid animals die, but once clinical manifestations appear the disease invariably ends fatally. Estimates varying from 5 to 33 per cent. have been made of the death-rate in untreated patients, but of those receiving early anti-rabic inoculations in Pasteur institutes, not more than 1 per cent. die. The mortality varies with the site of the bite, the interposition of clothing, the number of tooth-marks, the extent of tissue laceration and the rapidity with which efficient local treatment has been instituted. Head, face and neck bites are particularly dangerous, as well as bites from wolves and jackals.

*Treatment*.—This is entirely preventive, and in England the muzzling order and the strict quarantine of all imported dogs has led to the eradication of rabies. In endemic areas canine bites should be promptly treated, and the suspected dog chained up, muzzled and kept under observation. Should the animal be alive at the end of 10 days it is proof that the bitten person has not been infected. This rule, universally followed in Pasteur institutes, is based (1) on the knowledge that the infected dog never survives longer than 6 days from the onset of its illness, and (2) that the saliva of a rabid dog is never infective for more than 4 days before the onset of symptoms. In suspicious cases, especially the head, face and neck bites, treatment should be commenced without delay and discontinued if the dog survives.

The virus of rabies differs from that of yellow fever in not passing through the intact skin, and where there is a history of being licked by an animal suspected of

rabies prophylactic inoculation need not be advised unless fresh skin abrasions were present at the time.

*Local treatment.*—If seen within 30 minutes, bleeding should be encouraged by the application of a ligature just tight enough to obstruct the venous return and the parts bathed with permanganate solution. Subsequently, each tooth-mark should be probed separately and cauterised or treated with pure phenol. For 3 days the wound should not be sutured; this particularly applies in the case of face bites.

*Antirabic vaccination.*—Owing to the long incubation period, it is feasible to attempt immunising the patient either by the inoculation of attenuated, living, fixed virus, as in the Pasteur and Högyes methods, or by the injection of carbolised or etherised vaccines in which the fixed virus has been killed. The Pasteur treatment consists of a series of 18 injections of emulsions made from the spinal cord of rabbits which had been dried for periods of from 14 to 3 days. Semple introduced carbolised vaccine; the most potent preparation consists of a 5 per cent. carbolised suspension of sheep brain infected with Paris virus. In mild cases the course consists of 2 ml. injected subcutaneously each day for 7 days; in average cases of 5 ml. for 14 days; and in severe cases, such as head, neck and face bites, in wolf bites, or in children bitten on the bare skin, 10 ml. are injected daily for 14 days. Itchy swellings may appear at the site of the inoculations about the eleventh day, but other complications following inoculation are fortunately rare. Paralytic accidents, however, have been recorded with all methods; they include a mild facial neuritis, dorso-lumbar myelitis and an ascending paralysis of Landry's type which is fatal in about 30 per cent. of cases.

*Treatment of the paroxysm.*—No specific treatment is known. Measures directed to alleviate the suffering of the patient should be instituted. These include chloroform inhalations and morphine, hyoscine, chloral and atropine in large doses. Curare has been employed for the relief of spasms.

## ACUTE ANTERIOR POLIOMYELITIS

*Synonyms.*—Infantile Paralysis; Heine-Medin Disease.

*Definition.*—An acute infectious disease characterised, in its fully developed form, by local or widespread muscular paralysis consequent upon the destruction, by the action of a specific neurotropic virus, of anterior horn cells in the spinal cord or corresponding cells in the medulla.

*Ætiology.*—The disease occurs in both sporadic and epidemic manner and has its greatest incidence in countries in the temperate zones. The most severe epidemics have occurred in the countries of northern Europe and North America, but in the last 25 years it has appeared with increasing frequency in Australia, New Zealand and South Africa, and such island communities as Malta and Mauritius have not been spared. During the War of 1939–1945 a particularly virulent form was prevalent in North Africa and the whole Mediterranean littoral.

It shows a marked seasonal variation, being commonest in the hotter months of the year. In northern Europe the incidence usually begins to increase towards epidemic proportions in July and slackens off in October or November. Sporadic cases, however, occur throughout the year.

A conspicuous feature of the disease is its preference for the young, although no age is immune. In the early years of this century its maximal incidence among infants led to its being named "infantile paralysis" and at that time the greatest number of cases occurred in the second and third years of life. Before the age of 1 year the infant appears to be immune.

Over a period of 50 years there has been a steady tendency for the disease to attack older age groups, and at present the maximal incidence is between the ages



of 5 and 10. This curious change in age distribution, taken with the unfortunate fact that the incidence of paralytic poliomyelitis seems to increase rather than to decrease with the improved standards of hygiene in more advanced communities, suggests that whereas in primitive communities children come frequently in contact with the virus in early life and so acquire immunity, those in more advanced communities escape this early inoculation, some of them only to fall victims to a virulent attack in later childhood.

The successful transmission of the disease from man to monkeys by Landsteiner and Popper in 1909 and the subsequent researches of Flexner and Lewis and others as to the nature of the infecting agent proved to be landmarks in the development of our knowledge of virus diseases in general and of those of the nervous system in particular.

It is now known that the causative agent of the disease is a virus, which is amongst the smallest so far identified. It is distributed widely in the human race and is commonly a harmless inhabitant of the naso-pharynx and intestinal canal. By modern methods it can be recovered from the naso-pharyngeal washings and the faeces of both clinical cases and many contacts, as well as from flies and communal sewage in affected areas. It is now recognised that only a minority of the individuals harbouring the virus develop even mild symptoms of disease and that of these not more than a fifth develop paralysis. There is thus a large pool of unaffected "carriers" in any community that is affected and these probably play a major rôle in transmission of the disease. This is in accordance with the known fact that 50 to 80 per cent. of town dwellers in countries much affected by the disease have protective antibodies in their sera at a high titre. Three distinct types of the virus have now been identified: Type I (Brunhilda), which is at present the most virulent and carries the highest incidence of paralysis; Type II (Lansing), which can be adapted to be pathogenic to rodents; and Type III (Leon). All three types have been responsible for paralytic attacks in the human. They are serologically distinct, but it is at present by no means clear to what extent infection with one type confers protection against the natural disease caused by the other types. The rare occurrence of second attacks of the disease strongly confirms that cross immunity is incomplete.

A clinically recognisable attack of poliomyelitis, whether paralytic or not, leads to the development of specific antibodies in the blood which, with the rare exceptions mentioned above, confer lifelong immunity from a further attack. Such antibodies are not present in the sera of individuals from isolated and unaffected communities, or in those of susceptible individuals in affected communities. On the other hand, the high incidence of natural immunity among adults, especially the town-dwellers, in affected populations confirms the belief that one or more subclinical attacks occur during many such persons' lifetimes. The immune body is carried by the gamma-globulin fraction of the plasma and is at present the subject of intensive research in the hope of finding a satisfactory method of immunisation against the disease.

The method of spread of the infection has been a matter of controversy for many years. It has been generally accepted that unaffected carriers play a larger part in the process than do recognisable cases of the disease. Although the participation of flies in the spread of the disease cannot be excluded, it is clear that the principal agency concerned is human contact. The main matter of dispute has been whether the infection is carried by droplet spread from the naso-pharynx and upper respiratory tract, or by the various methods of faecal contamination from the gastro-intestinal canal. The evidence for droplet spread is strong and epidemiological studies have shown a close association between cases of the disease and human movement in circumstances in which spread by the excreta was unlikely. The undoubted association between tonsillectomy and the development of bulbar poliomyelitis also indicates the naso-pharynx as a potential source of infection. On the other hand, the major incidence of the disease in hot weather has always suggested that it was spread by

faecal contamination, and there is now convincing evidence that the gastro-intestinal tract acts as a portal of entry for the virus and that in most epidemics it is the principal one. The virus can be recovered from the stools of patients for several weeks after an attack, as well as from those of intimate contacts and from communal sewage. The method of transmission is largely by human contact operating through such agencies as contaminated food, eating utensils and latrines. It is possible that milk and water may also play a part. Although the virus can be recovered from flies in infected areas, the part they play as vectors has not yet been determined. It used to be said that case-to-case infection did not occur, but this statement will no longer bear critical examination. However, such occurrences are extremely rare in institutions where cases are treated with careful barrier nursing precautions.

There is still considerable uncertainty as to how the virus, when it reaches a susceptible host in adequate dosage, breaches the defences of the body surface and reaches the nervous system. There is evidence that in so doing it is aided by a lowering of the victim's general resistance, or by local trauma, such as tonsillectomy, or by local disturbance such as may cause the diarrhoea which often precedes attacks in which a gastro-intestinal origin of the infection is to be suspected. Since the work of Hurst and Fairbrother, later confirmed by Howe and Bodian, it is evident that the virus, having penetrated the body's defences, reaches the nervous system by axonal pathways. The original view that the olfactory nerves were the agents of transmission has been abandoned, and it is now thought that the nerve fibres of the gastro-intestinal canal and of the tonsils are responsible. The virus is capable of transmission along axones, but can only proliferate in the bodies of nerve cells. Examination of the nervous systems of humans, or of experimental animals dying of the disease, shows that the virus is widely distributed in the brain and spinal cord, but reaches its highest concentration in the anterior horn cells of the spinal cord, especially of the lumbar enlargement, the motor nuclei of the brain-stem and motor cells of the cerebral cortex. Another subject of controversy has been whether the entire sequence of events observed in acute poliomyelitis can be explained in terms of a process confined to the nerve cells, or whether there is an associated systemic infection. The high proportion of cases in which no paralysis occurs, the associated blood changes and the widespread occurrence of immune bodies in the blood-stream are points suggestive that a systemic invasion does take place, although the virus has only rarely been recovered from the blood in human cases and the visible pathological changes seen after death are confined to the nervous system. An interesting association has been shown to exist between intramuscular injections such as may be given for purposes of immunisation and the development of paralysis in neighbouring muscles during succeeding weeks. This is now believed to be due to the action of poliomyelitis virus determined by the specific local trauma of the injection.

**Pathology.**—The virus of poliomyelitis is an obligatory intracellular parasite, and its action takes place entirely within the nerve cell. The changes seen in the nervous system vary with the virulence of the infection. The virus has a special affinity for the anterior horn cells of the spinal cord and in severe infections these cells in portions of the cord undergo acute necrosis. If the experimentally infected animal be destroyed at this initial stage no lesions other than these cell changes are found, and the rapidly ensuing cellular exudation and meningeal infiltration seen in fatal human cases are not present. But the necrosis of nerve cells in the surviving patient is naturally soon followed by phagocytic processes, and amœboid (microglial) cells and polymorphonuclear leucocytes rapidly invade the affected areas and clear away the dead nerve cells. It is essential to bear in mind, however, that these processes are secondary and not, as used to be thought, the primary and essential lesion of poliomyelitis. In less severe infections, less acute forms of nerve cells changes are seen, and with these the cellular exudation is almost wholly of amœboid microglia cells. These phagocytic cells fill the perivascular spaces in the affected parts of the cord. Together with

leucocytes, these cells finally overflow into the cerebrospinal fluid. They may appear here even before the development of paralysis, and it was this early indication of meningeal infiltration that led to the view formerly held that a meningitis preceded the involvement of the nervous system. In the affected regions of the grey matter of the ventral horns, some cells always remain unaffected by the virus. Some degree of encephalitis is a constant feature, although it is not usually clinically manifest.

Lesions in the viscera have been described: namely, hyperplasia of the lymphoid tissue and splenic enlargement—but these are not constant, and their presence at the final stage of the malady is of uncertain significance.

*Cerebrospinal fluid.*—The fluid is clear, colourless or faintly yellow, and under normal or only slightly increased pressure, and the titre of chlorides and sugar is normal. The protein content is slightly increased at first and tends to rise during the first 3 weeks after the onset of the disease. The cell content of the fluid is very variable. In the majority of cases there is a pleocytosis of 20 to 100 cells per c.mm., but there may be more. The count is usually a mixed one, with lymphocytes outnumbering the polymorphs in a proportion of two or three to one. In some cases, however, a high proportion of polymorphs may be found at the onset usually giving place to a predominantly lymphocytic increase in subsequent punctures. The fluid may be normal in indubitable cases. The nature and number of the cells seem not to afford any prognostic indications.

*Blood.*—In the early stages of the malady, there is usually a polymorphonuclear leucocytosis, which may reach as high as 30,000. This leucocytosis disappears when the fever abates.

*Symptoms.*—It is now generally believed that infection with poliomyelitis virus is a much commoner event than was formerly supposed and that of those so affected only a relatively small proportion develop symptoms of a kind sufficiently definite to permit of a clinical diagnosis. Of these latter probably not more than a fifth are destined to develop paralysis. This has led to the recognition of three degrees of poliomyelitis, viz. (a) *formes frustes*, "abortive" cases, or "the minor illness", (b) pre-paralytic and non-paralytic poliomyelitis, (c) paralytic poliomyelitis. This clinical subdivision is justifiable and useful on practical grounds, but it should be understood that there is no corresponding pathological subdivision and that the three degrees shade off imperceptibly into one another.

(a) "*Formes frustes*" or the "*minor illness*".—Such cases occur sporadically and are particularly plentiful in times of epidemics. They can rarely be diagnosed with certainty although their nature may be suspected in the presence of an epidemic or retrospectively, when other cases have occurred in the same family or isolated community. The symptoms consist of malaise, headache, mild fever, aching in the back and limbs and sometimes a sore throat, or mild gastro-intestinal upset and are thus common to influenza, the pre-eruptive stages of the exanthemata and such virus diseases as infective hepatitis, or glandular fever. The disturbance subsides in 24 to 48 hours without residual symptoms and the spinal fluid, if examined, is usually normal.

(b) *Non-paralytic and pre-paralytic poliomyelitis.*—The symptoms are essentially the same as in the "minor illness," but rather more intense and prolonged. The onset is often abrupt and fever practically invariable. The temperature is commonly 103° or 104° F. and this pyrexia commonly lasts for 2 to 4 days and then gradually subsides, sometimes finally and sometimes to rise again a few days later and before the paralysis makes its appearance. Pains in the back and limbs are more severe and flexion of the spine is painful. Vomiting and anorexia are common and in many cases there is slight diarrhoea. After a day or so the general headache becomes intensified and occipital in position and is associated with the classical symptoms of meningeal irritation, namely irritability, neck stiffness and photophobia. The muscles of the back and limbs are often tender and may show tremor and depression or loss of their reflexes. There may be retention of urine.

Such a clinical picture in an adolescent, or young adult, in the summer or early autumn is extremely suggestive of poliomyelitis, but to those who have had extensive experience of epidemics the picture seen in young children is highly characteristic. Draper has given a vivid account of this stage from which the following account is taken. The child is commonly flushed and miserable, and may be drowsy, but it presents a typical appearance of mingled apprehension and restlessness, and may be very irritable. In severe infections the child breathes rapidly, appears preoccupied and in a state of tenseness. An ataxic tremor and involuntary muscular jerkings may be present. Extreme fearfulness, and confused and alarming dreams are common. The child is hypersensitive to even the lightest touch and resents being moved. Vomiting, probably of central origin, may also be present. Headache, pain in the neck and back, stiffness of the spine and pain in the back on active or passive flexion, diminution of tendon jerks, and some diffuse weakness all appear in sequence.

During this stage of the illness it is impossible to predict with certainty whether the symptoms will gradually subside, or whether paralysis will suddenly declare itself and if the nature of the disease has been recognised an agonising period of waiting is inevitable and may be prolonged for 2 or 3 days.

Generally speaking, severe fever and meningeal signs and depression of tendon reflexes are of grave significance, but mild premonitory signs may be followed by severe local or general muscular paralysis. It should be remembered that probably not more than one-fifth of the cases diagnosed, and in many cases, confirmed by C.S.F. changes subsequently develop paralysis.

(c) *Paralytic poliomyelitis*.—In these cases usually at the height of the constitutional and meningeal disturbance muscular paralysis declares itself. It may be confined to the muscles innervated by the spinal cord—the spinal form—or affect those innervated by the bulbar nuclei either exclusively or in addition to spinal paralysis—the so-called “bulbar poliomyelitis”, or polio-encephalitis.

1. *SPINAL FORM*.—The onset of paralysis occurs usually between the second and the fifth days of the constitutional disturbance, but may be delayed as long as the tenth day if the fever persists. From the moment of its first appearance it usually reaches its height within 24 hours, but in rare cases it may continue to become more severe for several days, or recrudescence after becoming stationary.

In distribution and severity the paralysis varies over the widest possible extent. At one end of the scale are those cases in which, within a few hours, all four limbs are completely paralysed and the patient is engaged in a life-and-death struggle with respiratory failure. At the other, are cases so mild that the paralysis is not recognised till the patient starts to get up. Generally speaking the legs and lower trunk muscles suffer more frequently and severely than the upper parts of the body, especially when diarrhoea has been a feature of the invasive period.

Wherever it occurs, the paralysis is of the flaccid, lower motor neurone type with loss of muscle tone, loss of voluntary power varying from weakness to complete paralysis and diminution or loss of the corresponding tendon reflexes. This is rapidly followed by wasting, which in severe cases is rapid and intense in degree. Until it has been seen, the rate at which the muscles dissolve under one's eyes can hardly be believed. Such muscles are frequently tender and sometimes show spasm, so that the development of contractures occurs both easily and rapidly. The paralysis is generally much more widespread and severe at its commencement than it is destined to be permanently. At first all four limbs may be completely helpless and later there may be complete recovery in all but one limb. The widely spread temporary paralysis is due to a recoverable affection of nerve cells, whereas the permanent paralysis is the result of actual destruction of nerve cells by the necrotic lesion. Usually the muscles first affected are the ones that show the greatest permanent damage.

In the rare “ascending” type the paralysis may gradually ascend from the legs and lower trunk to the upper limbs, and progressive deterioration of the respiratory

muscles during the first day or two after the onset of paralysis is relatively common and is probably due to progressive exhaustion of the nerve cells of the upper thoracic and cervical region, themselves a little damaged, by the failure of the lower thoracic muscles to carry their share of the respiratory burden. In cases where the cervical cord is involved respiratory embarrassment makes its appearance early and in the absence of artificial respiration in some form it may lead to a fatal outcome within a few hours of the onset of paralysis.

In cases which survive, the narrowing down of the initial paralysis begins to show itself after the end of the first week, and any muscle which will recover useful power will have done so before the end of the third month. The paralysed muscles undergo atrophy, which is more rapid and complete in those cases in which there will be no subsequent recovery; they give the reaction of degeneration. They are flaccid from the first, and in the course of time tend to develop a variable degree of contracture, and yet it is common to see a limb which remains permanently flail-like. Any muscle which shows a response to faradism 3 weeks after the onset will usually recover completely. When a limb is paralysed, there is usually a considerable degree of vasomotor paralysis, and there may be subsequent retardation of growth. Considerable deformities of the body and limbs may arise as the result of the loss of support, which results from the paralysis, from the action of unopposed muscles and from the contractures. Such deformity may involve actual dislocation of joints, as in the shoulder joint, when the deltoid is paralysed and the pectorals escape.

The local lesion of the spinal cord is by no means confined to the grey matter, and may occasionally involve the contiguous white matter of the lateral column sufficiently to give rise to signs of lesion of the pyramidal tract, and in rare cases of lesion of other neighbouring tracts, such as the spino-thalamic tract, with a result in a Brown-Séquard's syndrome of pyramidal deficiency upon the same side and loss of pain and temperature sense on the opposite side below the lesion. This is the so-called "myelitic" form. Paralysis of the cervical sympathetic is occasionally seen when the lower part of the cervical enlargement is involved, with the usual signs of a small pupil and low-lying lid on the affected side. It is, however, generally a transient event.

Disturbances of sensibility of an objective kind are rare, and are almost always transient, and amount to blunting of pain and temperature sensibility, from involvement of the spino-thalamic tracts which are contiguous to the ventral horns. Subjective disturbances are common, and consist of severe local pains in the limbs, back and neck. Tenderness of the muscles, and pain on moving the joints are sometimes very prominent, and may persist for many weeks. The dominance of the clinical picture by persistent pains in the periphery constitutes the so-called "neuritic" form of poliomyelitis.

The reflexes, both superficial and deep, are at first lost in the affected region, and indeed are generally absent throughout the body in the early stages of a severe case, from the general effect of the virus upon the nerve elements. In the later stages they return, or remain permanently absent, according as the muscles recover or not. The preservation of a tendon jerk or any sign of a returning reflex, either deep or superficial, in the early days of the illness is a most useful prognostic indication that the muscles concerned with the reflex will entirely recover.

Retention of urine is common during the first 10 days of the illness, particularly in the case of male subjects where the trunk muscles are involved. It is never permanent.

2. BRAIN-STEM FORM OR "BULBAR" POLIOMYELITIS.—Involvement of the muscles innervated by the bulbar nuclei may be present from the onset and may be encountered in the absence of spinal cord symptoms. This is commonly seen in the cases occurring as a complication of tonsillectomy. More often, however, it occurs as an extension of the disease in cases in which the cervical enlargement of the spinal cord is involved and respiratory complications are already present. Its onset is often

heralded by mental confusion and drowsiness, acceleration and irregularity of the pulse, irregularity of the respiratory effort and flushing and congestion of the skin and conjunctivæ. These symptoms may be confused with those of anoxia. Excessive bronchial secretion occurs and adds to the danger of this grave complication. Paralysis of the pharynx may be unilateral or bilateral, and leads to dysphagia and to the accumulation of secretions in the pharyngeal recesses. Laryngeal paralysis may be partial or complete and may lead to dangerous adductor spasm. Paralysis of the tongue may occur. The palate is commonly involved, giving rise to a nasal speech and regurgitation of fluids down the nose. Unilateral or bilateral facial palsy is common, but similar paralysis of the muscles of mastication is much more rare, but occasionally the patient may be unable to keep the jaw shut. Ocular paralyses are very rare and patients showing them are usually moribund. Occasionally, however, spontaneous nystagmus occurring in short bursts and at a rapid rhythm may be seen and is not of particularly sinister significance.

The occurrence of bulbar symptoms is always an event of grave prognostic significance, but if the patient survives the cranial nerve paralyses make a remarkably complete recovery.

**Diagnosis.**—When once paralysis is present the diagnosis of poliomyelitis seldom presents much difficulty. In children a localised paralysis has to be distinguished from such causes of "pseudo-paralysis" as acute rheumatism, osteomyelitis, syphilitic epiphysitis and scurvy with subperiosteal hæmorrhage. In all these there may be associated fever and general disturbance with pain and reluctance to move the limb.

In cases of generalised paralysis the group of diseases most likely to be confused with poliomyelitis are the peripheral neuritides, particularly acute infective polyneuritis and acute porphyria. In both of these the paralysis is symmetrical and at first peripheral in distribution and, although slight, some sensory disturbances are usually present. The finding of a C.S.F. with a high protein content, but no excess of cells, is a point in favour of polyneuritis. Cases of poliomyelitis affecting both legs and the lower part of the trunk may easily be confused with acute compression of the spinal cord in the dorsal region with a flaccid paraplegia, especially when this is caused by an infective lesion of the spine such as osteomyelitis. Careful attention to the history and the finding of sensory loss with a clear upper level will usually suffice to avoid this mistake.

Isolated bulbar poliomyelitis may be confused with focal lesions of the medulla such as syringobulbia, or vascular lesions and a very similar picture may be seen in botulism.

It is particularly in abortive cases and in the pre-paralytic stage that difficulty in diagnosis arises. Indeed it is often impossible to diagnose poliomyelitis with certainty, though it may be suspected in the presence of an epidemic or on account of the time of year.

In cases showing merely fever, malaise and some generalised muscular pains the differential diagnosis is from influenza, tonsillitis and the exanthems. These are rare in summer and early autumn. More difficult to distinguish are the premonitory phases of certain other virus diseases, namely infective hepatitis, glandular fever and virus pneumonia.

When signs of meningeal irritation are prominent the diagnosis is from the various forms of meningitis, though it should be borne in mind that all the conditions mentioned above may be associated with "meningism".

The pyogenic meningitides usually present a picture so definite that serious difficulty does not arise, but meningococcal meningitis may start insidiously and tuberculous meningitis relatively acutely. The distinction from these conditions can usually be made with certainty on the cerebrospinal fluid, but this may take a day or two.

Greater difficulty occurs with benign lymphocytic meningitis and with the meningo-encephalitis of mumps which may precede the parotitis as in both cases a pleocytosis

similar to that of poliomyelitis occurs with no fall in glucose, or chlorides and little increase in protein.

The meningeal reaction to a cerebral or extradural abscess may also give a mixed pleocytosis with a sterile fluid, but here there is usually a considerable increase in the total protein content.

**Course and Prognosis.**—A good deal has already been said on these aspects of poliomyelitis in the foregoing paragraphs. In abortive cases and non-paralytic cases, which represent the vast majority of the total, recovery is complete, though patients will often notice general lassitude and even a marked loss of weight for some weeks or months after the illness.

Purely local paralysis presents no threat to life and the patient recovers with a varying degree of local disability. It is not uncommon to see cases of complete paralysis of all muscles below one knee or of one shoulder girdle and spinal deformities may later develop from involvement of portions of the spinal musculature.

Cases of generalised paralysis are always in grave danger because of the likelihood of involvement of the respiratory musculature and this complication is the principal cause of death. However, if the emergency is surmounted, remarkable recovery of respiratory function occurs. In part this is due to the development of increased efficiency in the remaining respiratory muscles, including the accessory muscles, but partly to the fact that the initial loss of power in diaphragm and intercostals is often due to exhaustion rather than to irreparable anterior horn cell damage.

In cases surviving the first impact of the disease improvement in muscle tenderness begins after a week or so and recovery of function of muscle begins about the same time. It usually begins first in the muscles last affected, and in cases destined to make a good recovery it continues at a rapid rate for 2 to 3 months. Recovery of tendon reflexes or the faradic response often precede the return of voluntary power. Muscles which show no sign of recovery and have the reactions of degeneration at the end of this time are unlikely to make any useful recovery. After 3 months, recovery continues at a gradually slower rate for another 6 months, but most of the improvement during this period results from the development and adaptation of function in already active muscles rather than from further recovery of nerve cells.

In all but very mild generalised cases some degree of permanent wasting and weakness of muscles will remain which may necessitate the use of various appliances to improve function and mobility and various orthopædic procedures to the same end. In severe cases the patient may be left permanently confined to a spinal chair or wholly dependant for life upon some form of respirator and he is faced with all the problems of psychological readjustment that this implies.

In young children and, to a less extent in adolescents, the loss of muscle may lead to serious defects of growth in the limbs and to deformities both of the limbs and the trunk.

The occurrence of bulbar symptoms increases greatly the gravity of the prognosis, but if the patient survives the cranial nerve palsies usually undergo complete recovery.

Second attacks of poliomyelitis occur, but are exceedingly rare. They probably result from a susceptible individual encountering at different times strains of the virus which do not confer cross immunity.

**Treatment.**—The first problem that faces a physician called to see a case of poliomyelitis is disposal. Should the patient be left at home or moved to a hospital and, if the latter, to what hospital? In abortive and pre-paralytic cases this decision is a difficult one. If, on balance, the diagnosis seems likely to be poliomyelitis and particularly if the existing symptoms are severe, the decision should be for immediate transfer, as a respiratory emergency may arise suddenly at any time. If the case is mild, or the fever already subsiding, it may be justifiable to leave the patient at home. In that case absolute bed rest should be enjoined for there is satisfactory evidence that the taking of vigorous physical exercise in the pre-paralytic stage may not only

greatly increase the likelihood of paralysis occurring but may also determine its distribution. The child should remain in bed for 2 weeks after all fever and symptoms have subsided, and get about gradually during the third week. Contact with other children should be avoided for 3 weeks after the temperature becomes normal, and for the same time the excreta should be immersed in lysol for 12 hours before disposal. No restrictions need be placed on diet, though at first the appetite is usually poor.

If it is judged that the diagnosis is probable or beyond doubt—and this will include all paralytic cases in the acute stage—the case should be transferred to hospital and is notifiable. The choice of hospitals may, in this country at least, present a difficult problem. From the public health point of view admission to a fever hospital where facilities exist for complete isolation is the disposal of choice and is the accepted policy of the Public Health authorities. From the patient's point of view, this may also be satisfactory in large cities where sufficient cases occur to make it a practical proposition to assemble together the trained nursing staff, the experienced medical officers and consultants and the wide range of instrumental equipment needed to deal with the many emergencies that may arise during the course of a case of poliomyelitis. But in smaller centres and in the country fever hospitals are not so provided and are often unsuited to cope with acute cases of this disease. The alternative to a fever hospital is a well-equipped general hospital. Here cases can be nursed either in isolation cubicles or with barrier precautions, the standard of nursing is usually high and the full range of consultant and specialist assistance, both for the acute and convalescent stages, is available. Under such circumstances transmission of the disease to nurses, medical officers or other patients is exceedingly rare and, in the view of most of those in a position to judge, a general hospital is to be preferred to all but the best fever hospitals for such cases.

The ideal solution of the problem is the setting up of regional poliomyelitis centres where a specially trained staff both medical and nursing is immediately available and all instruments and equipment are kept permanently ready for use.

Whatever the hospital in which the case of poliomyelitis is treated it constitutes a potential emergency of the most dramatic kind. Treatment falls into three natural phases:

- (a) The acute illness lasting from the onset for 2 or at most 3 weeks.
- (b) The stage of neuronic recovery lasting for 6 months or so from the onset.
- (c) The stage of adaptation and rehabilitation lasting up to 3 years from the time of the acute illness.

(a) *The acute illness.*—Here the primary object of treatment is to ensure the patient's survival. He should be nursed on a soft mattress or air bed upon a stiff wire bed or fracture boards. All excreta, linen and feeding utensils should be sterilised and kept separate from those of the other patients and all attendants should wear masks and gowns. The diet should be light but as nutritious as the patient will tolerate.

All muscles showing weakness or paralysis should be put as far as possible in the position of physiological rest. The feet and toes should be supported at right angles to the legs by pillows and a vertical board. The knees should be maintained at 10° flexion by a slender bolster underneath them. If the deltoids are affected the shoulders should be kept abducted by pillows to as near as the patient will tolerate to 90°. The hand should be dorsiflexed at the wrist to 30° with the fingers and thumbs gently flexed round a small woollen cushion. Pain and spasm in muscles may be relieved by hot packs and the discomfort may necessitate the use of aspirin or other analgesic and even of morphine, provided that this is not contraindicated on other grounds. From the beginning all joints should be put through their full range of passive movement twice a day and the complete immobility formerly insisted upon is now regarded as harmful and responsible for much of the painful limitation of



movements at joints and muscular contractures which can be such a tiresome feature of the convalescent phase. Retention of urine is best treated by an indwelling catheter and seldom lasts more than 2 weeks even in severe cases. If cystitis develops it should be treated immediately by means of sulphonamides or the appropriate antibiotic and, if severe, this should be combined with tidal drainage and bladder washouts.

The complications of poliomyelitis which threaten life are respiratory failure and bulbar involvement.

*Respiratory failure.*—Although this commonly develops suddenly during the first 2 or 3 days of paralysis it does not do so without warning. Frequent and careful examination of the chest may reveal the progressive involvement of the intercostal muscles on one or both sides and may be confirmed by asking the patient to count aloud without drawing breath. An initial count of 50 or more may fall to 20 before the patient is conscious of dyspnoea at rest. Spirometer readings should be taken at regular intervals and starting at 3000 to 4000 ml. may fall on successive measurements to 1200 ml. or so before cyanosis is visible or subjective distress is experienced.

It is often the involvement of the diaphragm which precipitates a respiratory crisis and necessitates the use of some sort of artificial respirator. If the emergency develops suddenly, as it often does within 12 hours of the onset of paralysis, the decision to use the respirator presents no difficulty. If it develops gradually over several days from progressive exhaustion of the remaining respiratory muscles a difficult choice has to be made. There is a natural reluctance to submit a sick person to the terrifying experience of dependence for life upon a machine, but it should be remembered that this experience is much less of an ordeal if it occurs before it is obligatory. Furthermore, throughout the period of gradual respiratory failure the lungs are undergoing a process of lobular collapse and if atelectasis occurs it takes some days to re-expand the collapsed areas even with adequate respiration. Generally speaking, therefore, it is preferable to resort to a respirator too early rather than too late and a rapidly falling respiratory exchange as indicated by a vital capacity of less than 1500 ml. in an adult is an indication for the use of a respirator.

The effects of respiratory embarrassment are often aggravated by the accumulation of bronchial secretions, frequently excessive in amount, which the patient is unable to cough up. This complication can often be forestalled, especially in children, by postural drainage. The patient is laid face downwards on a thoracic bed with the head and chest sloping downwards at 30° to 45°. In other cases it may be necessary initially to suck out the secretions through a bronchoscope.

A number of artificial respirators are available for choice. That of most general application is the Drinker respirator and its various modifications in which the entire patient except for his head is enclosed in an airtight tank. The air in this is rhythmically sucked out by bellows operated by an electro-motor in such a way that the negative pressure so created draws air into the patient's thorax. A sorbo rubber collar secures an airtight fit round the neck and portholes are provided for nursing and inspection. The whole floor of the tank carrying the patient can be drawn out for more prolonged attention.

The tank respirator gives satisfactory results when properly employed, but certain risks are associated with its use. Secretions in the trachea and bronchi are liable to be drawn into the alveoli, ventilation can be too deep, or too rapid, with consequent disturbance of the blood chemistry or it may be insufficient and so give rise to progressive anoxia. The motor may break down and an efficient engineer is as much a part of the team in a respirator unit as efficient nurses and doctors. The patient's colour, pulse and subjective sensations are a better guide to the efficiency of respiration than blood-gas analyses.

Of other respiratory aids available, some operate by negative and some by positive

pressure. Various cuirass respirators which may be useful for transport act by suction, but enclose the thorax only. The Bragg-Paul respirator consists of a distensible jacket which encloses the chest and rhythmically expresses the air from the chest, relying, as does manual artificial respiration, upon the elasticity of the chest wall to re-expand the lungs.

Recently positive pressure machines operating with a face mask such as is used in closed-circuit anaesthesia have been introduced and are particularly useful in combination with the Drinker respirator for enabling the patient to remain out of the tank long enough for nursing care and physiotherapy. Whatever type of respirator is used the personalities and training of the attendants are of paramount importance and every effort should be made to avoid frequent changes in personnel.

*Bulbar poliomyelitis.*—When this occurs in the absence of respiratory involvement or of widespread mesencephalitis it is a relatively benign condition. Dysphagia may necessitate feeding by nasal catheter and the accumulation of secretions in the nasopharynx and upper respiratory passages may necessitate postural drainage or repeated suction. The occurrence of adductor spasm of the vocal cords may require tracheotomy. Recovery is the rule. Bulbar poliomyelitis with mesencephalitis and signs of more generalised polioencephalitis is usually a terminal event in a moribund patient.

It is when it occurs—as it usually does—as a complication on the second or third day of a case of spinal poliomyelitis of the cervical and thoracic cord with respiratory involvement that bulbar poliomyelitis presents a therapeutic problem of the greatest difficulty. It is associated with excessive bronchial secretion and often with laryngeal obstruction which with a patient already in a respirator has usually led to rapid death. In a recent epidemic in Denmark where such cases were common, the mortality was nearly 90 per cent. until the drastic measure of immediate tracheotomy and positive insufflation followed by regular suction was adopted. This procedure reduced the mortality to approximately 25 per cent., but the method makes the greatest possible demands upon medical and nursing attendance and is clearly only possible in specially developed centres. With the modern methods outlined above it is not uncommon for a patient to survive the immediate emergency only to become permanently dependant upon artificial respiration—a dilemma of a most poignant kind for all concerned.

(b) *The stage of neuronic recovery.*—During this period, which lasts for 3 to 6 months in severe cases, the objects of treatment are to promote the maximal recovery of nerve cells, and therefore of muscles, to restore function and to prevent contractures and deformities. The patient is best treated in a specialised convalescent unit such as is often associated with orthopaedic centres. Massage and passive movement of limbs should gradually give way to active movements carried out at first with slings or in warm baths and later against progressively increasing resistance. Weight bearing should be assisted by such devices as bannisters, crutches and calipers. Such devices as stationary bicycles and boats and the intelligent use of ball games play an important part and progress is more rapid in cheerful and well-run units where group methods are possible and the elements of competition and emulation can be made use of.

Care must be taken to prevent the development of deformities and where the trunk muscles are involved the patient should spend several hours a day lying prone on a flat bed to correct the tendency to develop a lower thoracic and lumbar kyphosis. Breathing exercises should be given.

After 6 months it is unlikely that more neurones will recover their function and improvement becomes much slower. It continues, however, for many months or even years by virtue of the increased adaptation of the patient to his disability and by the hypertrophy and taking over of new function by existing muscles.

(c) *The stage of adaptation and rehabilitation.*—This is really a continuation of the

above and may last 2 to 3 years. In it function gradually improves and the patient's range of activity increases. Instrumental devices may be used and in many cases the patient has to be trained for a new occupation, depending upon the nature of the residual paralysis and the natural aptitudes of the individual. After 2 years operative orthopaedic procedures may be needed to stabilise flail joints or to improve function by tendon transplants.

**Specific Treatment.**—The virus of poliomyelitis is not susceptible to any of the existing antibiotics or other known drugs. As early as 1910 Netter tried to minimise the extent or severity of the paralysis by injecting convalescent human serum, but without success. In spite of claims to the contrary, all subsequent attempts to affect the acute illness by antisera have proved useless. This is in conformity with what occurs in other virus diseases of the nervous system and it has been shown that in experimental poliomyelitis in order to prevent the development of the disease after the injection of virus into the nervous system the immune serum must be injected within 12 hours of the injection of the virus.

**PROPHYLAXIS.**—In view of the generally accepted observation that tonsillectomy may precipitate bulbar poliomyelitis, this operation should not be carried out during epidemics of the disease. Similarly injections of immune sera or inoculations against diphtheria should be avoided. Much progress has been made in recent years in the field of immunisation against poliomyelitis. Passive immunisation by means of serum or gamma globulin can play, at best, only a limited part in the prevention of the disease. Active immunisation with killed virus, on the other hand, offers better hopes of protection, and has been used extensively in the United States and other countries. The Salk formalin inactivated polyvalent vaccine received an initial setback in 1955 when over 200 cases of poliomyelitis in the United States were attributed to its use, but stricter safety standards for its manufacture and testing have since been imposed and millions of children have been inoculated without mishap. Active immunisation has also been achieved by giving suspensions of live attenuated virus by mouth to human volunteers. Virulent strains can be rendered avirulent by frequent passage through mice or cotton rat brain, while retaining their antigenic quality. The results, however, although encouraging, are still *sub judice*.

**PRECAUTIONS IN SCHOOLS.**—A common problem arises when a case of poliomyelitis occurs in a boarding school and medical advice is sought by the school authorities or the children's parents. It should be borne in mind that at present medical knowledge is insufficient to give an entirely satisfactory ruling in the matter. We do not know exactly how long an individual continues to pass virus in his excreta or droplets, nor do we know fully how the infection is spread, or how the virulence of the virus and the susceptibility of individuals may be measured. Furthermore, such is the fear of the disease in the public mind that parents cannot be expected to behave entirely rationally with regard to it.

If more than one case occurs in a school the best course is to put the school as a whole in isolation. All intercourse with other schools should be cancelled, the pupils should be confined within bounds, vigorous games and swimming should be suspended and any child developing mild symptoms should at once be confined to bed in the sanatorium. Ideally, the school should not be dispersed as it is likely that the majority of the pupils have already come in contact with the source of infection and may themselves be a source of danger to others. The arbitrary period of 3 weeks is usually accepted for isolation. Unfortunately, the majority of parents will insist upon removing their children and this cannot be prevented. Parents should be advised to notify their own practitioner immediately on the child's return home and he should be kept away from other children and from such places as swimming pools, cinemas, etc., for 3 weeks. Again, strict bed rest should be enforced if any mild febrile disturbance should show itself.

## VASCULAR DISORDERS OF THE NERVOUS SYSTEM

### ARTERIAL THROMBOSIS AND HÆMORRHAGE

Cerebral thrombosis and cerebral hæmorrhage seem hitherto to have been described in textbooks of medicine as quite separate conditions, almost antagonistic and mutually incompatible, between which it was possible and even highly essential to make a differential diagnosis for the purpose of applying very dissimilar lines of treatment in the respective conditions, each line of treatment being the worst possible for the other condition. It cannot, however, be too forcibly pointed out that primary arterial thrombosis and primary arterial hæmorrhage depend in every case upon degeneration of the arterial wall, and that every condition of degeneration of the arterial wall may cause either thrombosis or hæmorrhage indifferently. It is a usual experience to find in patients who have had several strokes that thrombosis was the cause of the earlier, and hæmorrhage of the final apoplexy. Even in that condition, which has always been held to be the most important antecedent of cerebral hæmorrhage—renal disease with high arterial tension—thrombosis and not hæmorrhage is the cause of apoplexy in many cases. On account, therefore, of the identity of the underlying pathological condition in every case, and the clinical association of thrombosis and hæmorrhage of the cerebral arteries, and the difficulty of distinguishing them clinically, the two conditions are here described together.

**Ætiology and Pathology.**—The arterial degeneration which may result in cerebral thrombosis and hæmorrhage is due to the following causes: (1) Arteriosclerosis, which is the common cause both of thrombosis and of hæmorrhage in the second half of adult life, and which is by far the most frequent cause of hæmorrhage. It must be especially borne in mind that cerebral atheroma may be local in the cerebral vessels, and unassociated with general atheroma of the systemic vessels. (2) Syphilis, which was formerly the commonest cause of thrombosis in the first half of adult life, and which is less frequently the cause of hæmorrhage. It may affect both the large and the small arteries, even to the smallest. All the coats of the artery are affected, and in the finest vessels there is conspicuous lymphocyte accumulation or "cuffing" round the vessel. (3) Periarthritis nodosa, Buerger's disease and other less common varieties of arterial disease. (4) Abnormal conditions of the blood especially when associated with heart failure, as in septicæmic conditions. Hæmorrhage into the brain may also complicate polycythæmia and acute leukæmia. (5) In association with new-growths of the brain, both thrombosis and hæmorrhage are common events, especially when the neoplasm is soft and rapidly growing. The vascular lesion may occur quite early in the course of the new-growth, and apoplexy may be the first sign of its presence. (6) Inflammatory conditions of any nature may cause thrombosis and hæmorrhage. The vascular lesions are usually small, but they may be extensive, and may cause death. (7) Traumatic lesions, such as the passage of a bullet through the brain, or a blow upon the head, or concussion from high explosives, may cause extensive thrombosis or hæmorrhage. (8) Cerebral hæmorrhage results often enough from the direct rupture of a true aneurysm or angioma, or of one of those irregular local thinnings of the vessel wall which is called a "false aneurysm", and may take place from an artery the wall of which is softened by disease, though there be neither thinning nor bulging of the vessel wall.

Syphilitic cerebral thrombosis is not usually a pure pathological process, for the vascular disease is often accompanied by acute syphilitic encephalitis, with much lymphocyte extravasation in the vicinity of the diseased vessels, and acute local œdema, which increase the ischæmia when thrombosis occurs. The symptoms of loss of

cerebral function are not all due to the thrombosis, but are in part due to the recoverable acute inflammatory condition, and it is for this reason that syphilitic apoplexy often shows much more recovery than do other varieties.

Thrombosis is a more common cause of apoplexy than is hæmorrhage, but it is much more frequently survived, while hæmorrhage is frequently fatal, within from a few hours to a few days of its onset. It follows, therefore, that in the necropsy room of a general hospital, hæmorrhage is seen much more often than is thrombosis, while in infirmaries, where the survived cases of apoplexy collect, thrombosis is almost invariably the lesion found to be responsible for the apoplexy.

Thrombosis tends to occur when an habitually high blood pressure is temporarily lowered and the circulation less active, and is always strongly suggested when apoplexy occurs during sleep and conditions of quiet, and after exhaustion, exposure to cold, severe purgation and in debilitated states generally. It is preceded by slowing of the circulation in the area affected, and this may be productive of prodromal symptoms. Or there may be slight local thromboses preceding the main thrombosis, also giving rise to prodromal symptoms. Thrombosis may thus have an ingravescent onset, especially when clotting occurs in distal branches of an artery and extends towards the main vessel; but, on the other hand, it may have an absolutely sudden onset when the clotting occurs primarily in a large artery. The immediate effect of the thrombosis is a condition of infarction with œdema, extending widely in the vicinity, and it is this œdema which causes the loss of consciousness so commonly seen a few hours after the apoplexy has occurred. The œdema tends to pass off in a few days, and the area bereft of circulation by the thrombosis tends to become narrowed by collateral circulation from surrounding regions, and any recovery of function within the affected region must be by collateral circulation from elsewhere. In many cases, however—perhaps the majority of those which are clinically ascribed to cerebral thrombosis—actual thrombosis does not occur, but cerebral tissue to which the circulation has been inadequate for a long time eventually undergoes softening rather abruptly. There is little essential difference between the two groups of cases, and it is customary to apply the term cerebral thrombosis to all. The affected area at an early stage is bright red in colour, and soon becomes soft and shrunken (red softening). Later, the blood pigments degenerate with the production of bilirubin and are partly absorbed, producing a yellow-coloured lesion (yellow softening). Finally, much of the softened tissue becomes necrotic and is absorbed, leaving one or several cystic cavities. These cavities are never so sharply defined as those resulting from embolism, because of the more complete necrosis occurring with the later lesion. Still, a severe arterial thrombosis occurring at an early age may result in a porencephaly. Cavities found in cases of apoplexy after years have elapsed, are too often attributed to hæmorrhage; in reality they are nearly all due to thrombosis. The cerebrospinal fluid in thrombosis is never found to contain blood, but some little time after the apoplexy it is often coloured yellow or yellowish-brown from escape of changed blood pigments, when the lesion has reached the surface of the convexity or the surface of the ventricle, and pleocytosis may be found after a recent softening.

Hæmorrhage, which is usually described as an apoplexy of sudden onset, may be so when the escape is from a large vessel. When the bleeding commences from a smaller vessel, the symptoms are not sudden in their onset, but gather rapidly. Such a hæmorrhage is much like an avalanche. Commencing from a small vessel the hæmorrhage tears a small cavity, and in so doing opens up fresh bleeding points, and with increasing destruction more and more bleeding occurs from every piece of torn tissue, until the hæmorrhage reaches such a size as to burst, commonly into the ventricle, and much more rarely on to the surface. Indeed, it is difficult to conceive how a hæmorrhage into such a soft and vascular tissue as is the brain should ever stop. As a matter of fact, it rarely does so, but causes death in the first attack of hæmorrhagic apoplexy, within from a few hours to a few days after the onset, from widespread

tearing up of the nervous tissue and bursting into the ventricle. One of the most important clinical distinctions between apoplexy due to thrombosis and apoplexy due to hæmorrhage is that the former is often survived, and that the latter is almost invariably fatal within a short time of the onset.

Hæmorrhage may occur anywhere within the nervous system, but its common seat of commencement is in the centrum semiovale, and the vessel which bursts is one of the perforating arteries, of which the lenticulo-striate which carries the name of the "artery of hæmorrhage" is the most common. Such bleedings are often called "capsular hæmorrhages". It must be pointed out that this term capsular refers to the region outside the corpus striatum or external capsule, and not to the compact internal capsule as it converges to the crus cerebri. The cerebrospinal fluid in cases of hæmorrhage contains blood within a very short time of the onset.

While both thrombosis and hæmorrhage may occur in any part of the brain, the semi-oval centre, the calcarine region and the pons are the common sites of both of them in that order of frequency. Hæmorrhage is rare except in these regions, while thrombosis is not uncommonly met with elsewhere.

**Symptoms.**—The nature of the symptoms in apoplexy will depend upon the site of the vascular lesion; and as the semi-oval centre is the commonest site, and as many arteries supply the fibres of the pyramidal tract in different parts of its course, hemiplegia is the common result: if the lesion is in the left hemisphere some degree of aphasia is commonly associated with the hemiplegia.

Thrombosis of the *anterior cerebral artery* in its distal portion causes paralysis and postural sensory loss in the contralateral leg, but if the vessel is thrombosed proximal to the origin of the artery of Heubner—which supplies part of the anterior limb of the internal capsule—the contralateral arm and face are also affected, so that hemiplegia results. The *middle cerebral artery* is rarely thrombosed as a whole except in syphilitic cases, which are now uncommon: thrombosis of the whole of this artery causes such extensive destruction in the corresponding cerebral hemisphere that the most severe hemiplegia, with postural loss and hemianopia results, accompanied by severe aphasia if the lesion is on the left side. Both of these arteries may be involved when thrombosis occurs in the *internal or common carotid artery*. The frequency of this condition has been disclosed by arteriography. In such a large artery the clot is at first mural and portions of it may break off and cause emboli in branches of the derived arteries. When the lumen of the internal carotid artery becomes completely obstructed the anterior and middle cerebral arteries continue to receive blood by way of the circle of Willis, and even the ophthalmic artery, which takes origin just before the bifurcation usually receives a blood supply sufficient to prevent the occurrence of blindness in the corresponding eye. While the middle and anterior cerebral arteries may remain patent the blood supply to them through the circle of Willis may be inadequate and, especially in elderly subjects, successive softenings of greater or less degree may therefore occur in the hemisphere of the affected side. It is consequently not uncommon for two or more incidents of partial hemiplegia to occur with intervals of days or weeks, or even months between them. The severity of the clinical pictures that may result from carotid thrombosis is consequently subject to very great variation, but in quite a number of cases the paralysis is surprisingly slight, and it is only by arteriography that the condition can be confidently diagnosed. In the worst cases, however, all the arteries derived from the internal carotid may be thrombosed and the condition may be fatal in the acute stage. In some instances both internal carotid arteries have been found to be occluded, and these have usually been cases of dementia. There is evidence that the thrombosed carotid artery may become recanalised. A considerable number of the patients who suffer from carotid thrombosis are men in the first half of life and trauma to the neck may be an important ætiological factor; in older patients the condition is usually associated with atheroma.

When the *posterior cerebral artery* is thrombosed the outstanding sign is contralateral hemianopia with sparing of the fixation point.

*Pontine apoplexy* involves the appearance of motor and sensory hemiplegia—first on one side and then on the other with the onset of coma; involvement of cranial nerve nuclei, e.g. with loss of lateral movements of the eyes—may be the first sign.

Cerebellar apoplexies and thrombosis of the *posterior inferior cerebellar artery* produce acute ataxia with forced movements and vomiting (p. 1440).

The onset in hæmorrhage is almost always rapid and may be sudden; in thrombosis it may be sudden or ingravescent; with embolism it is always instantaneous. Consciousness is lost or not, according to the severity of the initial lesion and the site it occupies, and to the magnitude of the processes which follow the initial lesion, namely, the œdema of embolism and thrombosis and tearing of the brain tissue in hæmorrhage. In hæmorrhage, consciousness is lost soon, and the rapid development of severe symptoms which progressively deepen, is a most important early indication that this is the nature of the lesion. In calcarine thrombosis the initial symptoms may be so slight as to pass unnoticed by the patient, whose first indication of defect may be, that he runs into objects on his blind side. Convulsion sometimes occurs at the onset, and this nearly always indicates thrombosis, rarely embolism, and never hæmorrhage. There may be some local spasm in the region of the cranial nerves in pontine hæmorrhage, but this is not convulsion.

*Conjugate deviation of the eyes* is a common feature of all apoplexy. When the lesion is irritative at its onset, and not too destructive, and always when convulsion occurs at the onset, there may be active conjugate deviation, the eyes being turned away from the side of the lesion and towards the paralysed or convulsed side in hemiplegic cases, or the blind side when hemianopia is present. But this active conjugate deviation lasts but a short while and is followed by a paralytic conjugate deviation in the opposite direction, both eyes being directed away from the paralysed side and towards the side of the lesion. This variety of conjugate deviation may last for a considerable time, but usually disappears with the onset of deep coma.

The pupils are often unequal; they may be contracted, or dilated widely, and may be insensitive to light. In severe apoplexy, when as the result of the cerebral shock or when hæmorrhage or œdema has so raised the pressure as greatly to reduce the physiological activity of all the intracranial elements with the production of deep coma, the pupils are widely dilated and insensitive. In pontine lesions, the pupils are often contracted to pin-point size, and this condition is of important localising significance.

In proportion to the severity of the general intracranial disturbance, respiration tends to be hurried, noisy and stertorous, and with increasing pressure to become irregular, grouped or of the Cheyne-Stokes type. The blood pressure tends to be raised and the pulse full in all conditions of apoplexy, provided the heart will respond to the requirement of an increased blood pressure in the face of an increased intracranial pressure. Swallowing is often impossible, and the sphincters may be relaxed or retention may occur.

In the usual variety of apoplexy where the lesion is in the area of the middle cerebral artery and the local sign of the lesion is hemiplegia, it will be obvious that when the general intracranial pressure becomes severe and the coma becomes deep, the hemiplegia becomes less apparent, or masked by the universal condition of paralysis consequent upon the general intracranial condition. The physician often sees the patient for the first time when there is considerable coma, and he must determine upon which side the lesion is situated, and endeavour to have some perspective as to prognosis by determining the severity of the lesion.

The following points will serve to determine the side of the lesion when these signs are present: (1) The paralytic conjugate deviation is towards the side of the lesion. (2) The corneal reflex, when any is present, is diminished or lost on the

hemiplegic side. (3) Painful stimulation will elicit less response or no response upon the hemiplegic side (hemianæsthesia). (4) The patient may respond by blinking to a feint made with the observer's hands towards the patient's eyes upon the sound side, and not on the hemiplegic side (hemianopia). (5) The limbs on the hemiplegic side when raised and allowed to fall passively, do so in a more lifeless, inert and flaccid fashion than upon the sound side. (6) And when there is any difference between the knee-jerks, abdominal reflexes and plantar reflexes, the former tend to be diminished and lost on the hemiplegic side while the plantar reflex will be of the extensor type on the hemiplegic side. It must be remembered in this connection, that a severe lesion of one cerebral hemisphere abrogates for a time at least most of the functions of the whole hemisphere, and that the hemianæsthesia and hemianopia, here referred to, do not necessarily indicate that the destructive lesion involves the visual and sensory paths. And further, that the condition of coma due to increased intracranial pressure of itself causes such signs as bilateral loss of abdominal reflexes and knee-jerks, and bilateral extensor responses in the plantar reflex.

The severity of the lesion may be judged—(1) From the depth of the coma; (2) from the degree to which the patient responds to any form of stimulation and from the general signs of nervous depression present—for example, a condition of complete bilateral flaccidity with complete loss of all reflex action and of all response to stimulation indicates a most severe lesion and (3) from signs of failure of respiration as shown by irregular, grouped or Cheyne-Stokes breathing. It is further important to arrive at a determination if possible as to whether the condition present is stationary, deepening or showing signs of amelioration.

Vomiting is not an uncommon occurrence in the early hours of apoplexy and before coma becomes deep. Hyperpyrexia is often seen in fatal cases before the end. It is especially common and may reach a high degree in pontine apoplexy. It may be preceded by initial depression of temperature. It is of fatal prognostic import.

Hemiplegia is the commonest sequel of vascular lesions of the brain. The signs which serve to indicate its presence in the comatose subject have already been enumerated. After cerebral thrombosis it may happen that the initial hemiplegia is completely recovered from, but unless this recovery begins early and progresses rapidly it is not likely to be complete. The essential feature of hemiplegia is the loss of voluntary movements on one side of the body, but as this loss begins to pass off, certain new features make their appearance. These are muscular hypertonus, increased tendon jerks and associated movements.

The restoration of movements follows a certain order. Deviation of the tongue and facial asymmetry clear up early; next, the leg begins to recover; and finally—and often very incompletely—the arm. The return of movements in the limbs is selective. In both upper and lower limbs, movement at the proximal joints recovers first and most completely. In the leg, extension and plantar flexion recover more completely than flexion and dorsiflexion. As a result, the patient can often stand when he cannot lift the foot and leg to step properly, and has instead to circumduct the limb when walking. In the arm, flexion movements recover first and best, while the fine skilled movements of the hand and fingers are frequently lost for ever.

The development of hypertonus, or spasticity is as selective as the return of movements. In the leg, the extensor group of muscles becomes spastic; in the arm, the flexor group. Thus, the arm tends to take up a position of adduction, with flexion at elbow, wrist and digits. The leg is always spastic in extension, and does not go into flexion contracture, as may happen in spastic paraplegia from spinal cord lesions. The degree of hypertonus varies, and is greatest when the loss of movement is greatest.

The tendon jerks are exaggerated, and there is clonus (knee and ankle) in the affected limbs. The Babinski plantar response persists, but the abdominal reflexes, which are initially lost on the affected side, sometimes return after a period of months.



The forced immobility of shoulder and distal joints in the arm may lead to the formation of adhesions.

The so-called associated movements are involuntary changes of posture of the paralysed limbs which accompany forceful voluntary movements, or such involuntary movements as yawning.

**CEREBELLAR APOPLEXY.**—This is usually the result of thrombosis of the posterior inferior cerebellar artery, which is a branch of the vertebral artery, and the clinical picture is very unlike that of cerebral apoplexy. The patient is seized with a sudden intense vertigo which throws him to the ground, as in Ménière's disease. Incessant vomiting and forced movements follow, the forced movements rotating the patient, so that he comes to rest prone, with that side of the face corresponding with the side of the cerebellar lesion in contact with the pillow. There is intense ataxy, usually bilateral at first, and later becoming confined to the limbs and trunk on the side of the lesion. The patient is unable to lift his head, or to maintain the sitting or standing position. When placed in such a position he positively dives to the ground when released. Nystagmus with the long slow movement to the side of the lesion, and a short fast movement in the opposite direction is conspicuous and the skew deviation of the eyes is sometimes seen. There is much general hypotonia of limbs and trunk which soon becomes limited to the side of the lesion. Head retraction, pain and stiffness of the neck and opisthotonos may occur. When the patient's condition recovers sufficiently to allow of examination, all the signs of a unilateral cerebellar lesion will be found. Consciousness is not often lost. Since the posterior inferior cerebellar artery also supplies the lateral region of the medulla, signs indicative of disturbance of this region are usually present, and these may dominate the clinical picture rather than the cerebellar signs. Chief amongst them are analgesia and thermaesthesia of the face and head, due to implication of the as yet uncrossed spinothalamic path, and of the limbs and body upon the opposite side, due to involvement of that part of the spinothalamic tract which has crossed below this level. Between these two areas of sensory loss there is often a gap where sensibility is normal, corresponding with that part of the spinothalamic tract which is crossing obliquely at this level, and therefore is too near the middle line to be affected. Paralysis of the motor vagus is often found from involvement of the nucleus ambiguus, and, from the extension of the lesion or of consecutive oedema towards and across the middle line, it sometimes causes severe dysphagia and dysarthria, and one of the great dangers of this form of apoplexy is extension of the thrombosis to that part of the medulla which contains the respiratory and other vital centres. When, however, such extension does not take place, and if the destruction of the lateral lobe is not too extensive, the most remarkable recovery may take place.

**Diagnosis.**—*The nature of the lesion.*—Thrombosis should be diagnosed, notwithstanding the presence of high arterial tension or renal disease, in all cases of apoplexy without organic cardiac valvular disease, when the onset occurs during sleep or under circumstances of quiet, depletion or exhaustion, and in all cases where prodromal symptoms are marked, or where the onset of the apoplexy is gradual, and in apoplexies occurring in advanced age, for then hæmorrhage is almost unknown. All slight apoplexies and nearly all those that survive the first 10 days after the ictus, are due to thrombosis. Thrombosis should be diagnosed in all primary apoplexies in young syphilitic subjects, and in this connection the serum reaction and the cytology and reactions of the cerebrospinal fluid are all-important in the diagnosis.

Puerperal apoplexy is mostly due to thrombosis of cerebral veins (see p. 1452).

The cerebrospinal fluid affords important indications, since hæmorrhage into the brain in most of the cases soon leaks on to the surface or into the ventricle. If blood is absent from this fluid a few hours after the ictus, thrombosis or embolism is highly probable and hæmorrhage is very unlikely. Any infarction coming to the surface may in the course of time cause the fluid to be blood-tinged or yellow. It is

important to bear in mind that the infarct conditions of embolism and thrombosis are followed by packing of the infarcted region with polymorphs, and that these may escape from the surface in such numbers as to load the cerebrospinal fluid with such a high polymorph pleocytosis as to suggest the presence of suppurative meningitis.

Hæmorrhage is a likely cause of apoplexy occurring during exertion, especially if it occurs at a moment of severe physical strain, or at the height of passion. It is always a probable lesion in cases where a previous thrombotic apoplexy has occurred, the final event, where multiple strokes have succeeded one another, being almost invariably hæmorrhage. An apoplexy with rapid onset and with symptoms rapidly deepening, with a quick onset of deep coma, and the development of pyrexia and signs of respiratory failure, is usually due to hæmorrhage. The certain test that an apoplexy is due to hæmorrhage is the presence of blood in quantity in the cerebrospinal space as proved by lumbar puncture. In cases of chronic nephritis and malignant hypertension, where the blood tension is very high, and where there is severe retinitis, hæmorrhage is the most likely cause of stroke.

Embolism should be diagnosed in all cases in which there is an obvious cardiac valvular lesion, particularly mitral stenosis, septic endocarditis, aortic disease or aneurysm. It is true that syphilitic cerebral thrombosis may occur with syphilitic aortitis, but the combination is rare, for syphilitic aortitis usually occurs at a much later age than does syphilitic cerebral thrombosis.

*The position and extent of the lesion.*—The position of the lesion may be judged by the nature of the initial signs, whether visual, sensory, motor or aphasic, cerebellar or pontine, and later by the permanent symptoms resulting from the lesion. It must be carefully borne in mind in this connection, that a severe lesion of a cerebral hemisphere may entirely abrogate the functions of that hemisphere during the acute stage, initially by a process of shock and afterwards by the occurrence of œdema in the vicinity of the lesion, which may spread widely. The extent of the lesion may be gathered by the severity or otherwise of the early symptoms and their rate of increase, and by early or immediate loss of consciousness, and by the completeness of the paralysis resulting. The more severe the extent of the lesion the sooner do grave signs of general cerebral failure appear.

*Differential Diagnosis.*—The diagnosis of coma due to a cerebral vascular lesion is usually made without difficulty from the history, and from the presence of unequivocal signs of local lesion of the brain. In a patient without history, and when the coma has become so deep as to remove the unilaterality of physical signs, the diagnosis may be difficult from other causes of coma such as uræmia and diabetes, poisoning by opium, alcohol and its derivatives and coal gas, and in cases of difficulty search is to be made for the usually obvious signs of these conditions. Uræmia may present especial difficulties, for it is often associated with cerebral vascular lesion, and transient hemiplegic attacks may occur in this condition. This is true also of the crises of essential hypertension, which are described in more detail on p. 1444. Absolutely sudden death which is so often recorded in death certificates as due to apoplexy, is usually associated with cardiac infarction. Apoplexy never causes sudden death. There is one recorded case of death from cerebral hæmorrhage in 5 minutes, but it is rare in any apoplexy for death to occur in less than 2 hours. Other conditions causing hemiplegia with coma must be taken into consideration. Epilepsy, especially when the convulsion is unilateral, may be followed by marked unilateral paralysis (Todd's paralysis), which may last for a considerable time. Here the history of recurring attacks and the complete recovery will easily prevent confusion.

Cerebral malaria and heat-stroke may closely resemble apoplexy, and should always come to mind when rapid coma follows the development of cerebral symptoms in circumstances where these causes are likely. The congestive attacks of general paralysis of the insane are peculiarly difficult to diagnose from apoplexy, and especially

so when occurring as the initial manifestation of the disease. These attacks take the form of rapidly occurring attacks of hemiplegia, aphasia, hemianopia, hemianæsthesia or of some combination of these conditions, usually associated with initial convulsions and followed by coma. The diagnosis of a syphilitic thrombosis is made with reason because of the positive serum reactions, and cerebrospinal fluid examination. If energetically treated, the patient recovers with rapidity and completeness. It is the too rapid recovery in a case of apparent syphilitic thrombosis which should suggest the possibility of the stroke being a congestive attack in general paralysis of the insane.

In all cases of coma without history, especially when there are signs of local cerebral involvement, a careful examination of the head should be made for traces of recent injury.

**Prognosis.**—In thrombosis due to atheroma the apoplexy may be rapidly fatal from extension of the thrombosis and secondary œdema. In cases which survive, considerable recovery may occur in proportion to the extent of the lesion, but in these subjects an apoplexy is usually the beginning of the end, since the underlying pathological causes, arterial disease and failing cardiac action, still exist and are not amenable to any radical treatment. It is astonishing, however, how many of the cases of apoplexy due to atheromatous thrombosis survive for years without any recurrence of the thrombosis or occurrence of hæmorrhage. A majority of the cases of apoplexy from syphilitic thrombosis make a fair recovery, which obviously depends upon how much permanent thrombosis occurs in the lesion of acute syphilitic encephalitis which is responsible for this condition, and upon the early application of appropriate treatment for syphilis. In some of these cases even, no recovery occurs.

In cases of hæmorrhage, the immediate prognosis is the gravest possible, the great majority of the cases surviving but a few hours.

**Treatment.**—When arterial disease is known to be present, the only measure which can in any way tend to safeguard the patient from apoplexy is moderation in all things: in diet, alcohol, mental and physical exercises, and above all moderation in all measures tending to cause marked variation in blood pressure. It is highly probable that no treatment influences the course and fatal issue of apoplexy due to hæmorrhage. Thrombosis and embolism, however, allow some scope for treatment, which should be the same in the two conditions; and as medical treatment in cases of hæmorrhage is useless and cannot avert the fatal result, one line of treatment may be recommended in all cases of apoplexy.

Absolute rest is, in the first place, essential when prodromal symptoms appear. Restlessness may be combated with bromides. If the patient is conscious, he should make as little effort as possible. His head and shoulders should be raised, special care being taken that the neck is not bent, and that nothing shall interfere with the return of blood from the head. If there is unconsciousness with stertor, the head and shoulders should be turned upon one side, so that the tongue does not fall back and impede respiration. Purgation should be avoided, and the bowel relieved at intervals by enemata. Food in a liquid form should be administered at regular intervals; and if there is any difficulty in swallowing, the food should be administered with the nasal tube. The bladder should be carefully watched from the first, lest retention should occur, and the catheter passed when necessary. Lumbar puncture should, when necessary, be performed for diagnostic purposes, and it frequently gives relief from symptoms due to the high intracranial pressure. Bed-sores and hypostatic bronchitis must be avoided by the usual measures. In the cases that survive the first few days, passive movements should be used daily to all the joints of the affected side in hemiplegic cases, for this will obviate the painful residual adhesions which form in the joints of the paralysed limbs, and especially in the shoulder joint, and subsequently cause so much pain and misery to the patient. With the return of the power of voluntary movement, active exercises take the most important place in treatment. The final stage of hand-and-finger movements depends

not alone on the severity of the damage done to the brain, but in part upon the thought given to devising active exercises for it and the assiduity with which the patient can be persuaded to employ them. To avoid fatigue it is best to ordain a given daily period of some minutes for systematic exercise. A rubber sponge of appropriate size, fixed in the palm by a strip of webbing passing round the hand, will limit the passive flexion of the fingers, and will provide a resilient resistance against which the patient may move his paretic digits. Massage is an adjuvant, but never a substitute, for active exercises in the patient who can undertake them. Electrical stimulation of the muscles is absolutely contraindicated. It has no other effect than to aggravate the spasticity that is so serious a hindrance to free movement. A hemiplegic patient after apoplexy, should be got upon his legs and encouraged to make attempts to walk as early as ever the returning power allows any possibility of the attempt.

## GENERALISED CEREBRAL ATHEROMA

**Ætiology and Pathology.**—For the ætiology and pathology of atheroma the articles on pp. 835, 919 should be consulted. In many subjects the cerebral arteries are affected at an earlier age and more severely than any others in the body. Males are the victims of generalised cerebral atheroma more often than females, and the symptoms, though most common in the sixties and later, are recognisable in the more severe cases soon after the age of 50. The brain is the seat of innumerable minute vascular lesions. There are numerous small softenings on its surface, and the cerebral cortex becomes thinned in consequence of degenerative changes. In the central parts of the brain, especially in the basal ganglia, small cysts develop from the softenings and eventually a mesh-like condition—the status lacunatus—may result.

**Symptoms.**—The onset of this condition is insidious and its course steadily progressive. Mental or physical changes may predominate and both are liable to abrupt exacerbations which are to be attributed to small cerebral vascular lesions. The mental symptoms are often noticeable first. The patient's range of interests becomes reduced and intellectual activities of all kinds are gradually discarded. Memory for recent events becomes faulty, while that for events long past remains unimpaired. Confusion is liable to occur and the patients become unable to adapt themselves to new circumstances and are obstinately conservative. Emotional control becomes impaired, and affective response may be inadequate. Previously existing tendencies to anxiety, or depression or paranoid traits may become exaggerated. Confusion and lack of attention may lead to incontinence and disorders of dress. Dysphasia is common and apraxia may also occur.

The physical symptoms take the form of a slowly developing muscular rigidity which has been called "pseudo-Parkinsonism". The facies becomes "set", movements become less free and in walking the step becomes gradually shortened until it may be only a few inches; this *marche à petit pas* is very characteristic. The patient becomes unable to relax his muscles and if as he lies in bed passive movements of the limbs are attempted by the examiner, great resistance is encountered. The grasp reflex may be discovered in one or both hands. The tendon jerks are exaggerated and the plantar reflexes indefinite or weakly extensor.

In some instances the most pronounced physical feature is a spastic paralysis of the muscles innervated from the pons and medulla and hence called "pseudo bulbar-palsy". The physical basis of this syndrome is uncertain; the lesions concerned are bilateral and may be situated in the anterior parts of the internal capsules or possibly in the brain-stem itself. The facies becomes set, voluntary movements of the lips are restricted, the tongue is spastic and looks small and cannot be protruded beyond the teeth, and movements of the palate, pharynx and vocal cords are all

similarly limited. The result is dysarthria of a degree which may render the patient's speech unintelligible, together with difficulty in mastication and in swallowing (dysphagia). There is no muscular wasting. The jaw jerk is exaggerated. The lips may be held apart and the saliva trickles from between them. Emotional movement temporarily inhibits the rigidity of the facies and is exaggerated as a consequence of the pyramidal impairment. Moreover, in consequence of the bilateral pyramidal disturbance uncontrolled laughter or crying may occur, and there is usually a tendency towards one or the other so that the patient who suffers from uncontrolled laughter may laugh even on hearing bad news, and the patient who suffers from uncontrolled crying may weep when he is amused. General atheroma is usually well marked and arterial hypertension may or may not be present. The state of the retinal arteries is not a reliable guide to that of the cerebral arteries.

**Diagnosis.**—If mental symptoms predominate in the early stages the diagnosis will have to be made from general paralysis of the insane and the absence of characteristic signs of nervous syphilis, together with negative findings in the blood and cerebrospinal fluid, will exclude the latter. Other forms of pre-senile dementia, such as Alzheimer's disease (see p. 1630) and Pick's disease (p. 1629), are not associated with the same degree of motor disturbance as is usual in atherosclerotic dementia. When physical symptoms predominate, the presence of atheroma and signs of early dementia, and usually the absence of tremor, differentiate the condition from paralysis agitans. When pseudo bulbar-palsy is present, the diagnosis from motor-neurone disease (amyotrophic lateral sclerosis) may be difficult, but the complete absence of wasting, the presence of rigidity in the facies and upper limbs and the association of atheroma are usually sufficient to make the distinction. When arterial tension is high and changes in the optic fundi are present the picture may closely resemble one of cerebral tumour, and the differentiation depends largely on the presence of arterial hypertension and the extensive retinal lesions, which distinguish neuro-retinitis (hypertensive neuro-retinopathy) from the papillœdema of raised intracranial pressure.

**Prognosis.**—The course of the disease is gradually downward and may at any time be terminated by a severe "stroke", but in general the patients survive for years and severe cerebral vascular accidents are uncommon among them. In the end the patient becomes bed-ridden and dies in consequence of an intercurrent infection, or, when he has reached a debilitated state, from a terminal cerebral thrombosis.

**Treatment.**—This can only be symptomatic, and the patient should be kept up and about as long as possible. It is unfair and unwise to put too much dietary restriction on him, and if he is a small or moderate eater no further limitation is required.

## HYPERTENSIVE ENCEPHALOPATHY

In a preceding paragraph on the differential diagnosis of apoplexy (p. 1441) mention was made of the sudden and transient cerebral symptoms associated with essential hypertension, and some further reference to them is necessary. It is known that the subjects of this variety of hypertension may ultimately succumb to cerebral hæmorrhage, but it should also be borne in mind that they are subject from time to time to what are known as "hypertensive crises". Similar attacks occur in acute nephritis and eclampsia. The patient has a high blood pressure. The attack is precipitated by a further rise in this, and develops with intense headache, sickness and sometimes drowsiness or even semi-coma. Examination will reveal the presence of hypertensive retinitis in most cases, but in a proportion there is a definite papillœdema with retinal hæmorrhages and exudate. Accompanying these symptoms there may be hemiparesis, hemianopia, focal or generalised fits, or other indications of a local cerebral lesion. The crisis is brief, lasting from a few hours to several days, and usually ends in recovery, but recurrence is likely, and finally many subjects develop

cerebral atheroma and succumb to cerebral hæmorrhage. Intervals of several months may intervene between succeeding crises.

The presence of papillædema is taken to indicate that cerebral œdema is complicating the situation. The transient nature of the crisis, and particularly the rapid appearance and disappearance of such symptoms as hemiparesis, exclude the possibility of arterial thrombosis or other material lesion of the kind, and spasm of the arteries has been invoked to account for the symptoms. There is no conclusive evidence that this occurs. Yet while the cerebral arteries are not under the same measure of vasomotor control as arteries elsewhere in the body, it is known that some such control exists, and it may be that in arterial hypertension more intense spasm is possible than in healthy arteries. At least, it may be said that no hypothesis better founded or more in harmony with the facts of clinical observation has been formulated.

**Differential Diagnosis.**—As has been indicated, the transitory character of the symptoms excludes gross vascular lesions such as thrombosis, and the same may be said of intracranial tumour and lead encephalopathy. Yet it may be admitted that while it is present the hypertensive crisis shows many points of resemblance to the last two named conditions, especially when papillædema is found. Plumbism in children and young persons not uncommonly develops with headache, vomiting, convulsions and focal signs, and the development of an intense papillædema, sometimes also with high blood pressure and albuminuria, and search for other indications of lead poisoning and careful history-taking are necessary to exclude this condition. In intracranial tumour, the systolic blood pressure is rarely above normal limits, the history is longer and the condition progressive. Uræmia can usually be excluded, since in essential hypertension the blood urea is within normal limits, and the only abnormality in the urine may be a trace of albumin.

**Treatment.**—Venesection is indicated as the first step, and when there is papillædema or other signs of cerebral œdema (convulsions, high cerebro-spinal fluid pressure) lumbar puncture and the withdrawal of cerebrospinal fluid, and also the intravenous or intramuscular administration of hypertonic solutions are necessary. As a measure of urgency from 50 to 70 ml. of a 50 per cent. solution of dextrose or sucrose may be given intravenously. For less urgent cases and as a measure that can be repeated for the relief of headache, 6 oz. of a 20 per cent. solution of magnesium sulphate may be given per rectum at 6-hourly or less frequent intervals. The convulsions may be treated by rectal administration of paraldehyde (240 to 360 minims in water), or by the hypodermic injection of gr. 3 of soluble phenobarbitone in solution.

The subsequent management of the case is that of the underlying essential hypertension: it should be borne in mind that the use of potent detensive drugs in patients with diseased cerebral vessels is accompanied by a great risk of thrombosis..

## CEREBRAL EMBOLISM

Cerebral embolism is infinitely less common than thrombosis.

**Ætiology.**—The embolus may be: (1) a fragment of blood clot, (2) a vegetation or detached portion of one of the cardiac valves or in rare instances an atheromatous plaque, (3) air bubbles or (4) globules of fat.

(1) The commonest cerebral embolus is a detached fragment from a clot which has formed in the left auricle in a case of auricular fibrillation. Less frequently it comes from a clot in the dilated auricular appendage in a case of mitral stenosis without fibrillation, or from one on the inner surface of the infarcted ventricular wall after coronary thrombosis. Other sources of clot emboli are aneurysms of the large vessels between the heart and the brain, a clot covering an atheromatous ulcer in the first part of the aorta, and clots which may form in the pulmonary veins and even in

the left heart in suppurative conditions of the lungs. In exceptional cases a congenital heart lesion may provide a route by which emboli from the systemic veins can reach the brain without passing through the lungs—paradoxical embolism (see p. 897).

(2) The emboli of the second group are most commonly small portions of infected vegetations from the cardiac valves in cases of subacute bacterial endocarditis. In other instances larger emboli are formed by vegetations from acute bacterial endocarditis.

(3) Air emboli are usually multiple. They may occur in association with operations on the lungs, and in the course of almost any operation in which a vein of medium or large size is opened. While emboli of more solid character will not pass through the pulmonary capillaries it is probable that air emboli do so, and consequently air emboli from almost any part of the body may reach the cerebrum. The commonest single cause of air embolism to-day is probably damage to the surface of the lung by the needle in the course of producing or refilling an artificial pneumothorax, and it occurs also during major operations on the lung. It may follow insufflation of air into the vagina, or it may occur in association with retained placenta, and even as a result of division of veins during the operation of Cesarean section.

(4) Fat emboli are a cause of cerebral complications after fracture of one of the long bones, and may cause death. Like air emboli, fat globules pass through the pulmonary filter.

Emboli usually pass into the middle cerebral arteries or their branches, because these are the direct continuation of the carotid arteries. Very rarely the internal carotid is obstructed, but if it is the circulation in its branches is usually maintained by the circle of Willis. Next in frequency is the posterior cerebral artery, and then the vertebral. Because of the mode of origin of the left carotid artery, emboli affect the left half of the brain more frequently than the right. In a case of subacute bacterial endocarditis, the cumulative effect of innumerable minute infected emboli may cause extensive softening in the left hemisphere at a time when the right hemisphere is little affected.

**Symptoms.**—The onset is immediate. A stroke due to embolism is the most suddenly occurring of all the apoplexies and there are no prodromal cerebral symptoms. Unless a large vessel, such as the middle cerebral artery, be occluded consciousness is usually not lost, but a stuporose state may occur either with the onset or after a few hours, and may last several days. Hemiplegia is the common physical syndrome and it may be of all degrees of severity, according to the size of the cerebral lesion. When emboli are numerous and of small size, and particularly when they are infected, as in subacute bacterial endocarditis the development of hemiplegia may be gradual.

**Diagnosis.**—Embolism should never be diagnosed unless there is evidence of cardiac disease, aneurysm or some other recognised source of emboli, but in the presence of such disease, especially of auricular fibrillation, it is the usual cause of any stroke which may occur. The diagnosis should not be rejected simply because the manifestations of apoplexy are slight.

**Prognosis.**—In cases of auricular fibrillation, the hemiplegia is in many cases not severe and good recovery is frequent, but when a large vessel is occluded the hemiplegia is usually very severe and complete, and it remains so. Further embolism is likely to occur eventually. In other cases the prognosis depends largely on the course of the causal condition which is responsible, and whether the emboli are affected or not. In cases of bronchiectasis, for example, the emboli, being infected, generally give rise to multiple cerebral abscesses. Puerperal cases of cerebral embolism in the absence of cardiac and other disease usually do well.

**Treatment.**—As far as the cerebral lesion is concerned treatment is the same as for thrombosis. In most cases the condition responsible for the embolism calls more urgently for treatment, and in cases of auricular fibrillation complete rest for

several weeks and appropriate treatment of the cardiac disorder is essential, in order to diminish the risk of further emboli occurring.

## INTRACRANIAL ANEURYSM

Aneurysms within the cranium are common and may conveniently be considered in four groups.

(1) Minute atheromatous aneurysms of the arteries at the base of the brain are frequent and may be numerous in elderly subjects, but only in rare instances do they cause symptoms. The clinical disturbances to which they occasionally give rise result either from bleeding, or from their pressure on, and even adhesion to, the adjacent ocular nerves, and are thus similar to those of the more important group which follows.

(2) Of the remainder, the great majority are "berry" aneurysms situated on or near the circle of Willis. An aneurysm of this kind develops at a bifurcation of an artery in consequence of a congenital defect in certain individuals of the elastic lamina at this point. It is thus not congenital, but develops at the site of a congenital weakness. The importance of "berry" aneurysms is that they may, and frequently do, rupture, causing subarachnoid hæmorrhage. Otherwise only a small proportion of them give any evidence of their presence. Aneurysms situated on the posterior or lateral portions of the circle may interfere with the third cranial nerve, giving rise to paralysis, which is, as a rule, partial, and which may be either gradual or sudden in its onset. Less commonly aneurysms situated laterally on the circle compress the optic tract just behind the chiasma, and so produce homonymous defects in the visual fields, and in rare instances aneurysms on the anterior communicating artery cause pressure on the optic chiasma with consequent disturbance, possibly of variable intensity, in the central or temporal parts of the visual fields.

(3) Aneurysms of the internal carotid artery are usually situated within the cavernous sinus. Such an aneurysm may develop gradually, or, more commonly, after an initial period of slow development, it may dilate rapidly or even suddenly, until it comes into contact with the wall of the sinus; or, again, it may rupture into the sinus, becoming an arterio-venous aneurysm (see also p. 929). Whether the development of the aneurysm be slow or rapid, the various oculo-motor nerves and the branches of the trigeminal nerve situated in the wall of the sinus become affected. The patient experiences severe pain in one side of the forehead, or in the forehead and cheek, and if the onset is sudden, he may vomit. Double vision comes on rapidly and may proceed to complete paralysis of the third, fourth and sixth cranial nerves, but the paralysis is more often partial. Ptosis is always a feature. The affected eye may become proptosed. When the lid is raised the patient may find that vision in the affected eye is impaired, but in some cases within a few days the vision improves greatly and the pain passes off, some ocular paralysis and proptosis usually remaining. If the aneurysm is situated above the cavernous sinus (supra-clinoid carotid aneurysm), the optic nerve may be affected by direct pressure and progressive visual impairment may be the first symptom. By suitable radiographic technique erosion of the great wing of the sphenoid, or of some part of the sella turcica may be demonstrated, or some degree of calcification may be seen in the wall of the aneurysm. Aneurysms of the internal carotid artery may be demonstrated also by arteriography. In cases in which there is an arterio-venous communication a bruit may be audible with the stethoscope, either over the affected eye, or over the carotid artery in the neck. Such cases are frequently treated by ligation of the common carotid or of the internal carotid artery, after a trial period of compression.

(4) *Angiomatous Malformations.*—The frequency of angiomas of the racemose or cirroid type has been revealed by arteriography. They occur most often in



the territory of the middle cerebral artery and are almost invariably arterio-venous racemose aneurysms—that is to say, instead of a capillary bed, a tangle of blood vessels is interposed between the arterial and venous systems: the arteries feeding the malformation are hypertrophied and dilated, and the veins draining it are dilated and pulsating and they contain arterial blood. As most of the arteries enter the cerebral hemispheres from the surface these angiomas typically appear on the surface and extend in a sector, often with a roughly pyramidal shape, deeply into the hemisphere and may reach to the ventricle. Cerebral tissue is found between the vessels of the mass, and cerebral tracts evidently pass through it without being affected until hæmorrhage or thrombosis occurs. There is some evidence that these angiomas gradually enlarge. The vessels composing the angioma are not perfectly formed arteries but are vascular channels of very imperfectly differentiated structure; for the most part they have very thin walls of irregular thickness, composed chiefly of fibrous tissue with some fragmentary and irregularly distributed muscular coat and even wisps of elastic tissue in their walls.

These angiomas threaten the lives of their hosts by hæmorrhage, and the hæmorrhage may be either intra-cerebral or extra-cerebral (subarachnoid) or both. It may occur at any age from childhood onwards, and it is rare for an affected patient to reach middle age without having suffered a hæmorrhage. In many cases fits of some kind, local or general, precede signs of hæmorrhage and sometimes occasional fits occur over many years. A symptom which is typical, but by no means constant, is a systolic bruit; it may be heard with the stethoscope all over the head or only over the carotid arteries, and in most cases it is at times audible to the patient. Headaches are common and occasionally are of a typically migrainous type and associated with vomiting; in other cases they are associated with a feeling of stiffness in the neck and are suggestive of slight leakage from the aneurysm. Until hæmorrhage or thrombosis occurs there are usually no abnormal physical signs to be found on clinical examination. When the combination of symptoms is suggestive arteriography is called for and the diagnosis is dependent on this procedure.

In a special group of cases there is an external as well as an internal angioma, the external manifestation being usually situated in the territory of the trigeminal nerve (Sturges-Weber syndrome).

A considerable proportion of these malformations (other than the Sturges-Weber group) are amenable to surgical removal or palliative ligation of vessels.

In rare instances similar malformations occur in the brain-stem, and by reason of the aggravations which result from small hæmorrhages, and the consequent remissions, the clinical course of the patient's illness may be very similar to that of disseminated sclerosis.

#### SUBARACHNOID HÆMORRHAGE

**Synonyms.**—Spontaneous Subarachnoid Hæmorrhage; Meningeal Hæmorrhage.

Bleeding into the subarachnoid space may be an accompaniment of head injuries and it may also follow intraventricular hæmorrhage, but the usual cause of uncomplicated, or, as it is sometimes called, "spontaneous" subarachnoid hæmorrhage, is rupture of a cerebral aneurysm on the circle of Willis or on one of its component arteries. What has been called here the "berry" aneurysm may rupture suddenly and freely, with the production of fatal apoplexy, or there may be recurrent leaking of blood in small amounts from such an aneurysm, leading to a syndrome of meningeal irritation. Whereas with cerebral hæmorrhage the bleeding occurs into the substance of the brain, and the latter is severely and irrevocably damaged, with subarachnoid hæmorrhage the blood is effused chiefly outside and over the surface of the brain, and although there is still a risk that the immediate consequences of the apoplexy may be equally disastrous, if the event is survived the chances of full recovery are infinitely greater.

(1) *The apoplectic syndrome.*—The patient may have been subject to frequent headaches, or the episode may be quite unheralded until a sudden intense headache, rapidly followed by sudden lapse into unconsciousness, signals the free rupture of the aneurysm. It may be thought that an ordinary cerebral hæmorrhage has occurred when the comatose patient is first seen, but in uncomplicated subarachnoid hæmorrhage examination reveals no evidence of hemiplegia. On the other hand, a bilateral Babinski plantar response will be obtained and there will be marked neck rigidity. At first both pupils may be small and sluggish, but in fatal cases the pupils ultimately dilate. Examination of the optic fundi may reveal sub-hyaloid hæmorrhage or papilloedema. Lumbar puncture produces a fluid that resembles pure blood.

Recovery from hæmorrhage of this severity is by no means uncommon. In fatal cases death commonly ensues within 24 to 36 hours or at some time during the first fortnight from fresh bleeding. If this period be safely passed the prognosis as to recovery becomes good. The course of the illness may, however, be prolonged. The patient gradually recovers from coma, taking possibly many days to regain full and continuous consciousness. The temperature rises after 24 hours and remains at 99.5 or 100° F. for about a week, and the urine may contain abundant albumin and some sugar—either of which may lead to an erroneous diagnosis if the possibility of its occurrence be not known.

Headache is intense and may last for 2 or 3 weeks, with irritability and some stiffness of the neck. The knee-jerks or ankle-jerks, or both, are commonly abolished a few days after the onset, but they return after a further week or two and in slighter cases sooner. The patient who has recovered from his coma shows at first little intellectual activity, but answers rationally and briefly when questioned. A few weeks later, however, he is liable to manifest psychotic disturbances of the Korsakoff type, having no recollection of his visitors when they come again and giving them confabulatory accounts of his imaginary doings, which show that he is disorientated in place and time. This disturbance soon passes off completely and in some cases is almost ephemeral, and the patient eventually regains his full intellectual powers.

From such a severe illness not every patient rises unscathed. Focal damage may be caused, either by the hæmorrhage or by subsequent clotting. If the aneurysm lies close to, or partly embedded in, the brain, its rupture may cause considerable cerebral laceration, which if not fatal may leave partial hemiplegic weakness. If the aneurysm be at the bifurcation of the basilar artery, clotting in or around it may give rise to thrombosis in one of the branches entering the brain-stem, with resultant motor or sensory hemiplegia of the opposite side of the body, associated, possibly, with oculo-motor paralysis on the side of the new lesion. Oculo-motor palsies also arise from involvement of the nerves in clot, and strabismus is perhaps the commonest residual defect.

(2) *The meningitic syndrome.*—In this case, the hæmorrhage is less abundant and therefore consciousness may not be lost. There is violent headache, restlessness, delirium, rigidity of neck and spine, Kernig's sign, bilateral extensor plantar responses, and sometimes diplopia and squint. Within a few hours, or somewhat later, ophthalmoscopic examination may reveal the presence of flame-shaped hæmorrhages in the nerve fibre layer of the retina, or massive hæmorrhage in the sub-hyaloid space. The last-named is characteristic of subarachnoid hæmorrhage. A low-grade papilloedema is occasionally also observed.

In small leaking hæmorrhages the cerebrospinal fluid is more or less heavily bloodstained, and may for 2 or more weeks be discoloured, yellow or brownish according to the amount of blood originally present.

(3) *The lumbago-sciatica syndrome.*—This uncommon condition, first described by Hall, commences with pain and stiffness in the lumbar region, followed by pains in the legs, and sometimes the leg-jerks are absent. Pyrexia is the rule. The diagnosis

depends upon the characteristic cerebrospinal fluid of subarachnoid hæmorrhage. The explanation of this syndrome is not clear and it is probable that in some cases at least the source of the hæmorrhage is in the spinal canal.

**Differential Diagnosis.**—The recognition of subarachnoid hæmorrhage is an easy matter in those cases in which the train of symptoms calls at once for the examination of the cerebrospinal fluid and blood is found in the fluid. Prior to lumbar puncture the distinction from other varieties of cerebral hæmorrhage can often be made: (1) by the age of the patient, practically all hæmorrhagic apoplexy in the first half of life being the result of ruptured aneurysm; and (2) by the history of preceding symptoms, such as headache, diplopia, ophthalmoplegia and migrainous phenomena. Arteriography performed as soon as the patient is well enough may demonstrate the aneurysm.

**Prognosis.**—When the aneurysm ruptures frankly and widely and the bleeding can be free, the outlook is hopeless, and death occurs in from a few minutes to a few hours; nor does drainage avert the consequences of so large an opening into a main arterial trunk. If, as so commonly happens, there is a slower leakage which perhaps is intermittent, the outlook will depend: (1) upon the cessation of the bleeding and the healing of the leak by clotting; and (2) upon the possibility of the free escape of the effused blood into the subarachnoid space. In many of the cases of subarachnoid hæmorrhage, the bleeding ceases and healing of the aneurysm, by clotting and calcification, occurs with complete recovery. In other cases there may be repeated attacks of leaking at intervals of weeks, months or even years, and again, many of such patients make good recovery in the end.

**Treatment.**—In the case of subarachnoid hæmorrhage the patient must be kept absolutely at rest, with the administration of sedatives. An immediate injection of morphine is indicated when the patient is not comatose and has the usual intense headache. It may be necessary also on the recovery of consciousness on account of headache and restlessness. In general, repeated lumbar puncture is inadvisable, as it may lead to recurrence of hæmorrhage, but if there be signs of raised or of rising intracranial tension (and progressive slowing of the pulse is generally a reliable indication of this), then lumbar puncture may be expedient. When recovery sets in, the patient should still be kept in bed for at least 4 and possibly 6 weeks. During the first fortnight recurrent hæmorrhage is more likely to occur than later during the course of convalescence. When the aneurysm is appropriately situated ligation of the common carotid artery of the same side is sometimes performed and in a few instances the neck of the aneurysm itself has been ligated or clipped.

## CHRONIC SUBDURAL HÆMATOMA

**Synonym.**—Pachymeningitis Hæmorrhagica.

**Ætiology.**—This condition is a consequence of hæmorrhage from veins. The latter name, now superseded, expressed the belief that it was inflammatory, and it was supposed that it was more or less confined to chronic alcoholic subjects and sufferers from general paralysis of the insane.

It is now known that the lesion is traumatic in origin, and is the result of venous hæmorrhage. Falls, especially those on the forehead or occiput, not at the time apparently productive of serious injury, may yet cause tearing of the cortical veins as they pass from the surface of the brain to enter the dural sinuses. The tear is commonly in the subdural space on one or both sides of the vertex. Thereafter blood leaks from time to time from the torn veins and collects on one or both sides of the vertex, external to the arachnoid membrane. Though by no means unknown in young subjects, this type of lesion is much commoner in patients over 50 years of age.

**Pathology.**—The periphery of the clot formed tends to organise so that a fine capsule is built up round the hæmatoma. The latter remains liquid in its centre, and such hæmatomas may reach a large size. The underlying cerebral hemisphere collapses in a peculiar way downwards and medially, and the brain-stem is thereby pushed over to the other side, so that the margin of the crus, which contains the pyramidal tract, may be indented by the free edge of the tentorium against which it is pressed. As a result of this interference with the pyramidal tract of the opposite side, a hemiparesis may be caused on the side of the hæmatoma.

**Symptoms and Diagnosis.**—The difficulty which still frequently surrounds the diagnosis of subdural hæmatoma depends in large measure upon a general unawareness that it is a not uncommon lesion, and from a survival of the old and now obsolete notion that its occurrence is largely confined to sufferers from the two affections named above. It must be emphasised again, therefore, that subdural hæmatoma may follow an apparently trivial head injury in persons at all age periods; that essentially its symptomatology is that of a space-occupying lesion, with a feature characteristic of hæmatoma: namely, a remarkable fluctuation in the course and severity of the symptoms; that owing to the frequently bilateral nature of the lesion the signs are apt to be difficult of localising interpretation; and finally that in the presence of such a blurred picture a history of head injury some days, weeks or even months before the onset of symptoms should always give rise to the suspicion that a hæmatoma, and not a new growth, may be present.

There is almost invariably a latent period in the development of a subdural hæmatoma. This may vary from a matter of days to one of weeks or months. On the whole, it may be said that in young persons the latent period is apt to be shorter and the symptoms more severe and of more rapid evolution than is commonly the case in elderly subjects. In young subjects, too, there is usually no difficulty in obtaining a history of head injury, either a fall upon the head or a blow sustained at sport or in some other way. The initial symptom is usually headache, fluctuating in intensity, apt to be most severe on awaking in the morning or on physical exertion. With the passage of days or weeks this becomes more severe and soon other symptoms are added to it. The patient has days on which he is drowsy. He may pass rapidly into stupor or even coma, emerging again to become almost normal. Transient accesses of diplopia with squint may be noted. Examination during a period of maximal symptoms may reveal a papilloedema, sometimes severe in rapidly developing cases. The plantar responses may, on one or both sides, be of the extensor type. There may be an inequality of tendon jerks on the two sides, the abdominal reflexes may be diminished on one or both sides. They may even be absent. Periods of mental confusion may also occur. In most instances there is no trace of blood in the cerebrospinal fluid.

The fluctuation in the severity of the symptoms, the fugitive character of the physical signs and the generally downhill tendency of the illness, despite the fluctuations, are amongst the features which are characteristic of subdural hæmatoma and help to differentiate it from that of intracranial new growth. When the syndrome develops rapidly, it is more common to meet a marked slowing of the pulse than in new growth.

Simple radiographic examination of the skull usually shows nothing more than marked displacement of the pineal shadow to one side or laterally and downwards, but if the patient's condition be not so critical as to forbid it, examination after injection of air into the theca (by the lumbar or cisternal route) reveals the outline of the hæmatoma and of the deformed cerebral hemisphere, while cerebral arteriography gives a striking and characteristic picture that is diagnostic.

In all cases there is a great liability to a rapid development of coma with a fatal issue. Yet, the occasional finding at necropsy of what is clearly a subdural hæmatoma of very long standing, unsuspected during life, shows that from time to time the

sequence of events briefly reviewed above fails to develop. It must, however, be confessed that even in such cases it is highly probable that careful clinical examination and an awareness on the part of the examiner of the symptom-complex of hæmatoma might have made diagnosis possible during life.

**Treatment.**—The features which should make clinical diagnosis possible have been described, but in the absence of arteriography certainty can be obtained only by an exploratory operation. This consists in bilateral trephine holes and tapping of the subdural space, and if necessary in the turning down of osteoplastic flaps and the evacuation of the cyst when found. It is clear that treatment is essentially surgical.

## THROMBOSIS OF CEREBRAL SINUSES AND VEINS

Thrombosis of the cerebral sinuses or veins may occur as a primary condition, or it may be secondary to infective processes spreading to the sinuses from contiguous infected regions.

**Ætiology.**—Primary thrombosis is a rare condition. It is said to affect the superior longitudinal sinus most commonly. It is more common in the first year of life than at any other period, when it may follow diarrhœa, bronchitis or the conditions of exhaustion met with in tuberculous disease and in congenital syphilis, and it may follow acute diseases, such as measles, diphtheria, etc. It may also occur at any age, up to advanced old age, in the terminal stages of cancer, pulmonary tuberculosis and other chronic diseases. It occurs in the puerperium, the antecedent confinement usually having been quite normal, and similarly it may occur after abortion.

The essential cause of secondary thrombosis is the advent of micro-organisms to the sinuses. The infection is often a mixed one, but the common organisms present are streptococcus, pneumococcus and *Bacillus coli*. The sinus may become infected as a part of a general pyæmia, or infection may spread directly through its wall from a focus of local disease, most commonly from an extradural abscess due to ear disease or frontal sinusitis. In most cases, however, the sinus becomes infected from a local spreading septic thrombosis of the veins which open into the sinus, from an infected spot at a distance. Thrombosis of sinuses may also occur from injury, as by bullet wounds and fractures of the skull, and may also result from surgical procedures in the region of the sinuses.

In the condition known as *otitic hydrocephalus* (see p. 1404), a sterile mural clot or deposit of fibrin beginning in the lateral sinus above an infected middle ear extends into the superior longitudinal sinus, or spreading sterile clot may obstruct both lateral sinuses, and consequent interference with the absorption of cerebrospinal fluid gives rise to hydrocephalus.

**Pathology.**—The affected sinus, if filled with clot, is distended and bulging, and feels to the touch as if it were injected with a solid mass. In many of the non-infected cases, however, the clot does not fill the sinus. This applies particularly to the superior longitudinal sinus, where there may be extensive mural clot with retention of a blood-channel. One or several veins draining into the sinus may become obstructed and thrombosed, and in cases in which the sinus is filled with clot, all the veins entering it may suffer blockage and thrombosis. Thrombosis of a vein causes intense congestion of the convolutions which it drains, and a moderate degree of subarachnoid hæmorrhage due to rupture of the small tributary veins. The underlying brain softens on its surface and, later, a saucer-shaped depression is left at the site. The cavernous and lateral sinuses do not drain the brain directly, and blocking of one of them does not cause so much cerebral disturbance as obstruction of the superior longitudinal sinus. Thrombosis of the cavernous sinus may, however, extend to the ophthalmic veins and cause blindness, and at the same time the nerves which lie in its outer

wall—the third, the fourth, the ophthalmic division of the fifth and the sixth nerves—may be paralysed.

In the infective forms, the clot very quickly breaks down into pus, and general pyæmia results, or the spread of infection along a tributary vein may give rise to a cerebral abscess.

**Symptoms.**—Many cases are infective and the clinical picture is greatly complicated by (1) the presence of infective disease in relation to the cranium, *e.g.* in the ear; and especially by (2) the onset of pyæmia. The symptoms due to thrombosis of individual sinuses or of cerebral veins are more easily recognised in the non-infective or primary cases.

**Superior longitudinal sinus.**—This sinus has two functions: (1) it is a channel into which drain the veins from the upper and medial surfaces of the cerebral hemispheres; and (2) by the Pacchionian bodies associated with it, it forms part of the mechanism by which the cerebrospinal fluid is absorbed into the blood-stream. Complete obstruction of the sinus by a clot gives rise to (a) extensive bilateral venous thrombosis on the surface of the brain, with resulting spastic paralysis of the legs and upper arms, the hands and face being spared; and (b) increased intracranial pressure, and in most cases some degree of papillædema. In many cases, however, the clot does not obstruct the sinus. Mural clot may obstruct one or more of the entering veins and thus give rise to hemiplegia, which may or may not be ushered in by convulsions; or again, bilateral paralytic phenomena of any degree may occur. There may be associated drowsiness or coma. On the other hand, the veins may not be obstructed and the clot may be so situated as to interfere with the absorption of cerebrospinal fluid through the Pacchionian bodies; paralytic phenomena are then absent, and the disturbance is limited to the manifestations of raised intracranial pressure—headaches, papillædema and, in some cases, vomiting. In otitic hydrocephalus the symptoms of this group alone are present.

**Lateral sinus.**—It is doubtful whether aseptic thrombosis of one lateral sinus gives rise to any symptoms, provided the other one is of normal size and communication at the torcular is free. Since the superior longitudinal sinus usually turns into the right transverse sinus, obstruction of the right lateral sinus may produce a moderate degree of hydrocephalus with headaches and papillædema. In most cases of lateral sinus thrombosis, however, the clot is infected and manifestations of pyæmia rapidly ensue. Meanwhile the clot may extend into the jugular vein, and cause pain and stiffness in the side of the neck, and occasionally the thrombosed jugular vein may be felt beneath the anterior border of the sterno-mastoid as a tender solid cord. There may be tenderness and swelling over the region of the mastoid emissary vein, and the cervical lymph glands may be enlarged. If when Queckenstedt's test is performed the jugular veins are compressed separately, compression of the vein on the side of the obstructed sinus causes little or no rise in the manometer, whereas compression of the other gives a normal result.

**Cavernous sinus.**—Thrombosis of this sinus is usually consequent upon septic spots or injuries on the face, sepsis in the frontal sinus or orbital cellulitis. Ordinarily the thrombus is infected. There is œdema of the orbit, with proptosis and œdema of the conjunctiva, forehead and face. Amblyopia, or blindness, is the rule, but the appearance of the fundus of the eye usually remains normal until the late stages. Paralysis of the ocular muscles and anæsthesia of the eye may also occur. The condition usually becomes bilateral within a day or two.

**Diagnosis.**—This usually depends on the presence of some of the conditions with which sinus or venous thrombosis is known to be associated. The possibility of clot in the superior longitudinal sinus and related veins should always be considered: (1) when any convulsive or paralytic phenomena comes on within a month of childbirth or abortion; (2) when in an elderly or debilitated patient manifestations, which may include alexia and visual disorientation, suggesting vascular lesions on

the two sides of the brain occur within a few days of each other; (3) when signs of hydrocephalus appear in association with or soon after an attack of otitis media, and there are no other indications of cerebral abscess and (4) when paralytic or convulsive phenomena occur soon after an injury near the vertex of the skull.

Lateral sinus thrombosis is almost exclusively associated with ear disease, and its presence can usually be confirmed by Queckenstedt's test. Thrombosis of the cavernous sinus presents such a characteristic picture that if an exciting cause is present the diagnosis is seldom in doubt.

**Prognosis.**—In the non-infective cases the prognosis as regards life is usually good. The paralytic phenomena generally make great and often complete recovery within a few weeks, but in the severe cases spasticity in the legs and upper arms may be left. Blindness or impairment of vision may follow cavernous sinus thrombosis. As to the infected cases the prognosis, formerly ominous, has been greatly improved by the introduction of the sulphonamide drugs and penicillin. With lateral sinus thrombosis, recovery usually follows prompt operation.

**Treatment.**—In the non-infective cases the first indication is to allay convulsions if present, and doses of soluble phenobarbitone up to gr. 3 at a time may be administered by intramuscular injection, or by mouth if that is possible. Anticoagulants may be employed to prevent the spread of thrombosis, but they should be used with full knowledge of the risk of toxic effects (see p. 847). For the paralytic phenomena, the treatment is identical with that of cases of cerebral arterial thrombosis.

The infective cases should be treated immediately as cases of septicaemia, and if the local exciting conditions are likely to involve any collection of pus, such as an epidural abscess, appropriate prompt surgical measures should be taken.

## SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

Before the War of 1914–1918 syphilis was responsible for far more cases of organic nervous disease than any other single factor, but during the last 40 years the incidence of neurosyphilis in the United Kingdom has shown a steady decline until it is now less than a tenth of what it formerly was.

It is known that in many cases of syphilis the meninges become infected with the syphilitic organism early in the secondary stage, but in most cases, especially if adequately treated, this infection dies out within a year or two. In a number of patients, however, it persists and may become very resistant to treatment. After an interval, which is seldom less than 2 years, syphilitic disease of the meninges and of the blood vessels of the central nervous system, may give rise to symptoms, and in other instances, after an interval varying between 5 and 30 years, disease of the cerebral parenchyma may become manifest as general paralysis of the insane, or degeneration of fibres in the posterior nerve roots and spinal cord may give rise to tabes dorsalis.

In meningeal and vascular syphilis the lesions are composed of miliary gummata. They commence with the collection of spirochaetes in the spaces surrounding the small arteries, and this is followed by an inflammatory reaction with oedema and the exudation of many lymphocytes and plasma cells around the small vessels. These cells may wander freely into the nervous tissues away from the vessels and may form clumps, often containing giant cells, and these too are miliary gummata. The initial periarteriolar inflammation is followed in many instances by invasion of the whole vessel wall (panarteritis), and often the most conspicuous feature in such panarteritis is a proliferative endarteritis which may give rise to thrombosis.

The sequence of events in the primary degenerative processes in parenchymatous

syphilis is less well known and these processes are as yet unexplained. In only one form of nervous syphilis, namely, general paralysis of the insane, is *Treponema pallidum* found in the parenchymatous elements of the central nervous system.

In cases of neurosyphilis the Wassermann reaction is usually positive in the blood. The most frequent exceptions to this are in cases of tabes dorsalis, in which disease the blood Wassermann reaction is negative in about 30 per cent. of cases.

The cerebrospinal fluid in neurosyphilis shows typically a group of changes, comprising lymphocytosis, excess of albumin, and a positive Wassermann reaction. The Wassermann reaction may, however, be negative in the fluid when it is strongly positive in the blood and this combination is commonly met with in cerebral meningo-vascular syphilis. It is thus essential in all cases in which syphilis is a possible cause of central nervous symptoms to examine the Wassermann reaction both in the cerebrospinal fluid and in the blood, since either may give a positive result when the other is negative. In some cases of neurosyphilis, particularly tabes, the cerebrospinal fluid is normal in every way.

## GENERAL PARALYSIS OF THE INSANE

**Synonym.**—Dementia Paralytica; General Paresis.

**Definition.**—This is a progressive disease of the brain due to syphilis, causing mental and physical deterioration and finally dementia and paralysis.

**Ætiology.**—Infection with *Treponema pallidum* (*Spirochaeta pallida*) is the essential cause, and the disease usually begins between 8 and 20 years after infection. The incidence is much greater among males than among females, and the onset of the disease occurs most often between the ages of 30 and 50. It may appear in adolescence as the result of congenital infection. The incidence among syphilitics in general has been estimated as high as 5 per cent., but among those who have been well treated in the early stages the incidence is probably less than 1 per cent. It formerly represented about 10 per cent. of all cases of neurosyphilis and nearly a quarter of those treated as hospital in-patients.

**Pathology.**—At necropsy the brain appears atrophic, the sulci being widened and the convolutions reduced in size. These changes are most pronounced over the anterior and middle portions of the hemispheres, but in some cases only the occipital poles escape. The meninges often show considerable thickening and opacity, and the pia adheres firmly to the cortex. On section the cortex is found to be reduced in thickness. The ventricles are enlarged as a result of the atrophy of the brain substance, and their ependymal lining appears granular or "frosted".

The essential changes are in the ganglion cells of the cerebral cortex. Microscopical examination under the low power shows that many of these cells have disappeared and that those remaining are arranged irregularly. The cells are often shrunken, and their nuclei stain deeply. In association with the neuromic damage there is a marked reaction of the glial cells and histiocytes (rod cells). The subpial lamina of glial tissue is increased. The histiocytes proliferate and hypertrophy and, when stained with Prussian blue, are found to contain iron in their cytoplasm—a pathognomonic finding. Many of the cortical blood vessels are surrounded by a perivascular "cuff" of lymphocytes and plasma cells, and the vessels often show proliferative changes in their endothelium.

*Treponema pallidum* can be demonstrated in the nervous tissue.

**Symptoms.**—For months before intellectual defect becomes apparent the patient has usually shown some defect of emotional control. He has become excitable, moody, liable to outbursts of temper and easily moved to tears by music or the cinema. Thereafter he begins to show a lack of concentration and persistence; he ceases to pursue his old interests and adopts new ones in rather rapid succession. At this



stage he is "full of ideas", but soon begins to show deficiency of judgment in applying them, seeing only the great advantages of his schemes and forgetting his own limitations. He assumes his ability to attain every wish, and this may lead to outbursts of wild extravagance. By this time he has become forgetful, inattentive to business and careless. Within a short time he has actual delusions concerning his own capacity, and he may boast of his physical power, wealth or social position, but the classical delusions of grandeur are now a rarity.

In many other cases the symptoms are merely those of simple dementia with gradual reduction of interests and of mental and physical activity. The patient's ability to perform his usual work is gradually impaired, especially if it is of a mental character, and when calculation is involved his mistakes become frequent. In a large number of such cases the patients are depressed in the early stages, and the subsequent delusions may be melancholic or hypochondriacal. As the disease progresses, memory becomes more and more defective, excitability and activity give way to apathy and lethargy, and delusions die out. The patient lies in his bed showing little sign of mental activity, indifferent to his surroundings, incontinent and more or less paralysed.

The first of the physical changes accompanying the mental deterioration is almost always tremor. Usually, if not always, it begins by affecting the voice, giving it a vibrant emotional quality, but this change usually escapes notice. When, however, the tongue, lips and cheeks become tremulous, the irregularity of articulation is pronounced. The typical tongue tremor is a backward and forward "trombone" movement of the organ, when the attempt is made to protrude it. Speech is often affected early. At first it is merely hesitant; later it becomes indistinct and irregular, syllables are omitted, interpolated or slurred, and the voice becomes feeble and lacks intonation. Utterance then becomes jerky, and consonants are slurred. Changes at a higher physiological level in the speech system also occur and cause elision of syllables or of words, and attacks of aphasia are not uncommon. As the memory fails, confusion arises in the construction of long sentences, proper names are forgotten, the choice of adjectives and verbs becomes more and more limited, and the vocabulary diminishes until only interjections are left. Written language suffers in the same way, and may show defects of execution and of ideation before spoken speech is noticeably altered. Tremor becomes marked in the hands and other parts of the body and, because of the unsteadiness of the hand the writing deteriorates, and with the intellectual deterioration words are often misspelt.

Apart from tremor there are no physical signs that can be counted upon in the early stages. Pupillary abnormalities are very common, but they simply indicate central nervous syphilis and have probably been present for some time before the onset of general paralysis. The complete Argyll Robertson phenomenon is not very common, but incomplete forms of it and inequality and irregularity of the pupils are usual. Signs of disturbance of the pyramidal system—extensor plantar reflexes and exaggeration of the tendon-jerks—usually occur before long. If any of the tendon jerks are absent, as is not uncommon, it is because of the presence of an element of tabes dorsalis. Incontinence of urine often occurs early, but it is more often due to lack of attention than to any failure of the sphincter reflexes. At a later stage control of both bladder and rectum is always lost. Sexual impotence is present in most cases for several years before mental symptoms appear, but in a few of the more acute cases the onset is accompanied or preceded by a phase of sexual excitement.

As the disease advances, the paralytic features become more pronounced. In the so-called "congestive attacks", hemiplegia or monoplegia appears, with or without an initial Jacksonian fit. Recovery occurs in the course of a few days or weeks, but the limbs gradually become weak.

Generalised epileptiform seizures are common and often aggravate the pre-existing symptoms, and in a large proportion of cases death eventually occurs in

coma following a fit. In some cases convulsions are the first manifestation to attract attention. When the patient is examined, however, it is usually found that he is already tremulous. Such cases are among the most favourable for treatment, because the disease may be arrested before mental deterioration has become apparent. Insomnia is frequent in the prodromal period, but in the early stages sleep is often excessive. Later, sleeplessness and motor restlessness are often troublesome symptoms.

*Tabo-paresis.*—The condition known as tabo-paresis consists of a combination of certain features of general paralysis with certain features of tabes. The mental symptoms are, as a rule, relatively mild, tremor and the speech disturbances are moderate, the knee-jerks and ankle-jerks are absent, and there is usually some sensory impairment of tabetic type and distribution; the pupil reactions are likely to be of the Argyll Robertson type, and optic atrophy may be present. A considerable number of cases of nervous syphilis in which optic atrophy is the first recognised feature develop as cases of tabo-paresis.

*SEROLOGICAL REACTIONS.*—Provided the patient has not recently received anti-syphilitic treatment, his blood will almost certainly give a positive Wassermann reaction. A negative result, however, should not be accepted as conclusive evidence against the presence of general paralysis of the insane. The cerebrospinal fluid in an untreated case usually shows an increase in the number of white cells and in the protein content, with excess of globulin; the Wassermann reaction is invariably strongly positive, and Lange's colloidal gold test almost always shows maximal changes in the first four or five tubes (paretic type of curve).

*Diagnosis.*—The diagnosis depends on the combination of mental changes with typical changes in the cerebrospinal fluid. Tremor is almost invariably present, at any rate in the voice. In the complete absence of tremor, even when the fluid changes are typical, it may be doubted whether the condition present is general paralysis of the insane and not one of the other forms of cerebral syphilitic disease. Cerebral meningo-vascular syphilis may cause mental deterioration and paralysis, but tremor is seldom prominent, and the changes in the cerebrospinal fluid, especially the colloidal gold reaction, are likely to be somewhat less intense.

In the absence of reliable examination of the cerebrospinal fluid or blood, the history of change in the patient's character, combined with intellectual deterioration, impaired emotional control and tremor, is almost sufficient for the diagnosis. Commonly the patient himself has little or no insight into his altered state, and may express his subjective sense of well-being and of intellectual acuity in glowing terms that arouse a suspicion of the true state of affairs in the trained observer. The non-syphilitic conditions which cause a similar gradual change are rare with the exception of arteriosclerotic dementia. The latter usually occurs at a later age than general paralysis and is associated with less tremor. In general paralysis pupillary abnormalities are almost constant and slurring articulation soon becomes added to the tremor of the voice.

In rare cases chronic alcoholism gives rise to an "expansive" mental state and tremulousness, which cannot with confidence be distinguished from general paralysis without examination of the cerebrospinal fluid. With delirium tremens visual hallucinations are a prominent symptom. Alzheimer's disease is a rare form of degeneration of the frontal lobes, which comes on in middle age and causes gradual mental deterioration associated with tremor. Pupillary abnormalities are absent (see p. 1630). In the absence of pupillary or other clinical signs of nervous syphilis it may be impossible to distinguish the depressed form of general paralysis of the insane from other states of depression. In many cases the tremulousness may suggest the correct diagnosis, but some tremor may also be seen in cases of depression with agitation due to other psychoses. When a history cannot be obtained and the patient is in a maniacal or a hypomanic state, the differentiation from other forms of mania may for a time be impossible.

**Course and Prognosis.**—The onset is usually insidious. The disease may then progress steadily or in the early stages show exacerbations with maniacal outbursts. In the absence of effective treatment death usually occurs within 3 years, and in a large proportion of cases the duration is about 1 year. If convulsions are frequent, the termination is likely to occur sooner, and acute cases may run their course in a few weeks. Usually the disease is less acute in women than in men.

The duration of tabo-paresis is generally a good deal longer than that of general paralysis, and in cases due to congenital infection the course is often prolonged.

**Treatment.**—**PROPHYLACTIC.**—The eventual occurrence of general paralysis of the insane may be feared in any case in which 2 years or more after infection the lymphocytosis in the cerebrospinal fluid is resistant to courses of antisyphilitic treatment. Preventive treatment then consists in a course of penicillin injections as in the curative treatment of general paralysis. If the interval from the time of infection is as long as 5 years and the colloidal gold curve is of the paretic type, such preventive treatment should not be delayed.

**CURATIVE.**—It is important that the physician in charge of a case of general paralysis should have clearly in mind both the possibilities and the limitations of treatment. Cure consists of two distinct parts—the eradication of the syphilitic infection from the brain, and the restoration of normal cerebral function. The means of treatment at our present disposal may accomplish the former and do not aim beyond that. The subsequent restoration of cerebral function depends on the recovery of such cerebral tissue as is capable of recovery, and we have as yet no means of influencing the natural course of this process. This recovery continues over a period of about 2 years and attains very different degrees according to the amount of damage already suffered by the brain before the disease was arrested, the acuteness or chronicity of the inflammation and other factors. While the corresponding mental recovery reaches a gratifying level in many patients in whom the disease is recognised and treatment begun reasonably early, there are many others in whom it is never sufficient to restore the patient to a position of social usefulness.

For the eradication of the syphilitic infection from the brain, penicillin now provides the method of choice. As, however, this treatment is relatively new, some physicians still prefer to re-enforce it with a (shortened) course of pyrexial therapy. The penicillin treatment consists of the administration of a minimum of 5 million Oxford units intramuscularly over a period of approximately 10 days; and it is now usual to give about 10 million units, in a single course, or in two courses. Having begun with injections of 15,000 units or so three times in the course of the first day, it is usual to proceed with doses of the order of 60,000 units every 3 hours until a total of 5 or 6 million units has been attained, i.e. 10 or 12 days more. Various methods of maintaining the concentration of penicillin in the blood with less frequent injections, e.g. one every 24 hours, are on trial, but none has yet obtained general acceptance. No penicillin is given intrathecally. During the course of penicillin therapy a mixture containing iodide of potassium (gr. 20 or gr. 30 to the dose) and mercuric chloride solution (1 in 1000) ( $\frac{1}{2}$  to 1 drachm in each dose) should be given by mouth, with the idea of aiding the absorption of gummatous elements in the brain and meninges.

It was discovered in 1917 that general paralysis could be arrested by malaria and for the next 30 years benign tertian malaria was used all over the world as a therapeutic measure. The patient was allowed to have from 6 to 12 rigors according to his physical state and then the malaria was stopped by quinine or mepacrine. The treatment was mostly carried out in special hospitals or clinics, with expert medical nursing staff, and under such conditions the mortality (from the disease and from the malaria) during the stage of active treatment was of the order of 10 per cent., but under less favourable conditions it was much higher.

When it was established that the pyrexia was the actual curative agent, various

more easily controlled methods of producing it were developed, the most successful of which was the heating of the body in a suitable cabinet by electrical "short waves".

After any successful treatment clinical improvement is very gradual. The first clinical effects are the reduction of tremor and of excitability, and an improvement in the patient's memory and alertness. During the next few months, improvement in favourable cases is pronounced, but 2 years elapse before the full effect is obtained. Changes in the cerebrospinal fluid with one important exception, are equally gradual. Within a few weeks of the end of successful treatment the number of cells in the cerebrospinal fluid falls to near the normal level (3 per c.mm.), indicating the cessation of active inflammation in the central nervous system, but the other abnormalities in the fluid show, for the time being, little change. The Wassermann reaction of the fluid usually dies out in the course of a year or so, but the paretic colloidal gold curve may persist for several years, and its presence is not to be regarded as a sign of syphilitic activity. If treatment has not been successful in eradicating the infection, the first sign of relapse is an increase in the number of cells in the cerebrospinal fluid and such increase will almost invariably be observable by the end of 6 months; consequently, if at the end of 6 months the cerebrospinal fluid contains more than four cells per c.mm., a further course of treatment should be given.

The effect of modern therapy is to arrest the active disease, and the clinical results depend chiefly on the degree of mental deterioration that had occurred before treatment was instituted. The most satisfactory cases are those in which convulsions or other acute phenomena have brought the patient under care before mental impairment has become obvious. However, patients with mental symptoms of short duration often do well. In cases of slower evolution, with evident mental impairment, arrest of the disease may leave the patient incapable of useful mental work and unfit to hold any position of responsibility.

In occasional cases cerebral degenerative changes of a non-specific character occur in later life and give rise to a secondary dementia.

## CEREBRAL SYPHILIS

**Synonym.**—Cerebral Meningo-Vascular Syphilis.

**Definition.**—In most of the cases to which the term "cerebral syphilis" is applied the chief incidence of the syphilitic process is upon the meninges and blood vessels, the brain being affected in a less degree and by secondary processes. Actual syphilis of the brain is uncommon. It occurs, however, in two forms: (1) Gumma of the brain, and (2) a diffuse gummatus infiltration throughout the cerebral hemispheres or even in the cerebellum, the meninges always being involved to some extent.

**Ætiology.**—Cerebral syphilis (as distinct from general paralysis of the insane) occurs in about 4 per cent. of all persons who acquire syphilis. The onset of symptoms is commonest from 1 to 5 years after infection, but it may be as early as 2 or 3 months or as late as 30 or 40 years. Characteristically, the patients are young men, but a "stroke" due to syphilitic vascular disease may occur at any age and at any interval after infection.

**Pathology.**—Both the meninges and the cerebral blood vessels are always affected, but the degree of involvement of each is subject to great variation. When the disease falls chiefly upon the meninges it most frequently causes a diffuse, subacute or chronic, gummatus leptomeningitis at the base of the brain. Less often it affects the coverings over the convex surface of the brain, and if so it is usually more intense over the frontal and parietal lobes than over the occipital and temporal. In severe cases a gelatinous exudate fills the subarachnoid space and extends along the vessels and nerves. Later, the newly formed tissue organises and forms sclerosed gummata. Hydrocephalus

may result. Many symptoms of cerebral syphilis are caused indirectly and result from hydrocephalus or vascular disturbances. In rare instances syphilitic infection gives rise to an acute diffuse meningitis indistinguishable without special tests from other kinds of acute meningitis (see p. 1461).

In cases where the main incidence falls upon the blood vessels, the arteries at the base of the brain, forming the circle of Willis or arising from it, together with their branches, are most often attacked. To the naked eye they show irregularities in size, due to thickening of their walls in circumscribed areas. Proliferation of the intima, together with a round-celled infiltration of the outer coats—endarteritis obliterans—is the characteristic microscopical change. In smaller arteries within the brain or on its surface the same changes occur, and these vessels, as well as those at the base, may be compressed or invaded by disease beginning in the meninges. In each case their lumen is narrowed or obliterated, thrombosis occurs readily and softening results in parts from which the blood supply is cut off. Obliterative changes also occur in the veins and perivascular spaces, and lead to further impairment of the nutrition of the brain.

*Gumma* of the brain is rare. When present it arises from the meninges and may be multiple, and the convexity of the hemisphere in the motor region is the site of election. A gumma may spread so as to involve the overlying bone.

**Symptoms.**—The symptoms of basal meningitis are partly general and partly local from involvement of some of the cranial nerves. The general symptoms are headache, lethargy and impairment of intellect and memory. The headache is deep seated and severe. The lethargy is variable and may pass off for a time or may deepen into stupor. Any one or several of the cranial nerves may be paralysed. Ocular symptoms are rarely absent, pupillary changes being the rule and external ocular palsies common. Mild papillædema is also common and optic atrophy may occur in one or both eyes. A symptom presumably due to involvement of the hypothalamus or of the pituitary is obesity. Diabetes insipidus sometimes occurs.

When the meningitis is distributed chiefly over the convexity of the cerebral hemispheres there may be long periods of intermittent headache, which is acute and usually situated near the vertex of the skull and the skull may be tender. In severe cases convulsions are common; they are most frequently generalised epileptiform fits, but Jacksonian attacks are not uncommon and are usual in the more chronic cases. Attacks of aphasia may occur. In all the more severe cases some mental impairment is the rule, usually simple dementia, but there may be mild delusions and emotional instability is common.

When the blood vessels are predominantly affected premonitory symptoms often occur before there is any severe "stroke". These consist of transitory weakness of one arm or other part of the body or of local twitching. Headaches are common. Hemiplegia is the usual syndrome which supervenes, and in some of these cases it is of the most severe type. In addition to the paralysis and spasticity there may be sensory loss in the affected limbs and complete or partial hemianopia. Aphasia usually accompanies right-sided hemiplegia. The Wassermann reaction is usually strongly positive in the blood.

**Diagnosis.**—This depends largely on the discovery of a positive Wassermann reaction. It is usually positive in the blood but in many cases it is negative in the cerebrospinal fluid. Pupillary abnormalities may be of great help in suggesting syphilis as a cause, but the possibility of a tumour in the mid-brain must be borne in mind. The Argyll Robertson pupil in its pure form is not common in cerebral meningo-vascular syphilis.

Jacksonian epilepsy or fits of any kind in patients—particularly male patients between 24 and 25—are suggestive of syphilitic meningitis or gumma, even though these are not now the commonest cause of such symptoms. This applies particularly if the attacks are of a peculiar character, such as an attack of automatism and amnesia.

Fluctuation in the symptoms is one of the features of the disease, and in the milder cases the patients may be well for months at a time.

**Prognosis.**—With antisyphilitic treatment a large measure of recovery is the rule but some mental impairment, headaches and occasional fits are common residual phenomena. Signs of hydrocephalus may persist in some degree. Hemiplegia may respond to antisyphilitic treatment, but in the majority of cases it is little affected.

**Treatment.**—**PROPHYLACTIC.**—If syphilis has been contracted, it should be thoroughly treated in its early stages. When the Wassermann reaction of the blood has been rendered negative, the test should be repeated once a year for the first 5 years and then every 2 years. The cerebrospinal fluid should be examined after the blood has been rendered negative, but an interval of 2 or 3 months should be allowed between the end of a course of treatment and the lumbar puncture. If the cerebrospinal fluid then gives a positive reaction, treatment should be continued and the fluid should be examined as before, 3 months after the end of the course of treatment.

**CURATIVE.**—As soon as the diagnosis is made, and in very acute cases even before it is established, antisyphilitic treatment should be begun, with potassium iodide and mercury by the mouth, and within a day or two a course of penicillin as described for general paralysis of the insane (p. 1458) should be started. The potassium iodide and mercury can be combined in the following mixture: potassium iodide, gr. 10 to 20; solution of mercuric chloride, mins. 30 to 60; arsenical solution, mins. 2½; chloroform water, fl. oz. ½. This should be taken with as much water as desired three times a day after food, but is not to be taken when the stomach is empty. If either dyspepsia or diarrhoea occurs, the mixture should be stopped for a time and replaced by one containing bismuth carbonate, gr. 15, instead of the solution of mercuric chloride.

## ACUTE SYPHILITIC MENINGITIS

This is a rare condition, almost confined to young men. It occurs usually within a year or two of infection and has even been associated with the secondary rash. A peculiar feature is that acute syphilitic meningitis or a condition closely resembling it (*meningo-récidive aiguë*) may occur during a course of arsenical injections, and there is some reason to believe that in such instances the treatment is a precipitating factor.

**Symptoms.**—The clinical picture is indistinguishable from that of other kinds of acute meningitis. Headache is intense, the temperature may rise to 102° or 103° F., the patient is delirious and may have maniacal outbursts, and stiffness of the neck is present, but Kernig's sign is not usually pronounced. The optic disks may be blurred and slightly swollen. The condition of the pupils is not usually of diagnostic value. The tendon and plantar reflexes are variable, as in other kinds of acute meningitis. The cerebrospinal fluid may contain 1000 or 1500 cells per cubic millimetre, of which as many as 30 per cent. or even more may be polymorphonuclear. The Wassermann reaction is strongly positive both in the cerebrospinal fluid and in the blood.

**Treatment.**—With the administration of potassium iodide and mercury by the mouth, and the injection of small doses (10,000 to 15,000 units) of penicillin intramuscularly at 6-hourly intervals, the fever and delirium quickly subside and the headache abates. Treatment must then be pursued on the same lines as for other forms of meningo-vascular syphilis. Good recovery is the rule, but some mental impairment is often left.

## TABES DORSALIS

**Synonym.**—Locomotor Ataxia.

**Definition.**—This is a disease of syphilitic origin characterised clinically by ataxia

of the lower limbs in walking and by numerous other signs, and pathologically by degeneration of the posterior columns of the spinal cord.

**Ætiology.**—Syphilis is the essential factor in causation. Little is known of the contributory factors which determine the occurrence of tabes dorsalis in some persons with syphilis and not in others. Males are affected a good deal more frequently than females. The onset is usually between the ages of 30 and 45 years, and usually between 5 and 15 years after infection. It may occur in both husband and wife—"conjugal tabes". It also occurs, not very rarely, as a result of congenital syphilis and then appears in adolescence or early adult life.

Tabes dorsalis was once the commonest form of neurosyphilis, but its frequency has shown a marked decline in recent years.

**Pathology.**—The most evident morbid change is degeneration in the posterior columns of the spinal cord. It is, however, generally believed that this is not primary but results from disease affecting the fibres, of which these columns are composed, before they enter the cord. These fibres and other fibres of the posterior spinal roots are most probably affected by syphilitic toxins, either where the nerves pass through the meninges or where the roots enter the spinal cord. As a secondary change the neuroglia around the degenerated fibres increases in amount and density. Hence the characteristic feature in sections of the cord in tabes is shrinkage and sclerosis of the posterior columns. The sclerosis usually appears earliest in the postero-lateral columns of the lower lumbar and upper sacral regions, but in advanced cases when the dorsal and cervical sensory roots are also affected the posterior columns are sclerosed throughout. In advanced cases the endogenous tracts of the posterior columns show degeneration, and in some the afferent tracts in the lateral columns are also affected. In addition, there is often a subpial or marginal degeneration practically all round the cord at many levels.

Atrophy of the optic nerves commonly occurs, and seems to be the result of a combined interstitial gummatous inflammation and primary degeneration of the nerve-fibres. The ocular palsies of tabes are probably mainly due to gummatous meningitis but there may be a degeneration of the nerve cells in the nucleus of the third nerve.

**Symptoms.**—Few diseases cause so many different symptoms. The most common features are: (i) "lightning pains"; (ii) objective disturbances of sensation; (iii) loss of tendon-reflexes; (iv) ataxia; (v) disturbance of pupillary reflexes, especially the Argyll Robertson pupil and (vi) impairment of bladder control. Less frequent are: (vii) visceral "crises", *i.e.* acute disturbances of function of certain viscera, of which gastric crises are the most common, but rectal, vesical and laryngeal crises also occur; (viii) atrophy of the optic nerves; (ix) trophic changes—(a) Charcot's disease of joints, (b) perforating ulcers of the skin and (c) a general trophic effect which renders the patients thin.

The usual syndrome is essentially that of degeneration of the posterior spinal nerve-roots, or of the corresponding nerve-cells in the posterior root ganglia and, in fact, of the afferent elements of the nervous system in many parts of the body.

**SENSORY DISTURBANCES.**—*Subjective.*—Lightning pains are usually the first symptom—sudden intense stabbing pains which seem to shoot into parts of the lower limbs. They occur at irregular intervals and usually in bouts, vary greatly in severity, and are often mistaken for "rheumatism" or "neuritis". These pains merit the closest attention. They are rarely absent, they often precede other symptoms by 5 or 10 or more years, and most important of all, they possess peculiar features which render them pathognomonic of tabes and allow the diagnosis to be made in a syphilitic subject on their presence alone. Although they are rarely absent, careful interrogation may be needed to disclose them. To the question, "Have you any pains?" the patient may answer "No". If then he is asked if he has rheumatism, he will often answer "Yes", and proceed to give an account of characteristic tabetic pains of

several years' duration. In other cases the patient mentions his pains, but their significance escapes notice because it is thought that they are too slight to be tabetic pains. *It must be made clear at once, therefore, that the peculiarity of the pains in tabes does not lie in their severity, for they vary from a trifling sensation of discomfort to almost intolerable agony, but in their distribution, in their direction of propagation, and especially in their arrangement in time.*

As a rule they come on in attacks, in which single momentary pains are repeated at intervals of a few seconds or minutes for several hours, the whole bout lasting several days or weeks. Between the attacks there may be long intervals of complete freedom from pain. The pains are felt most often in the lower limbs, but any part may be affected. They may be referred to the skin, to the muscles or to the bones. They are very common in the bony prominences around the knee and on the foot. The direction of radiation varies. In some the pain seems to shoot up or down a limb, but in a larger number it seems to strike the limb vertically as if a sharp object were piercing it from without. Some patients experience both kinds of pains. The onset of each pain is always sudden. If it is severe the patient may cry out, and if it overtakes him whilst walking he is forced to stop. The duration of each pain is usually momentary, but sometimes it lasts a second or two and fades away gradually.

Other pains with characters which are not peculiar to tabes are common. They are described as aching, burning or gnawing pains. Like the lightning pains, they alter with changes in the weather and are usually attributed to rheumatism. Other common subjective sensory symptoms are "pins and needles" in the extremities, a feeling of walking on a soft substance, and of constriction around the trunk or limbs. More important than these, because it often appears very early, is hyperæsthesia of the trunk, especially in its lower part. Light touches or applications of water at certain temperatures are almost unbearable. In cervical tabes sensory disturbances occur first in, and are more severe in, the arms.

**Objective.**—In association with the foregoing subjective disturbances, objective impairment of pain appreciation develops. For some unknown reason this impairment (hypalgæsia) has a strongly selective incidence, the areas at first affected being as follows: (i) a band across the chest; (ii) over the lower halves of the shins; (iii) on the nose and (iv) on the ulnar borders of the forearms. As the disease advances, the areas thus affected extend, and eventually pain appreciation may be impaired over the whole surface of the body. Deep pain appreciation becomes similarly affected.

**REFLEXES.**—Simultaneously with the involvement of the pain fibres, or very soon afterwards, the fibres which subserve reflex activities are affected, with consequent gradual interruption of the reflex arcs. The ankle-jerks and knee-jerks disappear. Loss of the ankle-jerks is an early sign in tabes, and often precedes loss of the knee-jerks by many years. The tendon reflexes in the upper limbs are lost early in cervical tabes, and are frequently absent in cases of the ordinary type. The triceps jerk is usually the first to go. The skin reflexes are often exaggerated to a degree rarely met with in other diseases. This is best seen on the abdomen, and is usually associated with hyperæsthesia to touch and temperature. The plantar reflex is usually normal. It is sometimes absent when sensory loss on the soles is severe, and in cases where sclerosis of the pyramidal tract exists as a complication of tabes the response is "extensor".

**HYPOTONIA.**—Muscle tone, which is a reflex function, gradually becomes affected too, and in any established case passive movement of the lower limbs reveals definite hypotonia. The decrease in the tone of the muscles is often well marked at a time when lightning pains are the only symptom of tabes, and loss of skin sensation the only other manifestation. It is shown by flaccidity of the muscles, and by an abnormal range of active and passive movement of the limbs. The leg can often be raised to an angle of 100° from the horizontal, with the knee extended, whereas a normal



person cannot raise it more than 60°, and excessive range of dorsiflexion of the foot is often a striking sign. In extreme cases the legs can be made to encircle the neck, the body can be flexed so that the head touches the bed between the knees, and the patient is able to imitate the tricks of the "double-jointed" man.

**ATAXIA.**—At a slightly later stage the coarser fibres in the posterior roots which are concerned with sense of position suffer in the same way as the pain and reflex fibres. The patient then becomes unable to appreciate exactly the position of his extremities. As a rule, the lower limbs are affected first and most. The patient becomes unable to direct the movements of his feet exactly, and fails to maintain his centre of gravity in the right position relative to them with the result that he becomes unsteady. The trouble is first noticed when co-ordinated movements have to be performed without the aid of vision, as when the patient is washing his face in the morning. This disability is partly overcome for a time by separating the feet so that the patient stands and walks on a wide base; he watches the ground and is much more unsteady with his eyes closed or in the dark. When standing with his feet together he is more unsteady with his eyes closed than with his eyes open (Romberg's sign). As the loss of sense of position advances and at the same time the controlling influence of muscle tone is lost, movements of the lower limbs become very irregular. In walking, the feet are raised too high and are brought down with irregular force, often too violently, so that the gait becomes stamping. The steps are of irregular length. The patient staggers from side to side and may fall. Eventually walking may become impossible. The same inco-ordination of movement occurs in the upper limbs but usually in less degree. The patient becomes unable to direct the movement of his hands and fingers exactly without watching them, later he becomes clumsy, and eventually may become unable to feed himself.

**SPHINCTER TROUBLES.**—These are the result of lowering of pain sensibility in the bladder which is the afferent element in the reflex of micturition. An increased distension of the bladder becomes essential before the act can be started and this fails before the bladder is completely emptied, and residual urine is present in slowly increasing quantity. Though this causes little or no inconvenience to the patient at first, it often leads to cystitis and renal complications. Later, difficulty in starting micturition and nocturnal incontinence are common. Acute retention of urine is sometimes the symptom which first brings the patient under observation, but retention at any stage of the disease may be attributable to enlargement of the prostate, and removal of the latter may give complete relief. Sexual desire and power are usually lost early in the course of the disease.

**OCULAR DISTURBANCES.**—While manifestations referable to spinal-root disturbances are developing, certain others arise in the areas supplied by the cranial nerves. The most important are abnormalities in the reactions, size and outline of the pupils, and pupillary disturbances of some kind are often the first signs of the malady. The Argyll Robertson pupil is the most characteristic abnormality, but it is not common in its pure form, namely, a very small pupil, which reacts normally to convergence but not at all to light, and does not dilate fully under the influence of a mydriatic (see p. 1343, 1466). Absence of the light reaction in one or both pupils, with or without retention of the convergence reaction, is usual, and atrophic changes in the irides are very common.

The size of the pupils varies greatly in different cases. Most often they are small, but pupils of moderate size are common, and sometimes they are widely dilated, though this is very exceptional and is usually associated with optic atrophy. It is not unusual to see pupils which, when contracted to accommodation, are not much larger than the head of a pin, but the "pin-point" pupils are rare. Inequality of the pupils or irregularity in their outline is present in most cases. In old tabetics in whom the disease has been present for very many years the pupils may be found wholly inactive both to light and on convergence. Partial bilateral ptosis usually

comes on at a later stage, and it is compensated for by elevation of the eyebrows. In addition there are a general flabbiness of the facial musculature and a greyish pallor of the skin. All these features combine to give the patient a somewhat distinctive facial appearance—the tabetic facies.

**Optic atrophy.**—Syphilitic optic atrophy is an important complication and occurs with such frequency that it is often called tabetic optic atrophy. It has been estimated that it is found in about one case in ten. It may be the first indication of neurosyphilis. The peripheral portion of the visual field is lost first, and charts of the fields at this stage have a most irregular outline. Central vision is the last to fail, and as long as it persists the impairment of sight may escape notice. The most acute cases proceed to complete blindness in 2 months, but the slow cases take many years or remain unilateral. The atrophy is primary, that is, it is not preceded by papilloedema. The disk becomes white and flat, and is sharply outlined. Cases of tabes which begin with optic atrophy do not, as a rule, develop much ataxia, but they often develop mental disturbances and become cases of tabo-paresis.

**VISCERAL CRISES.**—Occasionally attacks of intractable vomiting occur, each lasting a few days, and during this time the patient "cannot keep anything down". The vomiting may be associated with epigastric pain, but more often there is merely discomfort. Tabetic pains in the back are commonly associated with or precede the crisis. When the attack is over, the patient is quickly well again, but such attacks continue to occur at intervals of months or weeks. They often take place before other symptoms of tabes dorsalis have attracted attention, and the vomiting is not infrequently attributed to intestinal obstruction, or to perforation of the stomach, with the result that laparotomy is performed. Rectal crises consist of painful and prolonged tenesmus; vesical crises of severe dysuria and laryngeal crises of prolonged spasm of the larynx causing stridor, cough and dyspnoea.

**TROPHIC CHANGES.**—*Charcot's disease of joints.*—In some cases, usually those of a very chronic type, severe disease leading eventually to articular disorganisation, occurs in one or two joints. The first sign is usually rapid swelling in and around a joint, with effusion and oedema. The effusion, in slight cases, subsides slowly and the joint recovers, but more often the enlargement is followed by destruction of the cartilages, wasting of the ends of the bones, periarticular new-bone formation and destruction of the ligaments. The joint becomes disorganised, the range of movement is increased and crepitations of startling coarseness are heard and felt when the part is handled. The characteristic feature is the complete absence of pain. Dislocations occur readily, especially at the hip, and the presence of an arthropathy may be first revealed by the occurrence of a pathological fracture of the neck of the femur. The diseased joint sometimes becomes infected, most frequently in the foot. The joints most often attacked, and in order of frequency are: knee, hip, ankle, small joints of the hands and feet, the spine, shoulder and elbow.

Charcot's disease of joints is very frequently associated with negative Wassermann reactions, both in the blood and the cerebrospinal fluid. In one instance in which the blood and cerebrospinal fluid gave negative results, fluid aspirated from the affected joint gave a strongly positive reaction.

In certain tabetic patients changes occur in some of the bones, so that they break with a small degree of violence.

**Perforating ulcers of the skin.**—Trophic changes in the skin give rise to chronic ulcers, usually on the sole of the foot, which gradually increase in depth until the foot may be perforated. These ulcers, like the other trophic disturbances of tabes, are usually painless.

Tabetics tend to get thin, and a slow loss of weight is an early sign. If there is any tendency for the weight to increase, a paretic element is almost certainly present. Manifestations of syphilis in other organs are rare in the course of the disease, with the exception of aortitis, which occasionally occurs.

**Diagnosis.**—*Tabes dorsalis* is diagnosed by its clinical features. Examination of the blood and cerebrospinal fluid may not provide any evidence of syphilis; the Wassermann reaction is negative in one or the other in about 30 per cent. of cases and completely negative in both in about 15 per cent. The diagnosis rests on: (1) lightning pains; (2) characteristic sensory signs; (3) the Argyll Robertson pupil in one or both eyes; (4) absence of one or both ankle- or knee-jerks, or a definite diminution in one of them and (5) evidence of syphilis.

Patients rarely seek advice until the clinical manifestations are fairly well established, unless their early pains are severe or gastric crises occur. Even then it is nearly always found that the pupils are abnormal, the ankle-jerks are absent, and hypalgesia is present over some of the characteristic areas. The knee-jerks may still be present and even normal, but this should not interfere with the diagnosis if the ankle-jerks are absent.

Disseminated sclerosis often causes ataxia in the gait and may even in rare instances cause absence of the ankle-jerks, but signs of involvement of the pyramidal tract are usually definite, the light reflex of the pupil is retained, and superficial sensory loss, if any, has not the distribution and the selective character that are typical of *tabes dorsalis*.

Friedreich's ataxia is distinguished from *tabes* by the presence of pyramidal tract signs, dysarthria, nystagmus, pes cavus and usually some degree of scoliosis. Juvenile *tabes* is the most likely to be mistaken for Friedreich's disease.

The effects of cerebellar ataxia are usually pronounced in the upper limbs and in the articulation as well as in the gait, the pupils are not affected, the tendon-jerks, though possibly diminished, are not absent, and there is no sensory loss, and no sphincter disturbance. Because of these features the differential diagnosis from *tabes* is usually easy.

Peripheral neuritis causes loss of tendon-jerks and diminished sensation over the peripheral parts of the limbs, and frequently causes ataxia, but there is usually also a loss of power in the extremities and possibly wasting, there is no sensory loss on the chest and nose, the pupils are not affected, and in many cases the calves are very tender instead of being insensitive to pressure as they are in *tabes*.

Subacute combined degeneration of the cord associated with pernicious anaemia gives rise to ataxia, and loss of the ankle-jerks and knee-jerks, but the plantar reflexes are extensor, and the blood picture is that of pernicious anaemia, although the anaemia may not be pronounced.

There are two groups of cases between which the diagnosis is especially difficult, and, in an individual case, may be impossible. On the one hand, there is a group of cases of mild *tabes* occurring in adults but due to congenital infection, in which the blood-Wassermann reaction is negative and the cerebrospinal fluid is completely normal; and on the other, the group of non-syphilitic cases described by Foster-Moore and by Adie in which the patients have "tonic" or "pseudo-Argyll Robertson" pupils and absent tendon-jerks (see p. 1344). In the former group the typical patient is undersized and of poor physique. He comes under observation, as a rule, for some symptom which is not tabetic, fits being a frequent presenting feature; one or both pupils may be of true Argyll Robertson type and probably irregular in outline; and lightning pains, mild bladder trouble, or some other feature of *tabes* may be present. A family history of syphilis may be obtained. The typical patient in the other group is of normal physical development. The pupillary abnormality is probably limited to one eye, and the patient may be able to give a history of its onset. The irides look healthy. Apart from the abnormal pupil and some absent tendon-jerks the patient presents none of the multitudinous signs of *tabes*, and there is no history of syphilis in the family or in the individual.

**Course and Prognosis.**—In most instances *tabes dorsalis* is well established before some serious symptom brings the patient under observation. For this reason

it is usually impossible to determine the sequence and duration of the signs that are found, but if the onset of lightning pains and of ataxia are taken as landmarks, an idea of the extreme variability of the course of tabes in different cases will be obtained. In many patients the disease remains stationary in an early stage and causes no disability. In a larger number, however, inco-ordination appears after a pre-ataxic stage of 10 or 20 years. Some become ataxic within 5 years of the onset of pains, a few within a year. Once ataxia appears its rate of increase varies within wide limits. It may be so rapid that walking becomes impossible in a few weeks; it often increases very slowly, and only interferes seriously with walking after several years; while in a large number periods of increase alternate with long periods in which the symptom is either stationary or undergoes temporary amelioration.

The course of the other symptoms is equally variable. In general, irritative phenomenon—pains and crises—tend to diminish; while the manifestations of destruction of afferent fibres—diminished sensation, hypotonia, etc.—increase. Ocular palsies are frequently of short duration, and bladder and rectal symptoms are often temporary. It is impossible to foretell how any given case will progress, but there seems to be some connection between the period which has elapsed since syphilis was contracted and the rate of evolution of the disease—the longer the former the more benign the course. If the symptoms have increased slowly in the past, the future course is likely to be slow, whereas cases of rapid onset often progress rapidly. When optic atrophy occurs, blindness usually results eventually, and a proportion of these cases develop general paralysis of the insane.

The prognosis as to life is variable. Most tabetics die of intercurrent maladies or of some cardio-vascular complication. In many cases, as the result of efficient treatment, the malady undergoes arrest, and the patient may never become ataxic or grossly disabled. Such arrest may also be found in benign cases in persons who have at no time had any antisyphilitic treatment. Conversely, treatment is not always successful, and tabetics who have been rigorously treated may become progressively disabled. On the whole, the prognosis as to both working capacity and life is best in those cases in which the bladder can be kept free from infection.

**Treatment.—PROPHYLACTIC.**—This is on exactly the same lines as the preventive treatment of neurosyphilis in general. The diminution in the incidence of tabes dorsalis suggests that the present methods of treating syphilis in its early stages are much more effective in preventing tabes dorsalis than in preventing other forms of neurosyphilis.

**SPECIFIC.**—When tabes dorsalis is associated with a positive Wassermann reaction in the blood or in the cerebrospinal fluid, the specific treatment is the same as that described for general paralysis. Pyrexial treatment by short-wave therapy (but not by malaria) may occasionally be advisable, either because of persistent severe lightning pains or of abnormalities in the cerebrospinal fluid which are not abolished by repeated courses of penicillin.

When the Wassermann reaction is negative in the blood and cerebrospinal fluid, it is sometimes difficult to judge how much antisyphilitic treatment should be given, and the decision must depend on the clinical indications of activity of the disease. Lightning pains show that the disease is active. Even after all clinical evidence of activity has ceased, it is well to give the patient three or four times a year a month's course of a mixture of potassium iodide and liquor hydrarg. perchlor.

**TREATMENT OF SYMPTOMS.—Pains.**—These may be relieved with aspirin and other analgesic drugs. Morphine should not be employed. A course of antisyphilitic treatment usually reduces or stops the pains for a long time. Exposure to cold sometimes seems to precipitate or aggravate pains and should be avoided, as far as possible. In severe and intractable cases the operation of spino-thalamic cordotomy is justified.

**Ataxia.**—This can be greatly diminished in many patients by a course of Frenkel's exercises. Just as a normal person by practice and effort can learn to perform feats

of balance and muscular co-ordination which are impossible for one untrained, so the tabetic by concentrating his attention on his movements can be taught to make greater use of his remaining powers, and the results of re-educative treatment are often astonishing. In the more severe cases and when the patient is confined to bed, Frenkel's bed exercises should be employed. Constant supervision of the re-educative exercises is essential, and the treatment should begin in an institution or under the supervision of a skilled attendant.

**Bladder disturbances.**—When there is any difficulty in passing water a mixture containing 5 minims of liq. strychninæ thrice daily will be found useful. When the bladder is imperfectly emptied the use of the catheter should not be delayed. Only too often neglect of this matter leads to death from pyelo-nephritis. It is well to remember that serious infections may run a painless course and their presence must be sought for even when pain is absent. This entails an examination of the urine from time to time for evidence of inflammation in the urinary tract. If pus-cells are present in the urine, chemotherapy should be tried, and if this is unsuccessful, the bladder should be irrigated daily until the urine becomes normal. True incontinence of urine is often diminished by 5 minim doses of tincture of belladonna thrice daily, or by the use of the following pill: *R* Ergotin (Bonjean) gr. 1, Ext. Belladonn. gr.  $\frac{1}{2}$ . Ft. Pil. Sig. i t.d.s.p.c.

**Crises.**—Gastric crises, like the pains, are very resistant to treatment. The following should be tried: Tinch. chlor. et morph. co. min. 10 to 15, bismuth carb. gr. 15; Ac. hydrocyan. dil. min. 5, aq. ad fl. oz.  $\frac{1}{2}$ . Ft. mist. sig. One tablespoonful to be taken in water every 3 or 4 hours. Ephedrine, gr.  $\frac{1}{2}$  or gr. i may also afford relief, and may be given alternately with the mixture. The use of morphine is not justified. Rectal crises are sometimes relieved by small doses of grey powder with opium or pulv. ipecac. et opii. The lower bowel should be emptied daily by enemata. In mild cases with morning diarrhoea an enema or a suppository should be used before the first evacuation. Thereafter the patient should try to resist the desire to defecate, which soon passes away, and with a little training this troublesome symptom can usually be overcome. Laryngeal crises though very alarming are practically never fatal. They are usually relieved at once by an inhalation of nitrite of amyl.

**Optic atrophy.**—As soon as syphilitic optic atrophy is recognised energetic anti-syphilitic treatment is urgently called for, and for this condition particularly the use of penicillin has largely superseded other measures. No time should be lost in instituting penicillin therapy, but it should be started cautiously with doses of 10,000 to 15,000 units at 6-hourly intervals during the first day, and unless the case is an acute one, should be preceded for a day or two by the administration of potassium iodide and mercury by mouth, as described for general paralysis of the insane. The dosage of penicillin should be increased rapidly to at least half a million units daily, and a total of 10 million units should be given, mercury and potassium iodide being continued meanwhile and for some weeks afterwards. In acute cases, and especially when one eye is already blind, sympathectomy by excision of the stellate ganglion has been used for the purpose of increasing the circulation to the optic nerve on the better side. Previously malarial treatment was commonly used and some authorities still prefer to use this or some other pyrexial treatment as well as penicillin, but it is doubtful whether this is of additional benefit and the results obtained by various observers with penicillin alone are much better than those which preceded the introduction of this remedy.

After such a course of treatment the deterioration of vision is usually retarded and in favourable cases is arrested, but the patient must be kept under close supervision and any exacerbation of his visual symptoms should be regarded as a call for further treatment on the same lines as before. If the Wassermann reaction remains positive in the blood, the older antisiphilitic remedies may be employed, but arsenicals should be used judiciously and doses of 0.6 g. of neocarsphenamine should not

be exceeded; tryparsamide should not be given because of its toxic effect on the optic nerve fibres.

*Charcot's joints.*—As soon as this condition is discovered, the patient should be put to rest, the joint immobilised, and those measures used which tend to relieve the œdema and the effusion into the joint; and if occasion demands, the joint should be aspirated. When the joint becomes dry it should be rested for a long period. Arthrodesis is the most satisfactory treatment for the knee joint. In the case of the hip joint a satisfactory result is obtained with a caliper.

*Perforating ulcers.*—These should be curetted and dressed with a paste of iodine and starch.

## OTHER FORMS OF SPINAL SYPHILIS

### ACUTE TRANSVERSE MYELITIS

This condition is now fortunately rare in England. The patients are almost invariably males between the ages of 30 and 45, and the malady usually arises within a few years of infection, but it may come on at any time.

Over one or two segments of the spinal cord there is intense infiltration with small round cells and red cells and there may be small areas of softening. The surrounding meninges show similar local infiltration.

The symptoms are identical with those of acute transverse myelitis due to other causes (see p. 1542) and the ætiological diagnosis depends on the discovery of evidence of syphilis. As the onset is usually within a few years of the first infection the pupils are usually normal or not affected in any characteristic way: a history of syphilis is often obtainable: the Wassermann reaction is positive in the blood or cerebro-spinal fluid and usually in both.

Treatment with penicillin should be instituted carefully in all cases without waiting for the results of laboratory tests, and when the presence of syphilis is confirmed, it is probably helpful to add mercury and potassium iodide to the treatment (see p. 1461). A course of ten million units of penicillin is sufficient to eliminate the infection, but much of the damage to the spinal cord is of a permanent nature.

The first sign of recovery is usually some return to muscular tone in the lower limbs and this is followed by the development of extensor plantar and of withdrawal reflexes. Recovery of power and sensation continues slowly over many months but usually remains very incomplete.

### ERB'S SYPHILITIC SPASTIC PARAPLEGIA

This is a slowly developing condition which comes on many years after syphilitic infection. The spinal cord shows degeneration of the pyramidal tracts and some marginal degeneration involving particularly the direct cerebellar tracts.

Spasticity of the lower limbs becomes pronounced with corresponding weakness and typical reflex abnormalities. Sensory changes, if any, are slight, but vesical disturbances are the rule. Pupillary abnormalities may or may not be present.

### PACHYMEINGITIS HYPERTROPHICA CERVICALIS

In rare cases the dura mater in the cervical region undergoes a great gummatous and subsequently fibrous thickening, and the arachnoid and pia also become thickened and fused with it. The new tissue compresses the nerve roots, and weakness, wasting and sensory loss gradually develop in the arms. After a time the spinal cord is compressed and spastic paraplegia results.

## SYPHILITIC AMYOTROPHY

This closely resembles idiopathic progressive muscular atrophy (see *Progressive Muscular Atrophy*, p. 1554).

The spinal cord shows degeneration of the anterior horn cells, most pronounced in the cervical region, and also some syphilitic changes in the meninges and blood vessels.

The pupillary changes suggestive of neurosyphilis are absent in most of the cases. The muscular atrophy usually begins in the upper limbs, and, as a rule, the tendon jerks in the affected limbs are absent; the lower limbs may be normal, or may become spastic, or show wasting, or may merely lose their tendon jerks, but in some cases the wasting muscles retain their tendon jerks. Not infrequently there is some sensory loss of the tabetic type, and vesical disturbances are common.

The course may be steadily progressive, but in recent cases it is usually arrested by antisymphilitic treatment. In others the condition may remain stationary for long periods.

**Treatment.**—For all kinds of spinal syphilis the antisymphilitic treatment is the same as that described for general paralysis of the insane, and it should be controlled in the same way by examination of the cerebrospinal fluid.

## SUBACUTE AND CHRONIC SYPHILITIC MYELITIS

**Synonym.**—Subacute and Chronic Spinal Syphilis.

**Ætiology.**—The less acute forms may appear within the same age period and at the same interval after infection as the more acute, but on the whole they appear later.

**Pathology.**—The meninges become adherent and considerably thickened. They are infiltrated with small round cells, especially round their vessels. Similar infiltration is found round the vessels in the cord and along the septa. Changes in the nervous elements in the cord are usually limited to degeneration of fibres round the periphery.

**Symptoms.**—After a period of pain in the back, lasting weeks or months, there is a gradual development of spastic paraplegia. The latter may at first be variable. In most cases bladder control is impaired, and this may be the first symptom. There are usually some objective sensory disturbances in the lower limbs, but they are generally slight in comparison with the motor disturbances and may involve only certain qualities of sensation, e.g. appreciation of temperature, or of vibration, or sense of position in the toes. Evidence of *tabes dorsalis* may be present, in which case the knee-jerks and ankle-jerks may be absent, and the degree of spasticity is likely to be slight.

Symphilitic meningitis may affect the cauda equina. In that event it gives rise to a flaccid weakness of the parts below the knees, and weakness or paralysis of the vesical and anal sphincters. Some sensory loss may be found over the characteristic area on the buttocks, and perineum.

**Diagnosis.**—In the cases which occur within 5 years or so of infection the Wassermann reaction will almost certainly be positive in the blood or in the cerebrospinal fluid or in both. In those which develop many years after infection the Wassermann reactions may be negative. Pupillary abnormalities suggestive of neurosyphilis, and sensory loss of the tabetic type on the chest, arms and nose are likely to be present.

**Course and Prognosis.**—The former is very variable. Some cases show considerable remissions and aggravations; others a fairly steady deterioration. The rate of increase of paralysis may be very slow, or may lead to complete incapacity in a few weeks or months. Eventually urinary infection and bed-sores may develop.

Antisyphilitic measures arrest the disease, and usually bring about a fair degree of recovery.

**Treatment.**—This is the same as for other forms of spinal syphilis, together with special precautions for the bladder weakness (see under *Tabes*) and symptomatic treatment of the paraplegia.

#### SPINAL VASCULAR SYPHILIS

In rare cases the symptoms indicate that the chief incidence of the syphilitic disease is on the blood vessels of the spinal cord (see also *Acute Syphilitic Transverse Myelitis* on p. 1469).

Thrombosis of a segmental branch of the anterior spinal artery gives rise to sudden paralysis of the muscles of one side deriving their nerve supply from the same segment of the cord, e.g. paralysis of the deltoid and scapular muscles, and weakness of the triceps brachii muscle when the fifth cervical segment is affected. Similar paralysis in the opposite corresponding limb may occur within a few days. If the main anterior spinal artery becomes thrombosed in the cervical region, there is complete paralysis of both upper limbs with the exception of the hands. Either at once or within a few days sensory loss to pain and temperature appears in the arms. The muscles waste, and the clinical picture resembles that of syringomyelia. The tracts of the cord are little affected, and abnormal signs in the lower limbs are absent or slight. The Wassermann reaction is likely to be strongly positive in the blood, but may be negative in the cerebrospinal fluid.

At necropsy softening or cavitation within the cervical enlargement is found.

The treatment is the same as that of other forms of meningo-vascular syphilis.

#### CONGENITAL SYPHILIS OF THE NERVOUS SYSTEM

Affections of the nervous system are much less frequent in congenital syphilis than in the acquired disease. Viewed broadly, the pathological changes and the clinical manifestations are the same in both. Regarding the first, meningitis, endarteritis and gummata are common to both forms; but while *softening* from arterial disease is characteristic of acquired syphilis, *cortical cell atrophy and subsequent sclerosis* are prominent features in congenital cases. As for the symptoms, mental defects, with convulsions and spastic weakness of the limbs, are typical of congenital syphilis in contrast to the hemiplegias and monoplegias, with or without convulsions, which occur in the acquired form. It is noteworthy that the combination of obvious visceral and integumental lesions, with parenchymatous degeneration of the nervous tissue, is very common in the congenital, but not in the acquired disease.

**Symptoms.**—Many syphilitic infants suffer from convulsions during the first 2 years of life and in many cases these are given as the cause of death. In those who survive, fits may continue or they may begin again towards the end of childhood, the latter being more common. The fits in some cases have all the aspects of idiopathic epilepsy, and may continue throughout life without the addition of any symptoms suggestive of local brain disease. In another group, convulsions are followed by symptoms of hemiplegia or of spastic diplegia. The same defects may appear apart from convulsions. Hydrocephalus develops in some cases.

Mental impairment is one of the common features of the disease. Idiocy is rare. More often the defect is first noticed between the ages of 5 and 15 years. The child may merely cease to learn, and retain any acquirements he possesses, or he may lose his memory and become slowly demented.

Vision is often defective as a sequel of atrophy of the optic nerve or of choroido-retinitis or simply of interstitial keratitis, and bilateral deafness is not uncommon. Affections of the remaining cranial nerves are rare.



Juvenile general paralysis appears most often between the ages of 10 and 17 years. It has been seen as early as the eighth, and as late as the thirtieth year. In some cases it results from congenital syphilis, in others from syphilis acquired in infancy or in childhood. The physical signs are the same as in the adult form. The mental symptoms, as might be expected, differ from those in adults, when mental decay sets in before the appearance of the instincts and passions which form the content of the delusions in older patients. A boy of 12, for example, is not likely to have delusions regarding his wealth or his intellectual capacity or his sexual powers, although he may well have grandiose ideas concerning his physical strength. Optic atrophy is very common in juvenile cases, and as in adults, signs of tabes are present in many cases.

Juvenile tabes presents the same features as in adults. It is, however, very uncommon in its pure form because most cases begin with optic atrophy and go on to tabo-paresis. It is important to remember that in rare instances, tabes in an adult owes its origin to congenital syphilis or to syphilis acquired in infancy. In such cases the blood and cerebrospinal fluid are usually normal.

The diagnosis of congenital syphilis of the nervous system rarely causes any difficulty, as the patients almost invariably present some of the stigmata of their malady.

One or more courses of penicillin should be given until the cell-content of the cerebrospinal fluid becomes and remains normal and thereafter treatment by mercury should be carried on, but the results are often disappointing.

## THE DEMYELINATING DISEASES

### DISSEMINATED SCLEROSIS

**Synonyms.**—Multiple Sclerosis; Insular Sclerosis.

**Ætiology.**—After intracranial new-growths and cerebral vascular disease, disseminated sclerosis is probably the commonest incapacitating disease of the nervous system having displaced, in this country at least, syphilis of the nervous system. It has its highest incidence in northern Europe, is less common in North America and relatively rare among the white population of the Southern hemisphere.

Cases have been recorded in which the disease was first noticed after acute illnesses, such as scarlet fever, influenza and rheumatism; but it is probable that these simply made more prominent a condition already present. Febrile illnesses are usually followed by increase in the symptoms, and many patients with disseminated sclerosis relate that they became much worse after an attack of influenza. In the great majority of the cases there is nothing in the family or personal history to which the disease can be attributed. In one instance, confirmed by examination after death, it attacked a mother and her child, and a few similar cases, as well as the affection of several members of a family, or of a household, have been recorded.

The onset is most frequent between the ages of 16 and 30, the sexes being affected equally. It is rare for the disease to begin after the age of 55.

The cause is still wholly unknown. There is no sure evidence that any of the demyelinating diseases of the nervous system are directly due to the action of a filtrable virus. The signs of inflammatory reaction in this disease are compatible with the view that it is infective in origin, but it may be added that it behaves like no known infective disease.

**Pathology.**—The disease has been described by Nageotte and Riche as "an affection constituted by multiple inflammatory foci, varying greatly in size and

number, disseminated irregularly throughout the length of the cerebrospinal axis. The chief features of these foci are (i) their sharp outline, (ii) their irregular and capricious shape, (iii) the fact that they do not interrupt the axis cylinders, which are only demyelinated and deformed as they traverse the focus. Hence the absence of Wallerian degeneration. The abundance of neuroglia in the foci justifies the name sclerosis which has been given to the process.

These foci are visible on naked-eye examination, the fresh ones as greyish translucent patches, the older ones as greyish or pinkish shrunken areas. Grey and white matter are both affected, the foci having some predilection for the walls of the ventricles. The foci bear no necessary relation to blood vessels.

Under the microscope the older patches are found to contain proliferated neuroglia and nerve fibres which have lost their myelin sheaths. The axis cylinders in the sclerosed areas escape destruction for a long time. For this reason secondary degenerations do not occur in the spinal tracts, and sections of the cord between lesions at different levels present normal appearances. Ganglion cells are also spared; hence wasting of the muscles supplied by the affected segments is not a feature of the disease. In recent patches, œdema is present, with infiltration by lymphocytes, plasma cells and compound granular corpuscles around the blood vessels, especially in the adventitial sheath of the veins. It is highly probable that these inflammatory changes represent the initial lesion, and that the alterations in the nerves and in the neuroglia are secondary to them.

**Symptoms.**—In the early stages the axis-cylinders in the diseased areas are not interrupted completely, but suffer partial and temporary impairment, which alters in intensity with the severity of vascular and other inflammatory changes in the tissues around them. Moreover, as the inflammation subsides in one patch a new one develops and produces a different set of symptoms. Hence it is not surprising that the earliest symptoms are often slight and fleeting, or that they may first appear now in one part and now in another. In spite of this, however, certain symptoms and physical signs appear with remarkable regularity and render disseminated sclerosis, in the more advanced stages at least, one of the most distinctive and most easily recognised diseases of the nervous system.

It is remarkable that though the demyelinating lesions, which are often of considerable size, occur anywhere in the central nervous system and commonly involve the fillet, the lateral fillet, the spinothalamic paths and the peripheral neurones in their intermedullary course and the visual path, yet anything but the most transient loss of function seldom occurs in connection with these systems. On the other hand, the phylogenetically newer systems—the pyramidal paths and the proprioceptive system commonly suffer permanent damage. The optic nerve is a common site for the development of an area of the disease. This may be situated anywhere between the globe and the optic chiasma and produce the very characteristic picture of acute unilateral retrobulbar neuritis.

**MOTOR SYMPTOMS.**—Weakness in the lower limbs is the symptom for which many patients first seek relief. Beginning with a feeling of heaviness or stiffness in one or both limbs, the weakness, which may be limited at first to one group of muscles, increases, in some uniformly, in a large number with remissions or with periods of apparent recovery, until at last, after a time which varies from a few weeks to many years, it ends in severe spastic paraplegia. The physical signs are those of pyramidal lesions in general—increased tone in the muscles and exaggeration of the tendon reflexes, diminution or loss of the abdominal and cremasteric reflexes and Babinski's plantar response. They are of extreme importance, for some or all of them may be present when the patient's complaints are still trivial, and they are found so constantly in all stages of the disease that the diagnosis of disseminated sclerosis is rarely made in their absence.

The paralysis can often be distinguished from that of other pyramidal affections

by the variations in its severity from time to time, and by the occurrence of remissions or of apparent recovery, the improvement sometimes lasting for weeks or months, and, in rare cases, for many years. In most cases, moreover, examination will reveal some other sign—nystagmus, intention tremor, or pallor of the disk—which betrays the cause of the paralysis. In one large group of cases, particularly common when the disease begins after the age of 35, the symptoms are those of a steadily increasing spastic paraplegia without remissions and without any indication, either in the physical signs or in the history of extra-pyramidal disease. The gait may be but slightly altered, even when the tendon reflexes are greatly exaggerated and the plantar responses are "extensor". Later, it becomes spastic or spastic and ataxic. Sometimes ataxy makes walking very difficult, when the power in the limbs is only slightly impaired. In the arms there is often loss of power associated with exaggeration of the tendon reflexes. In some cases the arms are affected before the lower limbs, when astereognosis and loss of sense of position from a lesion in the course of the corresponding posterior column of the cord produce one of the commonest of the early symptoms—the "useless arm".

**TREMOR.**—The characteristic tremor in the arms appears on voluntary movement only, and increases in rate and amplitude as the goal is approached. For these reasons it is called intention, volitional or terminal tremor. It is sought for by causing the patient to touch his nose with the tip of one finger. In its minimal form the tremor appears as two or three jerky movements of the finger just as the goal is attained, or the finger reaches the nose without any abnormal movement and then oscillates, so that it slips away from the nose again or depresses it several times before coming to rest. The tremor may be noticed first in writing or in performing other delicate movements, such as threading a needle. Later, the rate and amplitude of the movements increase, and the tremor, although still greatest at the end, appears almost as soon as a voluntary movement begins. In advanced cases it prevents all useful movements, and the patient is unable to do anything for himself. The arms are affected earliest and most often, but nodding of the head is common, and any part of the body may be affected. Beside intention tremor, other types of inco-ordination of the limbs are occasionally seen, such as those characteristic of lesions of the optic thalamus or of the mid-brain or of the cerebellum.

**SENSORY SYMPTOMS.**—*Subjective.*—Numbness and tingling in the extremities and alterations in the sensation of various parts are common complaints. They are often transient, and may be the only symptoms during the premonitory period. Severe pains are rare, but many patients complain of stiffness or of aching in the limbs and in the back. Occasionally intense neuralgic pain of trigeminal nerve distribution is found.

*Objective.*—Severe cutaneous sensory loss is not common, but careful examination will often reveal areas of skin in which sensation is impaired. Occasionally the loss is severe, and may show so sharp an upper level as to suggest the presence of a spinal tumour. In many cases the sense of position and passive movements in the limbs is seriously affected, in others loss of vibration sense is the only sensory sign. An isolated loss of the last named, in the legs, is a phenomenon of diagnostic importance. Like the other signs, the sensory disturbances often show considerable variations in extent and degree at different examinations.

**OCULAR SYMPTOMS.**—Attacks of *double vision* are frequent, and highly characteristic of the disease. Close interrogation, avoiding the leading question if possible, will often elicit an account of these attacks when the patient has not mentioned them at first, either because he has forgotten them, or because it does not occur to him that a symptom so remote or so transient can have any bearing on his present trouble. This diplopia is of the highest importance, because it is often the sole complaint when the patient seeks advice for the first time, and because its presence, or a history thereof, is often the deciding factor in the diagnosis of early cases with spinal symptoms.

Double vision in a young person should always arouse the suspicion of disseminated sclerosis, and if it is associated with signs of pyramidal tract disease, the combination makes the diagnosis almost certain.

*Strabismus* is uncommon. Even when the patient is seen whilst complaining of double vision it is unusual to detect any limitation in the range of the ocular movements. *Ptoxis* is rare.

*Nystagmus* is present in more than half the cases, but not so frequently as an early sign. It is usually fine, rapid and horizontal, appearing only when the eyes are directed to the side. In some cases the eyes oscillate constantly whatever their position. Except in rare cases, there is no apparent movement of objects, even when the oscillations are of wide range.

*Visual failure.*—Diminution of visual acuity due to lesions in the optic nerves—*retrobulbar neuritis*—occurs sooner or later in many cases. It may precede all other symptoms by a period of several years. As in the case of the other symptoms, it is subject to exacerbations and periods of improvement. A young healthy person complains of rapidly increasing mistiness of vision, usually in one eye, sometimes in both or in one after the other, reaching its maximum in a few hours or days; this is often preceded or accompanied by pain about the orbit, which is increased on moving the eye. In the common unilateral case the signs are those of a lesion in one optic nerve; the pupil on the affected side is larger than its fellow; its direct reaction to light is impaired, but it contracts well consensually. Tests with a small object, preferably coloured, reveal a central scotoma. At the onset the disk is usually normal, but in a few instances the inflammation reaches the nerve head, in which event the disk is blurred and swollen. Later the disk may be pale or normal. Rapid improvement of vision is the rule. Special tests may reveal a persistent slight loss of visual acuity, and a partial central scotoma or, very rarely, a complete central scotoma. Subsequent acute attacks are common. In some cases the onset of visual failure is gradual. Usually the defect is slight, but it may be serious, although complete blindness never occurs. In these cases the disk is pale, especially in its temporal portion, and the field shows a central scotoma or narrowing at the periphery.

*MENTAL SYMPTOMS.*—Defective memory and slight impairment of intellectual power are common. Some of the patients are morose and subject to fits of depression, but the majority are surprisingly cheerful, and do not seem to suffer mentally even when their physical state is most pitiable. This unjustified cheerfulness is called "euphoria". In many cases there is considerable loss of emotional control, and ready laughter or weeping is fairly common. More often there is merely a tendency to laugh at trivial things.

*SPHINCTER DISTURBANCES.*—These troubles arise from interference with the long paths in the spinal cord by which volitional consent and inhibition are held upon the act of micturition. Therefore, lack of control in the form of hesitancy and precipitancy are common, and retention may occur. In rare cases, control over the rectal sphincter is lost.

*OTHER SYMPTOMS.*—Deafness, giddiness and tinnitus, sometimes with repeated vomiting, are common. Epileptiform convulsions are rare. In most instances the distribution of the signs will indicate that the lesions are multiple; but sometimes, although the patches are numerous, the signs are those of a single lesion, say of the internal capsule, of the mid-brain or of the cerebellum.

*CEREBROSPINAL FLUID.*—In many cases, even when the disease is in an active phase, the fluid is normal. In others there may be a moderate increase in protein, not usually more than 80 mg. per cent. and a lymphocytic pleocytosis of 10 to 30 per c.mm. The Lange colloidal gold test is negative in about half the cases. In the other half the test is positive and may be of the luetic or parietic type. The latter variety may be strongly marked, and when occurring in association with a negative Wassermann reaction is very suggestive of disseminated sclerosis.

**Diagnosis.**—The combination of spastic weakness of the legs with "Charcot's triad" of symptoms—namely, intention tremor, nystagmus and scanning speech—which is so widely and so erroneously regarded as characteristic of the disease and as necessary to its recognition, is rarely seen except in the later stages of disseminated sclerosis. As this malady usually presents itself to us in its initial stages, when it may and should be diagnosed, it commonly consists in a group of signs of involvement of the pyramidal tracts: namely, increased tendon jerks, Babinski plantar responses, absent abdominal reflexes, a little weakness of dorsiflexion of one or both feet, possibly also some weakness of flexion of the proximal segments of the lower limbs, and usually a degree of impairment, or loss, of vibration sense over the malleoli. In many cases, this is all we can find, but in an otherwise healthy young adult, it is a syndrome more likely to be due to disseminated sclerosis than to any other pathological process.

Perhaps there may be confirmatory signs, such as a little nystagmus, slight intention tremor or sensory ataxy of an arm; it may be pallor of the temporal half of one or of both disks—a pathognomonic sign. If some or all of these signs have, as it were, been arrived at after such a fluctuating course as we have seen to be so typical of most cases of disseminated sclerosis, then diagnosis can be no longer in doubt, and it is comparatively seldom that pathological examinations of blood or cerebrospinal fluid are really necessary for this end.

When, after some years, the disease is fully developed it still retains its individuality. The patient is commonly euphoric, there is frequently tremor of the head, and sometimes of the whole body, when the patient tries to stand or walk. The arms are unsteady, the legs spastic and weak—sometimes showing a tendency to pass into the condition of "paraplegia in flexion". There is little sphincter control left, but cutaneous sensibility is commonly almost or quite intact.

At whatever stage disseminated sclerosis comes under observation, a careful enquiry into the history of the illness is important, and to elicit this requires a knowledge of the natural history of this disease as it has been outlined here.

Disseminated sclerosis has to be diagnosed from various diseases, of which we will consider the following:

**Hysteria.**—The serious mistake of attributing the early symptoms of this relentless disease to hysteria can be avoided by the taking of an accurate history combined with a careful examination of the nervous system. Pallor of the disk, absence of the abdominal reflexes, or a distinct difference between them at corresponding points on opposite sides, unequal exaggeration of one or more of the tendon reflexes when compared with their fellows, an extensor plantar response on one or both sides—any one of these signs alone would render a diagnosis of hysteria untenable.

**Compression of the cord.**—When the signs in disseminated sclerosis are purely spinal, the diagnosis from *spinal tumour* presents real difficulties. The first may be mistaken for the latter, when the paralysis increases steadily without remissions and is associated with sensory loss extending upwards to a definite level, while the reverse error may be made when the symptoms caused by a tumour are purely motor, or vary in intensity, or are associated with nystagmus.

**Friedreich's ataxia.**—This may be suggested by the presence of ataxy in a young patient with disseminate sclerosis. The distinction can be made at once, for in the latter disease the tendon reflexes in the lower limbs are exaggerated, whereas they are lost early in Friedreich's disease.

**Subacute combined degeneration of the cord.**—In the rare cases where disseminated sclerosis has its onset in middle-aged subjects, the combination of manifestations indicative of involvement of the posterior and lateral columns of the cord together with the presence of paræsthesia may closely simulate subacute combined degeneration. Investigation of the blood for changes of pernicious anæmia and of the gastric juice for free HCl. will usually render the differential diagnosis certain.

*Spinal syphilis* may also produce a paraplegia of variable onset which may be associated with evidence of scattered lesions elsewhere in the nervous system. An examination of the blood and spinal fluid will usually clear up any doubt.

*Cervical spondylosis* in middle-aged and elderly subjects may give rise to a fluctuating lesion of the cervical cord which is very apt to be misdiagnosed as disseminated sclerosis.

**Course and Prognosis.**—Despite the remarkable fluctuations which may mark its course, the disease ultimately disables the sufferer and is the cause of his death. Nevertheless, it is important to remember that after the initial outbreak of symptoms, some patients regain normal physical capacity, lose all abnormal physical signs and lead a normal life for several years; 5, 10 and 15 year periods of this kind are by no means rare, and in general it may be said that the period of evolution of the disease is longer than is generally supposed. On the other hand, a few cases run a rapidly downhill course from the onset. The later in life disseminated sclerosis makes its first appearance, the more benign its course, and sufferers may be found who have reached old age without gross or total disablement. Commonly, after two or three fresh exacerbations with intervening recoveries of greater or less completeness, a slowly increasing permanent disability sets in. It is not possible to say that those cases which run the longest and less distressing course owe this to treatment, for many untreated cases fare relatively well. But there are certain factors which do appear to influence its course unfavourably in most, though not in all, instances; thus, intercurrent illness, especially if it be febrile, injuries which disable the patient for a short period, all surgical interventions—including the therapeutic interruption of pregnancy which is designed to avert the frequently seen exacerbations that follow the puerperium—and prolonged or recurrent physical exhaustion.

**Treatment.**—The behaviour of disseminated sclerosis makes the assessment of any mode of treatment extremely difficult, and a failure to appreciate the wideness of its fluctuations and the length and completeness of some of its remissions is responsible for many therapeutic claims that in the hands of those best acquainted with this malady fail to justify themselves. So far, there is no remedy which exerts any constant or certain influence upon the course of the disease.

The most important general considerations in treatment are to provide complete rest in bed during an acute relapse, and to arrange for a sheltered life during periods of remission or when the disease has become established.

Of drugs, arsenic is the remedy which has had the longest vogue, and many believe that it is of value, though it cannot in any sense be regarded as curative. It may be given as Fowler's solution, starting with a dose of min. 3 t.i.d. and increasing it to min. 8 t.i.d. over a period of 3 to 4 weeks. If this method is used, it is best to stop all arsenic for a week at the end of each complete course. Not every patient can tolerate doses larger than min. 3 or min. 4 three times daily. This method is probably as useful as that of intramuscular injection, but considerations of expediency may dictate the use of the latter method.

A more recently employed drug is quinine hydrochloride in doses of gr. 3 to 5 twice daily, continued over a long period. Here, again, intolerance may intervene and prevent this. Periodic courses of quinine bismuth iodide have also been advocated. Other recent forms of medication include liver therapy, pyrexial therapy, protein shock therapy and vaccine therapy. None of these has justified itself, and when it is recalled that a febrile illness commonly aggravates the severity of disseminated sclerosis, it is scarcely surprising that pyrexial therapy should sometimes have the same result.

The fact that disseminated sclerosis is sometimes—though not always—adversely affected by a confinement has led to the increasing advocacy of terminating pregnancy at the third month to avert this ill effect. But this procedure is exposed to the same objection as a full-term delivery or any surgical procedure, and sometimes has the

same unfortunate influence upon the course of the malady. It is therefore not a therapeutic measure that can be justified by its results. The correct procedure is to take every possible measure to maintain the health and nutrition of the pregnant woman, and to afford her at this time and after the puerperium more than the ordinary amount of rest. This is the rational, if not always the acceptable, line of treatment. Further, women suffering from the disease in an active phase should be advised against becoming pregnant.

Of great importance is the right ordering of the patient's life, when practicable, and the avoidance of fatigue in the early stages of the disease.

## OTHER DEMYELINATING DISEASES OF THE NERVOUS SYSTEM

There exist a number of other diseases of the central nervous system having considerable pathological affinities with disseminated sclerosis in that they depend upon a demyelinating process predominantly of the white matter, which may be either diffuse or localised and predominantly cerebral or spinal in incidence.

Of these disorders Schilder's disease, in which the morbid process is confined to the brain (p. 1412), and acute encephalomyelitis associated with acute specific fevers (p. 1411), the incidence of which may fall on either the brain or spinal cord or upon the two together, have already been considered in the article on encephalitis.

There remains for consideration the syndrome of neuromyelitis optica.

There are points of considerable resemblance between these three disorders and disseminated sclerosis, particularly as regards their pathology, but there are equally significant points of difference, and whether or not they are ætiologically related cannot at present be affirmed.

## NEUROMYELITIS OPTICA

**Synonyms.**—Diffuse Myelitis with Optic Neuritis; Devic's Disease.

**Definition.**—A form of disseminated myelitis, preceded or accompanied by retrobulbar neuritis, with or without papilloedema. It is commonly acute in onset, and may end in death or in arrest with residual disabilities. Complete recovery is rare. Persons of all ages from adolescence onwards may be affected.

**Ætiology.**—Nothing whatever is known of its causation, and therefore it has been suggested that the disease is infective. None of the neurotropic viruses is known to produce the demyelination which is the characteristic lesion of the disease, nor is there any evidence that this is bacterial.

**Pathology.**—The spinal cord shows either diffuse or multiple disseminated lesions. They may be confined to a few segments of the cord, or may be found from end to end of this structure. The essential feature of the lesions is a demyelination of axis cylinders. There is also round-celled perivascular infiltration, an intense proliferation of microglial cells and a multiplication of tiny vessels in the affected areas. The optic nerves present the same type of lesion, namely, an intense demyelination of the nerve fibres. In general the pathological changes are more intense than those of disseminated sclerosis and show less evidence of partial remission.

**Symptoms.**—The blindness which indicates the optic nerve lesion may precede or may follow the appearance of paraplegic symptoms. The latter develop rapidly, and may spread upwards until sensory loss and muscular weakness reach the upper thoracic level. Blindness, with some swelling of the optic disk, and central scotoma may ensue. The patient may become progressively worse and die; or the paralysis

may become stationary and in rare instances proceed to complete recovery of both power and of vision; or the subject may be left with disability of varying severity.

The paraplegia is that characteristic of a diffuse spinal lesion in that there is sensory loss, paralysis and loss of sphincter control.

**Treatment.**—No treatment has any clear influence upon the course of events. *Arsenical preparations have been employed—as for disseminated sclerosis.* The management of the case is that of any case of paraplegia.

## HEREDITARY AND FAMILIAL DISEASES

### 1. FRIEDREICH'S ATAXIA

**Synonyms.**—*Friedreich's Disease; Hereditary Ataxia.*

**Definition.**—An hereditary disease characterised clinically by a progressive ataxia, and pathologically by the degeneration in the spinal cord of the posterior columns, lateral columns (pyramidal tracts), and spino-cerebellar tracts and in the cerebellum of a number of the Purkinje cells.

**Ætiology.**—Transmission occurs both through the males and the females. Indirect heredity is the most common, for the reason that the subjects of this disease are usually afflicted in childhood and incapacitated by the time adult life is reached, and therefore they do not procreate. Direct heredity is, however, by no means so uncommon as has been supposed. Isolated cases in which no heredity can be traced are not rare. The first signs of the disease usually appear in early childhood and before the sixth year; but symptoms may not be evident until a few years later. In a considerable number of cases, however, the onset is delayed until the time of puberty, while in a few examples it may be delayed until after the age of 30 years. As a rule the age incidence is approximately the same in each child-rank of the same family; but sometimes the phenomenon of "anticipation" is well marked, the disease appearing at an earlier age in each succeeding generation. *The disease is said to be slightly more common in males.*

**Pathology.**—The spinal cord is unusually small, and apparently this smallness may be congenital, and the posterior roots tend to be small, grey and poorly myelinated. The essential change is a primary degeneration of certain neurones in the dorsal column of the spinal cord, of the pyramidal tracts and of the spino-cerebellar tracts, both dorsal and ventral. This degeneration commences first in the periphery of the axon, which slowly dies back towards the nutrient cell body.

The degeneration of the dorsal columns is usually the earliest change, and remains the most prominent feature throughout. The degeneration of the fibres of the pyramidal tract appears later.

The spino-cerebellar tracts are constantly degenerated, the direct cerebellar tract being the most seriously involved. The cells of Clarke's column, from which the direct cerebellar tract takes origin, and around which the pyramidal tracts end, degenerate and disappear, as does also the network of collaterals which surrounds these cells. Consequent upon these degenerations, and secondary to them, well-marked neuroglial proliferation or sclerosis occurs. *The cerebellum may be normal, or it may show varying degrees of atrophy of Purkinje's cells, or of any other of its cell elements, and of the tracts connected therewith.*

**Symptoms.**—The onset is always insidious, and physical signs of abnormality usually precede any complaint on the part of the patient or his relatives. The first symptoms are generally complained of between the sixth and the tenth year of childhood; but if a careful examination be made of the younger members of the families upon which Friedreich's disease is incident, *physical signs of the disease, especially*



the extensor response in the plantar reflex, the retraction of the great toe and some degree of pes cavus may often be found before the sixth year.

Ataxia is always the first sign to appear, and this is shown by an awkwardness of gait and a tendency to stumble and fall readily. Sometimes it is obvious from the history, that the ataxy dates from the earliest years of infancy when it is said that the child was never strong on his legs from the time of learning to walk, and that he could never run properly or join on equal terms with other children at play. As the disease progresses, the gait slowly becomes more irregular and clumsy. The patient walks with his feet upon a broad base, and staggers and reels from side to side; but, notwithstanding this, he keeps a fairly direct line of progression. He takes short steps which are unequal, and which are irregular in relation to the line of progression, and the movement of each foot as it is raised is poorly co-ordinated. There is never the undue excursion and noisy stamping of the feet which are so characteristic of the gait of tabetic patients.

In standing, the body oscillates from side to side in slow and clumsy fashion, and coarse tremors of the head and trunk are constant features in advanced cases (titubation). Sometimes Romberg's sign is present; but this is never so well marked as in tabes, and it is frequently absent. The ataxy invades the upper extremities, as a rule, later than the legs. There is first clumsiness with the finer movements, and then little by little with all the movements. It closely resembles the ataxia due to gross disease of the cerebellum, and differs from that which occurs in tabes. That irregular breaking of a movement towards the end of its accomplishment, which has been long termed "intention tremor", is frequently seen.

Irregular involuntary movements, often described as like those of chorea or of myoclonus, occur in advanced cases, and are most frequently seen in the head and neck as nodding movements and jerky tremors. Nystagmus is usual; it is generally seen with lateral deviation of the eyes, and may be very irregular. Dysarthria is almost constant, and is gradually progressive. At first the speech is of the slurred "cerebellar" type, but with increasing ataxia it becomes scanning or drawing.

The strength of movements is at first little impaired; but as the disease advances and the pyramidal degeneration increases, the power is gradually lost in proportion to the degree of the pyramidal degeneration, which varies greatly in different cases. The lower extremities are affected first and most, and later the arms, and in severe cases at a late stage paralysis may be almost universal.

The condition of the muscular tone depends upon the relative degree of degeneration in the posterior roots and in the pyramidal tracts respectively, the former tending to abolish and the latter to increase it. As a rule the influence of the posterior root degeneration is preponderant and, therefore, the limbs are flaccid and hypotonic, but occasionally they are somewhat rigid. Contractures are the rule, but these are confined to the lower extremities. The most constant of these produces the characteristic "pes cavus". Moderate wasting of the small muscles of the feet and hands is not very uncommon. Sensibility is but little affected; but in most cases minute examination reveals slight relative loss to touch, pain and temperature, most marked at the periphery of the limbs and diminishing upwards. Similarly there may be slight loss of sense of position in the limbs, and diminished vibration sense.

The ocular movements are almost always intact apart from the already described nystagmus. In rare instances strabismus, diplopia and ptosis have been recorded. The pupils are not affected. Optic atrophy is a rare phenomenon in Friedreich's disease, yet it has been reported in quite a number of otherwise typical cases.

Mental symptoms are usually not conspicuous, but some of the patients are of poor mentality from the first, while others show a tendency to severe mental degeneration in the later stages of the disease. Emotional instability, irritability and outbursts of temper may occur.

Absence of the tendon reflexes is a most characteristic feature, and is often the

first objective sign of the disease, but in cases in which there is a major degeneration of the pyramidal tracts, the knee-jerks may persist or even be brisk into the advanced stages of the disease. The abdominal reflexes gradually disappear. The plantar reflex is invariably an extensor response. The sphincters usually escape. The cerebrospinal fluid presents no abnormality.

Spinal curvature is very common, and may reach a severe degree. It consists of a scoliosis of the dorsal region, and often with some kyphosis, and with a compensatory reverse lumbar curve. The cause of this deformity is probably the defect in the postural tone of the muscles.

**Diagnosis.**—In uncomplicated cases the diagnosis is a matter of no great difficulty on account of the strikingly distinct nature of the symptoms. Friedreich's disease can hardly be mistaken for tabes, since the history of heredity, the peculiar deformity of the feet and spine, the extensor plantar reflex, the speech affection and the nature of the ataxy contrast strongly with the loss of pain sensibility and of deep sensibility, the pupillary changes, the sphincter trouble, the abnormal Wassermann reactions and the abnormal cytology of the cerebrospinal fluid in tabes. The distinction from disseminated sclerosis presents more difficulty; but in this disease the onset never occurs in childhood, there is no heredity, the deep reflexes are never lost and the spinal deformity does not occur.

**Course and Prognosis.**—The course of the disease is usually progressive in slow and irregular fashion, and the prognosis is therefore in every case serious; but the average duration of the disease is over 30 years, and in some cases it seems to have no tendency to shorten life. The prognosis is worse and the course more rapid in those patients who have shown disability from the time of learning to walk. In some cases the disease appears to become arrested. Intercurrent maladies, febrile illnesses and debilitating influences generally, may have an effect in hastening the advance of the disease, and bringing about a fatal termination. Confinement to bed from any cause whatever has a bad influence upon the ataxy, and upon the capacity for walking.

**Treatment.**—No treatment is known which specifically affects the malady. General tonic treatment, and all measures which improve the general health and mental well-being, often have a surprising effect in improving the ataxy. Re-educational training of the limbs and trunk in the form of Frenkel's exercises are most beneficial. Properly designed boots to ensure the most advantageous use of the deformed feet must be provided.

## 2. DELAYED CEREBELLAR ATROPHY

Of all the primary atrophies of the cerebellum it may be said that their aetiology is unknown but the cause probably endogenous. In some forms there is clear evidence of heredo-familial factors but not in all. Some of them appear in early infancy, while others manifest themselves in later life and are hence called "delayed". The infantile forms are extremely rare. Of the delayed varieties, much the least uncommon is an atrophy of the cerebellar cortex—*Marie's delayed cortical cerebellar atrophy*.

**Ætiology and Pathology.**—This disease affects both sexes, and shows itself at any age from 45 onwards. The lesion is bilaterally symmetrical, and is most marked on the upper anterior parts of the cerebellum. It is essentially a cortical atrophy, with disappearance of the Purkinje cells as its characteristic feature. Familial incidence has been described by Holmes and others.

**Symptoms.**—The clinical picture is that of a slowly developing ataxia of gait, accompanied by a disorder of articulation; ataxia of the upper limbs develops later, but nystagmus rarely occurs. In many cases the tendon jerks are exaggerated, indicating an element of spinal degeneration.

same unfortunate influence upon the course of the malady. It is therefore not a therapeutic measure that can be justified by its results. The correct procedure is to take every possible measure to maintain the health and nutrition of the pregnant woman, and to afford her at this time and after the puerperium more than the ordinary amount of rest. This is the rational, if not always the acceptable, line of treatment. Further, women suffering from the disease in an active phase should be advised against becoming pregnant.

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**Definition.**—A form of disseminated myelitis, preceded or accompanied by retro-bulbar neuritis, with or without papilloedema. It is commonly acute in onset, and may end in death or in arrest with residual disabilities. Complete recovery is rare. Persons of all ages from adolescence onwards may be affected.

**Ætiology.**—Nothing whatever is known of its causation, and therefore it has been suggested that the disease is infective. None of the neurotropic viruses is known to produce the demyelination which is the characteristic lesion of the disease, nor is there any evidence that this is bacterial.

**Pathology.**—The spinal cord shows either diffuse or multiple disseminated lesions. They may be confined to a few segments of the cord, or may be found from end to end of this structure. The essential feature of the lesions is a demyelination of axis cylinders. There is also round-celled perivascular infiltration, an intense proliferation of microglial cells and a multiplication of tiny vessels in the affected areas. The optic nerves present the same type of lesion, namely, an intense demyelination of the nerve fibres. In general the pathological changes are more intense than those of disseminated sclerosis and show less evidence of partial remission.

**Symptoms.**—The blindness which indicates the optic nerve lesion may precede or may follow the appearance of paraplegic symptoms. The latter develop rapidly, and may spread upwards until sensory loss and muscular weakness reach the upper thoracic level. Blindness, with some swelling of the optic disk, and central scotoma may ensue. The patient may become progressively worse and die; or the paralysis

may become stationary and in rare instances proceed to complete recovery of both power and of vision; or the subject may be left with disability of varying severity.

The paraplegia is that characteristic of a diffuse spinal lesion in that there is sensory loss, paralysis and loss of sphincter control.

**Treatment.**—No treatment has any clear influence upon the course of events. Arsenical preparations have been employed—as for disseminated sclerosis. The management of the case is that of any case of paraplegia.

## HEREDITARY AND FAMILIAL DISEASES

### 1. FRIEDREICH'S ATAXIA

**Synonyms.**—Friedreich's Disease; Hereditary Ataxia.

**Definition.**—An hereditary disease characterised clinically by a progressive ataxia, and pathologically by the degeneration in the spinal cord of the posterior columns, lateral columns (pyramidal tracts), and spino-cerebellar tracts and in the cerebellum of a number of the Purkinje cells.

**Ætiology.**—Transmission occurs both through the males and the females. Indirect heredity is the most common, for the reason that the subjects of this disease are usually afflicted in childhood and incapacitated by the time adult life is reached, and therefore they do not procreate. Direct heredity is, however, by no means so uncommon as has been supposed. Isolated cases in which no heredity can be traced are not rare. The first signs of the disease usually appear in early childhood and before the sixth year; but symptoms may not be evident until a few years later. In a considerable number of cases, however, the onset is delayed until the time of puberty, while in a few examples it may be delayed until after the age of 30 years. As a rule the age incidence is approximately the same in each child-rank of the same family; but sometimes the phenomenon of "anticipation" is well marked, the disease appearing at an earlier age in each succeeding generation. The disease is said to be slightly more common in males.

**Pathology.**—The spinal cord is unusually small, and apparently this smallness may be congenital, and the posterior roots tend to be small, grey and poorly myelinated. The essential change is a primary degeneration of certain neurones in the dorsal column of the spinal cord, of the pyramidal tracts and of the spino-cerebellar tracts, both dorsal and ventral. This degeneration commences first in the periphery of the axon, which slowly dies back towards the nutrient cell body.

The degeneration of the dorsal columns is usually the earliest change, and remains the most prominent feature throughout. The degeneration of the fibres of the pyramidal tract appears later.

The spino-cerebellar tracts are constantly degenerated, the direct cerebellar tract being the most seriously involved. The cells of Clarke's column, from which the direct cerebellar tract takes origin, and around which the pyramidal tracts end, degenerate and disappear, as does also the network of collaterals which surrounds these cells. Consequent upon these degenerations, and secondary to them, well-marked neuroglial proliferation or sclerosis occurs. The cerebellum may be normal, or it may show varying degrees of atrophy of Purkinje's cells, or of any other of its cell elements, and of the tracts connected therewith.

**Symptoms.**—The onset is always insidious, and physical signs of abnormality usually precede any complaint on the part of the patient or his relatives. The first symptoms are generally complained of between the sixth and the tenth year of childhood; but if a careful examination be made of the younger members of the families upon which Friedreich's disease is incident, physical signs of the disease, especially

the extensor response in the plantar reflex, the retraction of the great toe and some degree of pes cavus may often be found before the sixth year.

Ataxia is always the first sign to appear, and this is shown by an awkwardness of gait and a tendency to stumble and fall readily. Sometimes it is obvious from the history, that the ataxy dates from the earliest years of infancy when it is said that the child was never strong on his legs from the time of learning to walk, and that he could never run properly or join on equal terms with other children at play. As the disease progresses, the gait slowly becomes more irregular and clumsy. The patient walks with his feet upon a broad base, and staggers and reels from side to side; but, notwithstanding this, he keeps a fairly direct line of progression. He takes short steps which are unequal, and which are irregular in relation to the line of progression, and the movement of each foot as it is raised is poorly co-ordinated. There is never the undue excursion and noisy stamping of the feet which are so characteristic of the gait of tabetic patients.

In standing, the body oscillates from side to side in slow and clumsy fashion, and coarse tremors of the head and trunk are constant features in advanced cases (titubation). Sometimes Romberg's sign is present; but this is never so well marked as in tabes, and it is frequently absent. The ataxy invades the upper extremities, as a rule, later than the legs. There is first clumsiness with the finer movements, and then little by little with all the movements. It closely resembles the ataxia due to gross disease of the cerebellum, and differs from that which occurs in tabes. That irregular breaking of a movement towards the end of its accomplishment, which has been long termed "intention tremor", is frequently seen.

Irregular involuntary movements, often described as like those of chorea or of myoclonus, occur in advanced cases, and are most frequently seen in the head and neck as nodding movements and jerky tremors. Nystagmus is usual; it is generally seen with lateral deviation of the eyes, and may be very irregular. Dysarthria is almost constant, and is gradually progressive. At first the speech is of the slurred "cerebellar" type, but with increasing ataxia it becomes scanning or drawling.

The strength of movements is at first little impaired; but as the disease advances and the pyramidal degeneration increases, the power is gradually lost in proportion to the degree of the pyramidal degeneration, which varies greatly in different cases. The lower extremities are affected first and most, and later the arms, and in severe cases at a late stage paralysis may be almost universal.

The condition of the muscular tone depends upon the relative degree of degeneration in the posterior roots and in the pyramidal tracts respectively, the former tending to abolish and the latter to increase it. As a rule the influence of the posterior root degeneration is preponderant and, therefore, the limbs are flaccid and hypotonic, but occasionally they are somewhat rigid. Contractures are the rule, but these are confined to the lower extremities. The most constant of these produces the characteristic "pes cavus". Moderate wasting of the small muscles of the feet and hands is not very uncommon. Sensibility is but little affected; but in most cases minute examination reveals slight relative loss to touch, pain and temperature, most marked at the periphery of the limbs and diminishing upwards. Similarly there may be slight loss of sense of position in the limbs, and diminished vibration sense.

The ocular movements are almost intact apart from the already described nystagmus. In rare instances strabismus, diplopia and ptosis have been recorded. The pupils are not affected. Optic atrophy is a rare phenomenon in Friedreich's disease, yet it has been reported in quite a number of otherwise typical cases.

Mental symptoms are usually not conspicuous, but some of the patients are of poor mentality from the first, while others show a tendency to severe mental degeneration in the later stages of the disease. Emotional instability, irritability and outbursts of temper may occur.

Absence of the tendon reflexes is a most characteristic feature, and is often the

first objective sign of the disease, but in cases in which there is a major degeneration of the pyramidal tracts, the knee-jerks may persist or even be brisk into the advanced stages of the disease. The abdominal reflexes gradually disappear. The plantar reflex is invariably an extensor response. The sphincters usually escape. The cerebrospinal fluid presents no abnormality.

Spinal curvature is very common, and may reach a severe degree. It consists of a scoliosis of the dorsal region, and often with some kyphosis, and with a compensatory reverse lumbar curve. The cause of this deformity is probably the defect in the postural tone of the muscles.

**Diagnosis.**—In uncomplicated cases the diagnosis is a matter of no great difficulty on account of the strikingly distinct nature of the symptoms. Friedreich's disease can hardly be mistaken for tabes, since the history of heredity, the peculiar deformity of the feet and spine, the extensor plantar reflex, the speech affection and the nature of the ataxy contrast strongly with the loss of pain sensibility and of deep sensibility, the pupillary changes, the sphincter trouble, the abnormal Wassermann reactions and the abnormal cytology of the cerebrospinal fluid in tabes. The distinction from disseminated sclerosis presents more difficulty; but in this disease the onset never occurs in childhood, there is no heredity, the deep reflexes are never lost and the spinal deformity does not occur.

**Course and Prognosis.**—The course of the disease is usually progressive in slow and irregular fashion, and the prognosis is therefore in every case serious; but the average duration of the disease is over 30 years, and in some cases it seems to have no tendency to shorten life. The prognosis is worse and the course more rapid in those patients who have shown disability from the time of learning to walk. In some cases the disease appears to become arrested. Intercurrent maladies, febrile illnesses and debilitating influences generally, may have an effect in hastening the advance of the disease, and bringing about a fatal termination. Confinement to bed from any cause whatever has a bad influence upon the ataxy, and upon the capacity for walking.

**Treatment.**—No treatment is known which specifically affects the malady. General tonic treatment, and all measures which improve the general health and mental well-being, often have a surprising effect in improving the ataxy. Re-educational training of the limbs and trunk in the form of Frenkel's exercises are most beneficial. Properly designed boots to ensure the most advantageous use of the deformed feet must be provided.

## 2. DELAYED CEREBELLAR ATROPHY

Of all the primary atrophies of the cerebellum it may be said that their ætiology is unknown but the cause probably endogenous. In some forms there is clear evidence of heredo-familial factors but not in all. Some of them appear in early infancy, while others manifest themselves in later life and are hence called "delayed". The infantile forms are extremely rare. Of the delayed varieties, much the least uncommon is an atrophy of the cerebellar cortex—*Marie's delayed cortical cerebellar atrophy*.

**Ætiology and Pathology.**—This disease affects both sexes, and shows itself at any age from 45 onwards. The lesion is bilaterally symmetrical, and is most marked on the upper anterior parts of the cerebellum. It is essentially a cortical atrophy, with disappearance of the Purkinje cells as its characteristic feature. Familial incidence has been described by Holmes and others.

**Symptoms.**—The clinical picture is that of a slowly developing ataxia of gait, accompanied by a disorder of articulation; ataxia of the upper limbs develops later, but nystagmus rarely occurs. In many cases the tendon jerks are exaggerated, indicating an element of spinal degeneration.

**Diagnosis.**—With the foregoing features it is natural that the disease should frequently be mistaken clinically for disseminated sclerosis. The later age-incidence, the absence of nystagmus, of disk changes, of spasticity and of loss of sense of position and the steady progress of the malady should make the diagnosis of disseminated sclerosis untenable; while the reeling character of the ataxia and the sibilant instead of staccato quality in the articulation disclose the real nature of the disease. In *tabes dorsalis*, with which it may be confused because of the ataxia, numerous characteristic signs are present by the time ataxia becomes pronounced, and dysarthria is not a feature of *tabes*.

**Treatment.**—No treatment is known to have any effect on the degenerative process.

### 3. FAMILIAL SPASTIC PARALYSIS

**Ætiology.**—This rare disease is sometimes hereditary, but is more commonly familial and incident upon several children of the same parents. Sporadic cases also occur. The onset is gradual in early life, and usually occurs after the sixth year.

**Pathology.**—The pathological changes consist in a primary degeneration of the pyramidal neurones which apparently takes place in terms of the length; those supplying the lumbo-sacral region, being lower and longer, are earliest affected; those supplying the brain stem, being shortest, are the last to be affected. Degenerative changes in the neurones of the posterior columns of the spinal cord are often present, showing the transition to the pathological type of the hereditary ataxies.

**Symptoms.**—The clinical aspect consists in the slow development of spasticity and weakness, first and most in the legs, which gradually increases and progresses to the trunk and upper extremities, and involves the face last and least. The usual signs of pyramidal involvement are present in the loss of abdominal reflexes, increased deep reflexes and extensor type of plantar reflex. The malady is progressive, increasing to complete paralysis, and in its course contractures of the spastic muscles occur, that of the foot and leg producing some degree of *pes cavus*, while, above this, *flector* contracture at hip and knee is met with. Optic atrophy is by no means uncommon. Mental symptoms do not occur in uncomplicated cases, neither is epilepsy observed.

**Diagnosis.**—This malady is most easily confused with cerebral diplegia; but the latter disease appears much earlier, as soon after birth, in fact, as defective movement in the child can be ascertained. Further, cerebral diplegia is not a progressive disease in the majority of the cases, and it is often associated with mental deficiency and recurring convulsions.

**Treatment.**—This is the same as that of Friedreich's ataxia except that the purpose of exercises, if given, should be to secure the best use of the spastic lower limbs instead of to overcome ataxia.

### 4. CEREBRO-MACULAR DEGENERATION

#### 1. THE INFANTILE FORM

**Synonyms.**—Warren Tay-Sachs Disease; Amaurotic Family Idiocy.

**Definition.**—A family disease of infancy occurring chiefly, but not entirely, in the Hebrew race, affecting children during the first year of life, who are apparently quite healthy when born, and characterised by—(1) progressive mental impairment, ending in absolute idiocy; (2) progressive paralysis of the whole body; (3) progressive diminution in sight, ending in absolute blindness. Pathognomonic retinal changes are constantly present, consisting of a large and conspicuous "cherry-red

spot" in the region of the macula, and, in addition, optic atrophy occurs later and (4) a fatal termination in the marasmic state before the age of 2 years.

**Ætiology.**—Nothing is known of the ætiology of the disease apart from its familial and racial incidence. The tendency to the disease is unquestionably congenitally installed.

**Pathology.**—This is very striking. It consists of a progressive degeneration of the nerve cells from the highest to the lowest, and ultimately there may be no normal cells remaining anywhere in the nervous system. The degeneration takes the form of swelling of the cell protoplasm, and of the dendrites with chromatolysis, swelling of the hyaloplasm and destruction of the cell fibrils, followed by disappearance of the nucleus, and finally by absorption of the remains of the cell. The degenerating nerve cells are characterised by the accumulation of granules of lipoid substances which resemble those observed in other cells of the body in Gaucher's disease, Niemann-Pick's disease and the Hand-Schüller-Christian disease. Every cell of the central nervous system both of the brain, spinal cord and spinal ganglia is in the end similarly affected.

**Symptoms.**—There are few diseases in which the *clinical manifestations* are so perfectly uniform as in this malady. The children have all been born at full term, and in perfect health. They thrive well during the first 3 to 6 months of life, when they gradually become listless and apathetic, cease to take interest in the surroundings, and begin to show signs of the visual failure which ends in blindness. Later, the child is unable to sit up, or to hold up its head. The limbs, which may be slightly spastic at first, become flaccid and motionless. There is a gradual increase of all these signs. The mental defect becomes more and more noticeable, the paralysis more extreme, complete blindness follows and the patient sinks into a condition of marasmus, in which he dies. Convulsions, nystagmus and strabismus are sometimes present.

The retinal changes are pathognomonic and are due to a degeneration and disappearance of the nerve cells of the retina and their processes, which constitute the fibres of the optic nerve. This change is most intense in the region of the fovea centralis, where the retina thins and disappears over a circular area, exposing the vascular choroid. This gives rise to the characteristic appearance, on ophthalmoscopic examination, of a cherry-red spot in the region of the macula. This spot is actually a hole in the retina exposing the choroid. The optic disk shows progressive atrophy.

**Diagnosis.**—Distinction has to be made between this and other forms of progressive diplegia. The symptoms are so distinct that a physician, who is acquainted with the disease, and able to recognise the retinal picture, can hardly fail to make the correct diagnosis.

**Treatment.**—No treatment is of any avail.

## 2. OTHER FORMS OF CEREBRO-MACULAR DEGENERATION

In addition to the classical infantile form described in the preceding article, two other forms are well known in which the pathological changes are similar but much less severe than in the Warren Tay-Sachs disease, and there is also a similar familial incidence, but the onset of the malady occurs later in life and the course is less rapid and the result far less serious. The later the onset in life the slighter and less progressive are the symptoms. The cherry-red spot at the macula, so constant in the infantile form, does not occur in the later forms. The characteristic retinal change is a disturbance of the retinal pigment commencing in the macular region, rather like retinitis pigmentosa, accompanied by honeycomb changes at the macula and sometimes by optic atrophy. The *juvenile* form occurs in later childhood and is characterised by the association of the retinal changes and visual defect with some degree of mental deterioration. The *adult* form is the least progressive of any, and the



manifestations are the visual defect and retinal changes in the absence of mental deterioration.

## 5. HEPATO-LENTICULAR DEGENERATION

**Synonyms.**—Progressive Lenticular Degeneration; Wilson's Disease.

**Definition.**—A rare progressive disease of the nervous system, often familial, characterised by involuntary movements, rigidity and hypertonicity, with contractures, without signs of pyramidal disease; and by dysarthria, dysphagia, emotionalism and progressive emaciation. Several closely related clinical forms of the disease bear distinctive names: *tetanoid chorea* (Gowers), *pseudosclerosis* (Westphal), *progressive lenticular degeneration* (Wilson) and *torsion spasm*, and *dystonia musculorum deformans* (Thomalla). Cirrhosis of the liver occurs in all forms. The Kayser-Fleischer zone of corneal pigmentation occurs in the first three forms, but has not yet been recorded in torsion spasm. The most constant nervous lesions are found in the corpus striatum.

**Ætiology.**—The disease often occurs in children of the same parents, but there is no evidence that it is congenital or hereditary. The age of onset has been as early as 7 years and as late as 26 years. The primary and essential lesion is in the liver; its cause is unknown. Syphilis is not a factor.

**Pathology.**—A multilobular cirrhosis, with "hobnail" liver is always found after death. There is good evidence that the cirrhosis is not slowly progressive, but is the result of a number of attacks of acute hepatitis. The hepatitis has caused death in some members of affected families before nervous symptoms appeared. The nervous lesions are purely degenerative. In Wilson's cases they were almost confined to the lenticular nucleus, especially the putamen. Every degree of degeneration was seen, from discoloration and sponginess of the nucleus in rapidly fatal cases, to shrinkage and atrophy, and even to complete disintegration and excavation of the ganglion. Later observers have described lesions in many other parts of the nervous system. The lesions are often most intense in the corpus striatum, but the noxious agent has no strictly selective action on any one anatomical group of ganglion cells, or on any limited area of the nervous system. It is now known that the degenerate basal ganglia contain excessive amounts of copper compounds and that there is a persistent excess of this element in the urine as well as an increased urinary excretion of amino-acids.

**Symptoms.**—In many cases there are no symptoms of disorder of the liver during life. In other cases an account is obtained of symptoms referable to acute hepatitis before the onset of nervous symptoms—attacks of diarrhœa and vomiting, pyrexia, jaundice, migrainous headaches, hæmatemesis and sometimes definite ascites.

**Treatment.**—No curative treatment is known, but there is evidence that symptoms are improved and the progress of the disorder delayed by treatment with dimer-caprol (British Anti-Lewisite).

## 6. KERNICTERUS

**Definition and Ætiology.**—A yellow pigmentation of certain of the basal ganglia, associated clinically with motor disorders of the type known as extra-pyramidal, and found as a rare phenomenon in children who, normal at birth, develop jaundice within the first 3 days of life.

In neonatal jaundice the brain may be diffusely pigmented, or more rarely the pigmentation may be confined to the putamen, subthalamic and dentate nuclei, the cornu Ammonis and fascia dentata. To the latter variety of jaundice of the brain the name "Kernicterus" has been given by Schmorl. The nerve cells in the affected masses of grey matter show evidence of destruction and degeneration, while the nerve fibres are demyelinated.

**Symptoms.**—The child is healthy at birth, but within a few days develops intense jaundice, usually the form known as hæmolytic disease of the new-born (see p. 745) and now known to be due to Rhesus incompatibility between the parents, though kernicterus has been found in association with septic jaundice. The onset of jaundice is followed within 24 hours by tonic and clonic movements, muscular rigidity and opisthotonos, alternating with periods of flaccidity. If the child survives, involuntary movements of choreoathetoid form develop within a few weeks. Emotional instability and mental retardation appear as the child grows older.

**Diagnosis.**—Athetosis and comparable forms of involuntary movement are not rarely seen in children, and are in the majority of instances not associated with kernicterus. Yet when a case of such motor disorder is seen in a child in respect of whom there is a history of neonatal jaundice, the possibility of this disease should be borne in mind. Again, the development of marked symptoms of organic nervous disease immediately after the appearance of severe jaundice in a newly born infant should lead to a consideration of this condition as the probable pathological basis.

**Prognosis.**—There is a marked tendency for these patients to die during infancy or childhood of intercurrent disease, but a minority survive to adult life with a varying degree of mental impairment and disorder of movement.

**Treatment.**—There is no curative treatment and endeavour should be directed towards education and towards training in co-ordinated movements. In cases where sufficient intelligence exists much can be done by patient training, especially in the hands of trained workers.

## 7. NEUROFIBROMATOSIS

**Synonym.**—Von Recklinghausen's Disease.

**Definition.**—A complex disorder involving principally the skin and nervous system, and characterised in the former by the development of abnormal pigmentation and a great variety of tumours, and in the latter by the presence of multiple neuro-fibromata in the peripheral and less frequently the central nervous system.

**Ætiology.**—The disease is both hereditary and familial, though isolated cases occur. *Formes frustes* are common. Although the characteristic features evolve during the life of the patient, the malady undoubtedly results from congenital abnormality. It is often associated with other congenital and developmental anomalies of the nervous system and skeleton, and subjects of the disease show a remarkable propensity for neoplastic disorders.

**Pathology.**—The cutaneous lesions comprise fibromata, many of which are degenerate, naevi and areas of pigmentation. In the nervous system multiple fibromata occur in the peripheral and cranial nerves and in addition meningeal tumours and gliomata of the brain and spinal cord may be found.

**Symptoms.**—Of the essential features of the disease, the cutaneous lesions are usually the first to make their appearance. Some may be present at birth, others develop during childhood, adolescence or adult life. They present a great variety of forms. Abnormal areas of pigmentation are commonest. These have the appearance of café-au-lait patches, and vary in size from a mere freckle to a large zone involving a whole limb. Many are between the sizes of a sixpence and a shilling. The cutaneous tumours appear gradually. Some are pedunculated or sessile fibromata, often pigmented and usually soft to the touch. Others are naevoid in composition. They may attain great size, coming to form the large redundant folds of tissue known as plexiform neuromata. The fully developed cutaneous picture is that known as molluscum fibrosum.

The tumours on the nerve trunks are also fibromata but usually firmer than these in the skin. They may occur on any of the peripheral nerves, the limb plexuses, or the intraspinal portions of the nerve roots. Those peripherally situated are usually painless and seldom interfere with the function of the nerve on which they grow. They are occasionally painful on pressure. Those which originate on the spinal nerve roots produce the picture of spinal compression, commonly preceded by a long period of root pain. They are frequently multiple. Within the cranial cavity neurofibromata are most often met with on the acoustic nerves, but may occur on any of the cranial nerves and produce symptoms characteristic of their position.

Von Recklinghausen's disease is often found in association with other congenital anomalies, such as spina bifida, meningocele, cervical rib, syringomyelia, mental deficiency and epilepsy.

The tumours are liable to undergo malignant degeneration and it is not uncommon to find other tumours, such as meningiomata and gliomata in patients with this disorder.

**Course and Prognosis.**—In many cases the condition is compatible with a long and relatively normal life, though there is a tendency towards slow progression. Danger to life results only from central lesions in the cranial or spinal cavities, or from the rare malignant degeneration in the peripheral tumours.

**Treatment.**—Nothing is known to modify the natural course of the disease. Central tumours should be removed surgically as they arise, and cosmetic improvement can often be achieved for the cutaneous and subcutaneous lesions.

## 8. TUBEROSE SCLEROSIS

**Synonyms.**—Adenoma Sebaceum; Epiloia.

**Definition.**—A condition characterised clinically by the symptom triad of multiple cutaneous tumours of the cheeks and face, mental deficiency, and epilepsy, and pathologically by the presence in the brain of areas of gliosis of a peculiar type.

**Ætiology.**—Hereditary and familial incidence is common, but many isolated cases occur. No other factors are known. The sexes are equally affected.

**Pathology.**—The characteristic lesions of the brain consist of nodular tuberous masses, which are most plentiful under the ependyma of the ventricles, into the cavities of which they project like candle-gutterings. Similar nodules can be seen and felt scattered throughout the cortex, and rarely in the cerebellum or spinal cord. They consist of dense tangles of neuroglia cells, many of markedly pathological type. The cutaneous tumours consist of an overgrowth of the sebaceous glands embedded

in nœvoid and fibrous tissue. Tumours also occur in other tissues, namely rhabdomyomas in the heart and kidneys, and the so-called "phakoma" in the retina.

**Symptoms.**—These usually make their appearance in early childhood. Varying degrees of mental defect from feeble-mindedness to idiocy are universal. Epilepsy usually begins within the first few years of life and though any form may occur, generalised convulsion is the commonest. The characteristic skin lesions make their appearance during childhood, in the form of numerous verrucose, shotty papules on the butterfly area of the cheeks and nose. These are red or reddish-brown in colour, and the intervening skin is red and shiny. The extent and degree of this condition of sebaceous adenoma becomes more marked as the child grows older. Numerous other cutaneous tumours and congenital anomalies similar to these occurring in Von Recklinghausen's disease are met with.

**Course and Prognosis.**—The course is very slowly progressive. Most cases spend their lives in institutions for mental defectives, but frequently attain a considerable age.

**Treatment.**—Symptomatic treatment is indicated for the epilepsy, and when possible procreation should be vetoed and the patient cared for in a suitable institution.

## CEREBRAL DIPLEGIA

**Synonyms.**—Congenital Spastic Paralysis; Lobar Atrophic Sclerosis.

**Definition.**—A group of clinical conditions, dependent upon lack of, or imperfect development, or degeneration of the nerve cells of the cerebral cortex, basal ganglia or cerebellum. This agenesis of nerve cells may affect those cells of the pyramidal system which are the latest to develop before birth, namely those for the supply of the lower extremities and the resulting clinical condition is cerebral spastic paraplegia or *Little's disease*, or all the cells of the pyramidal system may be affected, producing generalised spastic rigidity. Again, the higher regions of the cortex may be affected, and the result is congenital idiocy. Similar affections of the cells of the basal ganglia result in congenital bilateral athetosis, and congenital chorea. When the cerebellum is involved, congenital cerebellar ataxy results. Further, there may be any combination of the above conditions.

**Ætiology.**—The malady may be apparent at the time of birth, as the child may be born with contractures present. More often, the signs of deficient or perverse movement, or of mental deficiency, appear during the first year of life, as the signs of cerebral activity commence to be exteriorised. In most cases no heredity can be traced, but sometimes several children of the same mother may be affected, and direct heredity has been known.

**Abnormalities of birth** are frequent. Premature, or precipitate birth, prolonged birth from uterine inertia rather than from dystocia, and asphyxia neonatorum are all common. The child is frequently the first born of its mother.

Collier has expressed the probable pathogenesis of cerebral diplegia as follows: "If we regard the brain from the time of its earliest stages of development as a field sown with seeds (neuroblasts), which germinate at different periods of foetal life, and the germination is not even complete at the time of birth, the germination of all the elements in due time and their complete development being necessary for the formation of the perfect brain, then we may liken the cause of diplegia to some baneful influence, such as a frost, which acting at a particular time, may spare those seedlings which are well developed and able to withstand it, and those seeds as yet not germinated, but which causes havoc among the tender germinating seedlings, either to their death or severe maiming. In some cases, as, for example, in *Little's disease*, the neuroblasts thus affected may, after a period of retarded development, ultimately become strong plants and complete their development. It is of interest that in the

highest degrees of cerebral agenesis—anencephaly, pituitary abnormalities seem to be constant."

A well-defined variety of cerebral diplegia associated with congenital deafness is now known to occur as a result of the mother suffering from rubella in the early months of pregnancy.

**Pathology.**—The essential histology of the affected regions is that of non-development, paucity in numbers and degeneration of the nerve cells, with corresponding absence, poor development, degeneration or a combination of these states, of the tracts which spring therefrom. The pyramidal tract, for example, may be found absent throughout, or it may reach to the medulla, or to the cervical region only, and so show at what period development was arrested. The changes in the nerve cells are followed by secondary gliosis. The final result is termed atrophic sclerosis. More often certain regions are profoundly affected, while others escape relatively or completely; but the distribution is always symmetrical upon the two hemispheres. The convolutions are unduly hard to the touch, and their surfaces often present a worm-eaten and faceted appearance. This irregular form of the convolutions, with wide, separating sulci, gives the brain a characteristic appearance, like that of a walnut kernel.

**Symptoms.**—The clinical picture of the several forms of cerebral diplegia presents a combination in varying degrees of certain characteristic symptoms, always bilaterally distributed, though sometimes more severe on one side than on the other. These symptoms are: muscular rigidity, paresis, perverse movements, contractures and increased deep reflexes. Mental deficiency, optic atrophy and ataxy are other important symptoms. The signs of the disease become obvious during the first year of life or soon after. In severe cases, soon after birth, the nurse, in washing the child, is the first to notice the stiffness of the limbs, or the regular assumption of a curious bodily attitude. Otherwise, the abnormalities may not be obtrusive, until the child should sit up or learn to get about, when weakness, rigidity, perverse movements and pes cavus may call attention, or backwardness in learning to walk and to talk, and mental deficiency may first suggest that there is something wrong with the child. The following are the common types of the disease, but it must be remembered that any combination of, or transition between, the types may be met with.

1. *Generalised rigidity; general congenital spastic paralysis.*—There is extensive defect of the pyramidal system. The rigidity and weakness affect the whole of the musculature.

2. *Paraplegic rigidity; congenital spastic paraplegia; Little's disease.*—The pyramidal deficiency is confined to that supplying the lower part of the trunk and lower limbs.

3. *Congenital bilateral athetosis and congenital chorea.*—The agenesis affects the cells of the basal ganglia, with the appearance of irregularity of movement, and of spontaneous involuntary movements, which may be of an athetotic, choreic or irregular type. A certain variable degree of general rigidity is present in these cases.

4. *Congenital cerebellar ataxy.*—The agenesis affects the cerebellum with the appearance of cerebellar ataxy. In this type, the limbs are flaccid, and in mixed cerebral and cerebellar types there is a tendency to hypotonicity of the muscles, instead of rigidity.

5. *Congenital idiocy; restless idiocy.*—The agenesis affects those parts of the brain concerned with the higher functions. These children are emotionless, restless and unteachable. The skull often shows frontal or occipital microcephaly.

6. *Microcephalic idiocy*—where the agenesis is of the whole brain and the skull remains very small.

**PARESIS AND RIGIDITY.**—Except in severe cases, in which the weakness amounts to complete paralysis, there is more rigidity than weakness, and it is often astonishing that there should be so much power in the presence of such a degree of rigidity.

The lower extremities are generally the most affected, the upper to a less degree, and the facial region still less. Movement is slow and clumsy, and spontaneous involuntary movements are often present in the limbs. Contractures accompany the rigidity, and if walking is possible the gait is digitigrade from contraction of the calf muscles, the knees are flexed from contracture of the hamstrings, the thighs are rotated inwards, and the knees pressed together, rubbing against one another. More severe adductor spasm gives rise to the cross-legged progression. The rigidity and contractures, when severe, may give rise to peculiar attitudes and deformities. A mask-like expression of face, with wide palpebral apertures and large open mouth, is not infrequent. Slobbering is very common. The head may be rigidly retracted, but more commonly the chin is pressed down upon the chest. The spinal column generally shows some deformity in the way of kyphosis, lordosis or scoliosis, and *pes cavus* or *equino-varus* is the rule.

**PERVERSE MOVEMENTS.**—Under this heading must be grouped the very constant maladroitness of voluntary movement, the facial over-action and grimacing in speech and in mimetic expression, choreic movements, athetotic movements and intention tremor. Common sensation and the muscular sense are unimpaired. The sphincters are unaffected. The deep reflexes are increased, but are often difficult to obtain when rigidity is very marked. The trunk reflexes are often absent, the plantar reflexes usually are extensor in type. Since the growth of the skull follows and conforms with that of the brain, cranial abnormalities are common. There may be microcephaly, asymmetry and flattening in the region of the central convolutions, or a furrow corresponding with the interhemispheric fissure, or frontal or occipital smallness and flattening. Every degree of mental reduction may be met with, from slight mental dullness to complete amentia. But this by no means corresponds with the severity of the bodily symptoms, for the mental defect is often most severe when the bodily symptoms are slight, and conversely. In some cases, very high intelligence persists, when there is utter uselessness of the limbs, and when speech is hardly intelligible. Primary optic atrophy occurs in a small number of cases. Inequality of the pupils and slowness of light reaction are not uncommon. Nystagmus is often met with. Convergent strabismus occurs in about one-third of the cases. Convulsive attacks are of common occurrence, and in about one-eighth of the cases epilepsy becomes established.

**Diagnosis.**—When the symptoms are well marked, the diagnosis presents little difficulty, since the disease dates mostly from birth, or is discovered during the first year of life. Paraplegic rigidity may possibly be confused with other forms of paraplegia, and, especially, with that resulting from spinal caries. Certain cases of pontine tumour may closely resemble generalised rigidity. The occurrence of such conditions during the first 2 years of life is, however, very rare.

**Prognosis.**—In many cases of generalised rigidity, and in all cases of paraplegic rigidity, there is a tendency to slow amelioration of the rigidity, an increase of voluntary power and control of the muscles in the course of time, especially under the influence of careful training, and in paraplegic rigidity, if the mental acuity be not seriously impaired, laborious treatment may result in an almost normal condition of the limbs by the age of puberty. On the other hand, some cases of generalised rigidity become progressively worse, and succumb, usually before the end of the fourth year. Bilateral athetosis and choreic diplegia, as a rule, follow a very slowly progressive course, without tendency to a fatal result. Paraplegic rigidity apart, a great many of the cases of all forms of diplegia succumb before the sixth year, and in those who survive this age, the tenure of life is short, few reaching far into the third decade of life.

**Treatment.**—In those cases with a marked degree of mental impairment, and in those which show a course of progressive degeneration, no treatment is of avail. In slighter cases of generalised rigidity, and in paraplegic rigidity, treatment is to be

directed to the prevention of contractures, to regaining of voluntary control, and the improvement of mental acuity. There is, perhaps, no disease which demands greater patience and persistency in carrying out of suitable treatment, and there are few diseases in which more brilliant results may be produced from apparently hopeless cases by pertinacity in treatment. It is in the early years, when treatment is for the most neglected, that good results are more quickly and readily obtained. From the first, regular massage and passive movements should be employed. Voluntary movement should be encouraged, as far as possible, and as power and movement increase, gymnastic exercises of every kind should be employed. Rigid apparatus for prevention of deformity and to reduce contracture is harmful, for it increases the weight of the limb, and interferes with movement, which is the remedy with which paralysis is to be combated. Tenotomy is of great service in the relief of deformity and contracture, and should be soon followed by passive movements. It should never be performed, unless a fair degree of voluntary power is present. Many of the patients seem to improve more rapidly if thyroid be administered in moderate daily doses.

### INFANTILE HEMIPLEGIA

While in childhood hemiplegia of slow onset is due to the same causes as in adults, cerebral tumour being the common cause, yet the majority of the cases of infantile hemiplegia of rapid onset are examples of diseases peculiar to children, to which no comparable disease occurs in adults, and to such cases the term "infantile hemiplegia" is restricted. These conditions are due to gross organic lesions of the brain, and for this reason must be strictly separated from the cerebral diplegias which are the result of cell lesions and not of gross lesions.

**Ætiology.**—In two-thirds of all the cases, the onset occurs within the first 3 years of life. The malady becomes increasingly rare as childhood advances. A few of the cases are of prenatal origin and a few are due to syphilitic foetal vascular disease. Again, a very few cases are due to obstetrical events during birth, by which the cerebrum is injured. Acute infective diseases play a very important rôle in the causation of the disease, for about one-third of all the cases develop the malady during the course of a known infection. By far the most important of such fevers are measles and scarlet fever, but hemiplegia may occur in the course of pertussis, small-pox, rubella, diphtheria, dysentery, pneumonia, typhus, typhoid, mumps, malaria, chorea and endocarditis. While there can be no doubt that primary vascular lesions are responsible for many of the cases in which this condition complicates the specific fevers (whooping-cough, for example, may cause cerebral hæmorrhage, marasmic conditions in any fever may cause thrombosis of cortical veins, and chorea and endocarditis may cause embolism), yet in some cases an inflammatory lesion of the brain or encephalitis is present.

**Pathology.**—The following lesions are met with, either alone or combined in order of frequency: (1) Atrophic sclerosis; (2) cyst formation; (3) shrunken patches resembling wet wash leather, with some degree of atrophic sclerosis in their vicinity and (4) porencephaly. The general appearance of these lesions which appear to be varying degrees of the same process, suggests the end result of a vascular disturbance usually confined to the area of distribution of the middle cerebral artery. There is evidence that many of them result from cerebral embolism occurring immediately after birth in association with the closing of the ductus arteriosus.

**Symptoms.**—The onset is rapid, and in two-thirds of all the cases the disease is ushered in by convulsions, which may be unilateral, but are more frequently general, and are frequently repeated during a period of from a few hours to 24 hours, after which the patient sinks into a subconscious state, from which he gradually emerges in the course of a few days, to show the signs of some cerebral defect, usually hemi-

plegia, sometimes hemianopia, or aphasia, or any other sign of local cerebral or cerebellar lesion. Pyrexia often accompanies the convulsion, and vomiting is common. The onset may be without convulsions or loss of consciousness.

The relation of the onset of the paralysis to the convulsion varies. It may reach its height immediately after the initial convulsion, or slight hemiparesis may occur which deepens after each subsequent convulsion. Sometimes the early convulsions leave no paralysis, but this appears towards the end of the first week, either suddenly with fresh convulsion, or gradually, as the patient recovers from the comatose state. The paralysis at its onset is flaccid, and involves the whole of one side of the body to a greater or smaller extent. An initial monoplegia is of extreme rarity. The paralysis may not reach the greatest intensity until the end of the second week. Subsequently it lessens, in some cases disappearing completely in from a few weeks to 3 months; in others, it may show no sign of improvement. The limbs, at first flaccid, subsequently become spastic and develop contractures. In the course of years there may be great arrest of growth on the affected side, and this is not necessarily proportional to the degree of paralysis, but apparently depends upon the degree of destruction which has occurred in the parietal lobule. Post-hemiplegic spontaneous movements of an athetoid, choreic or irregular kind are common, and are attributable to lesions in the corpus striatum and subthalamic grey matter, for which regions encephalitis shows an especial predilection. Epileptic fits recur at varying intervals in about half of all cases of infantile hemiplegia. These always commence upon the affected side and are sometimes confined to it. Mental deficiency is met with in all degrees, in relation to the position and extent of the cerebral cortex which is involved in the lesion.

**Diagnosis.**—The nature of the malady at the onset, with convulsions, may possibly be suggested by prodromal pyrexia, by the severity and long duration of the convulsions, and by the prolonged subconscious state that often follows. Convulsions occurring several days after the onset of specific fevers should strongly suggest the diagnosis. When the signs of hemiplegia or of other local cerebral lesions appear, the diagnosis presents no difficulty.

**Course and Prognosis.**—In a very small proportion of the cases the patient does not survive the initial manifestations of the disease, and dies in convulsions. Apart from this event, infantile hemiplegia has little tendency to destroy life. The initial flaccid hemiplegia tends to improve and gives place to a slowly improving spastic hemiplegia, which, with the return of some power, shows perversity of movement, stiffness and slowness, ataxy, athetosis and choreic movements or tremors according to the position of the lesion. The spontaneous movements appear within a year of the onset. Slow improvement may go on for years, but cases with much mental reduction or in which recurring epilepsy is frequent, improve but little.

**Treatment.**—We know of no measures that avail to prevent the occurrence or lessen the severity of the cerebral destruction which occurs in these cases. Too often the damage to the brain has happened as soon as a diagnosis is possible. When the paralysis has developed, treatment is to be directed to the prevention of rigidity and contractures by regular passive movements, to regaining voluntary control by encouragement and patient exercises, and to the improvement of mental acuity. Where there is much contracture and deformity, tenotomies are of great service, provided there be some voluntary power in the muscles, the tendons of which are to be divided. Recurring convulsions should be treated as idiopathic epilepsy.

Severe cases of this disorder as they reach childhood and adolescence present a very characteristic picture. The infantile hemiplegia is associated with some degree of failure of growth in the affected limbs and with perverse movements. In addition, epileptic fits, mental retardation and violent temper-tantrums are characteristic.

Such cases have, of recent years, been increasingly treated by complete surgical removal of the damaged hemisphere. This "hemispherectomy" is usually followed



not only by cessation or improvement in the fits but by a marked improvement in the mental enfeeblement and the temper-tantrums. Even more surprisingly, the severity of the hemiplegia instead of being increased is diminished.

## PAROXYSMAL DISORDERS OF THE CENTRAL NERVOUS SYSTEM

### EPILEPSY

**INTRODUCTION.**—Epilepsy, in the widest sense, may be defined as a persistent liability to occasional seizures. The seizures may be associated with organic disease of the brain or a toxic state, and if so the epilepsy is said to be symptomatic. If the attacks are of such a nature that they point to a focal lesion of the brain (see p. 1497), and particularly if consciousness is retained during the whole or a considerable part of the seizure, the term Jacksonian epilepsy is applied to them. More commonly there is no discoverable organic disease of the brain and no toxic state (*e.g.* uræmia, eclampsia) with which fits are known to be associated, and the epilepsy is then described as "idiopathic" or "essential". It is becoming more and more common to restrict the use of the general term "epilepsy" to this last variety, but it is apparent that the clinical division of the cases of epilepsy into symptomatic and idiopathic cannot be absolute, if only for the reason that organic cerebral disease may not declare itself except by the occurrence of fits. In the absence of other indications of cerebral disease there is no positive feature by which either variety can be recognised.

### SYMPTOMATIC EPILEPSY

The known causes of symptomatic epilepsy are numerous. In addition, the diagnosis is often based on assumption because some item in the history of the case provides a basis for supposing that organic cerebral disease or injury has occurred, and it requires much knowledge and good judgement to assess whether such an assumption is well founded. Injury of the brain of any nature whatever, whether from violence from without or from disease within, may cause epilepsy. Cerebral tumours, agnesia, encephalitis, meningitis, cerebral-syphilis, abscess and certain types of vascular lesions give a high percentage of epileptic sequelæ or accompaniment. Another cause of symptomatic epilepsy that should be borne in mind when a previously normal person who has lived abroad develops fits is cysticercosis of the brain. Acute intoxications with lead, alcohol, absinth and many other poisons may evoke epileptiform fits, as may also eclampsia, uræmia, hyperpiesis, cholæmia and the specific fevers of childhood, and although in these conditions the epileptic phenomena do not usually recur after the intoxication has terminated, nevertheless, any one of them may be the apparent beginning of persistently recurring epilepsy.

### IDIOPATHIC EPILEPSY

**Definition.**—A liability to fits or minor seizures, prone to recur over long periods of time or even throughout life, without any discoverable organic disease of the brain or other known cause of fits.

The fit is a disturbance of function, due to a sudden excessive and uncontrolled discharge of nervous "centres" and this is believed to be due to a disturbance of the metabolism of the cells in which the abnormal discharge originates. Of the nature of this metabolic disturbance we are still ignorant and as far as we know it is not associ-

ated with any recognisable change in the histological appearances of the cells concerned. The metabolism of nerve cells in activity is accompanied by changes of electric potential and under suitable circumstances the potential changes in the cerebral cortex can be recorded by the electro-encephalogram. Normally they are rhythmical alternations at the rate of 8 to 12 per second (the  $\alpha$  rhythm) and the best records of them are obtained from the occipital region of the head when the patient closes his eyes and relaxes. At the time of an epileptic fit there are repetitive excessive electric discharges all over the cortex and these are followed by a period of electrical inactivity lasting some minutes. At the time of a *petit mal* attack the E.E.G. shows a single "spike", indicating one excessive discharge, occurring all over the cortex or a succession of spikes. In many epileptic patients the electrical record indicates that intermittent abnormalities of the rhythm are present during the intervals between the

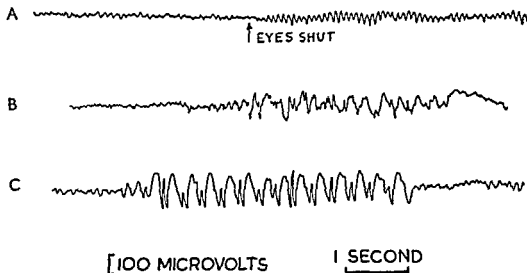


FIG. 2

## ELECTRO-ENCEPHALGRAMS

A. Normal alpha rhythm, largely absent with the eyes open and appearing when they are closed; 11 cycles per second.

B. An episode of waves of mixed frequency in a case of idiopathic epilepsy.

C. An outburst of spike and wave complexes at 3 cycles per second accompanying a *petit mal* attack.

By the kindness of Dr. W. A. Cobb.

fits and some of them are similar to those associated with a fit, *i.e.* they are "sub-clinical" attacks. Abnormalities of the rhythm of potential variation are present in many other conditions besides epilepsy, but when the complex known as the "spike and wave" appears on the record it is believed to be indicative of epilepsy. Many epileptic patients, however, do not show this abnormality on their records and the records may either be quite normal or may show other non-characteristic abnormalities. Electrical abnormalities are found alike in "idiopathic" and in "symptomatic" epilepsy, but in the former they are more constantly present, and are, in general, more widely diffused over the cortex and more readily modified by such activities as over-breathing.

**Ætiology.**—It is important to be clear in our minds what we mean by the cause of epilepsy. In symptomatic epilepsy organic disease of the brain is usually present, but in idiopathic epilepsy there is no organic disease with which the liability to fits can be associated: moreover, the same organic disease, *e.g.* a glioma of one frontal

lobe, may be associated with fits in one case and not in others. It is thus evident that the organic disease is not the immediate cause of the liability to abnormal discharges, but it is a more remote cause. Of the more immediate cause (or causes) of the liability to attacks almost nothing is known, beyond the indications of metabolic disturbance in nerve cells that have already been referred to. Of remote causes of the liability in addition to organic disease of the brain, *heredity* is the most important. While this factor is regarded much less seriously now than formerly, the fact remains that in a still considerable proportion of cases, a history of epilepsy in a near relative is obtained. Moreover, recent electro-encephalographic observations by Lennox suggest that in the parents (one or both) of epileptic subjects abnormally wide fluctuations in the rhythm of the brain potentials are unduly common, and it may be that while epilepsy as such is not inherited, some instability of cortical cell function may be inherited, which, in combination with other factors leads to the appearance of epilepsy under certain (as yet unknown) circumstances.

In the vast majority of cases of idiopathic epilepsy the tendency to fits first reveals itself in childhood or adolescence. In 70 per cent. of cases attacks have begun by the age of 20, and in 85 per cent. by the age of 25. In a small number of cases idiopathic epilepsy first manifests itself in the fourth or fifth decade, but far more frequently fits coming on after the age of 25 are symptomatic of organic cerebral disease. Often children starting to have fits in adolescence have had convulsions in infancy.

The frequency of fits in the same patient is subject to great variability, so that the liability to abnormal discharge evidently fluctuates. When it is sufficiently great, there must also be a final exciting cause which starts off the attack—especially the major fit. Of the cause(s) of fluctuations in the liability to attacks and of the exciting causes of fits we are, again, quite ignorant. The most that can be said is that something is known from empirical observation of the conditions in which fits often occur. These are subject to great variability from patient to patient, but often show great uniformity for the same individual.

More than half of all (convulsive) attacks occur during sleep. There are many individual patients whose attacks invariably occur during sleep, and this is often called nocturnal epilepsy, but the liability attaches to sleep, whether nocturnal or diurnal, and the Sunday afternoon "nap" in front of the fire is frequently productive of fits in such patients. Of the nocturnal fits, many occur soon after the patient has fallen asleep, but still more in the last few hours before waking. There are some epileptics who never have fits except in sleep, and in general the liability to fits during sleep is much greater than during the waking state. The next greatest frequency of attacks attaches to the first hour or so after waking. Many patients have their attacks usually or invariably when washing in the morning or dressing, or about breakfast time, so much so that for the average patient the liability during this first waking hour seems considerably greater than for any other hour of the twenty-four. During the rest of the day the liability to attacks for the average patient is much less, but this is not to say that many fits do not occur during the day, and occur sometimes under the most unpredictable circumstances. In general the patient seems less liable to attacks while intent on the day's activities than when inactive, relaxed or lounging or dozing. In the evening, especially in the last hour before bedtime, the average liability to fits is again increased, and some patients usually have their attacks at this time, but in general the evening liability is not nearly as great as that of the first morning hour.

In women there is a pronounced increase of liability to fits in association with the menstrual period, beginning about 5 days before the onset of menstruation and lasting till the end of 48 hours after its termination, with its maximum in the 2 days preceding the menses. In many women who are relatively mild cases of epilepsy the attacks occur only at such times.

There is a popular idea that emotional excitement has an influence in precipitating fits in epileptic patients, but it is rarely that the personal histories of patients provide any confirmatory evidence for this and the only emotion that seems to have any effect in increasing the liability to attacks is fear, and even that is doubtful. In a few patients concentration on studies has an adverse effect.

Physical disturbances such as vertigo, nausea, vomiting seem also to increase the liability to fits, as also does physical injury. General anæsthetics often precipitate fits in epileptic subjects, and an injection of novocain seems to increase the liability so that an attack may occur after some hours.

The retention of water in the body, brought about by the intake of a large amount of fluid and the injection of pituitrin subcutaneously, leads to the occurrence of a fit in 50 per cent. or more of susceptible subjects and this has been used as a diagnostic test for epilepsy, but such a test is rarely called for if adequate attention is given to the description and circumstances of suspected fits.

**Symptoms.**—**PRODROMATA.**—The circumstances which immediately precede the occurrence of an attack are of some importance. As has been mentioned, it is uncommon, speaking generally, for an attack to occur when the attention is fixed, or when some act is being performed, and from this it follows that the epileptic is relatively or absolutely free from attacks when at work and doing, and only in rare cases comes to harm or injury from accident. Some patients are able, by effort of will in fixing attention, or by the performance of some vigorous action, to arrest attacks which threaten or have even begun.

Sometimes a change in the general condition of the patient may make him aware, or may acquaint those around him, that an attack is pending, and such signs of altered health may herald an attack for from a couple of hours to a week. Headache, irritability, restlessness, euphoria, depression, lethargy, somnolence, unusual appetite and a peculiar vacant look may all be met with in this connection.

Not infrequently the attack is preceded by paroxysmal manifestations which are in reality minute attacks, such as partial lapses in consciousness, a sense of strangeness, "dreamy state", jactitations of any of the muscles exactly resembling those seen in uræmia, slight auras, giddiness, sneezing and yawning.

**DESCRIPTION OF THE ATTACKS.**—The varieties of the epileptic attack are legion, and several types may occur in the same subject—indeed, it is unusual for fits to be always of the same type in one subject. They tend to vary both in degree and nature. They are usually divided into "major" attacks, in which spasm is conspicuous, and the less spectacular "minor" attacks, in which spasm is not a prominent feature. This distinction is purely artificial, for most patients have attacks of both varieties, and the two merge by insensible gradations the one into the other.

The following description will serve to illustrate the more definite manifestation of epileptic attacks:

**GENERAL CONVULSIVE FITS** (*haut* or *grand mal*).—There is some reason for believing that every major attack has a local commencement in some region of the brain, and that it is in reality a local fit which rapidly becomes general. When such an attack commences with a local aura there is proof positive of local commencement. When it commences with conjugate deviation of head and eyes to one side, this is a certain indication that the disturbance commences in the opposite hemisphere. When the spread of the disturbance is so rapid as to cause instant loss of consciousness there is no memory to retain the initial event of the attack. The seizure may begin with any of the local manifestations described later, the epigastric aura and giddiness being two of the most frequent. Or the patient may only be aware of his attacks from the condition in which he finds himself after their occurrence. The tonic spasm commences with conjugate deviation of both eyes to one side, followed by rotation of the head to the same side. The blood pressure falls, the countenance is for a moment pallid, the eyes widely open, the pupils dilated, the corneæ insensitive. The march

of the tonic spasm usually causes head retraction and opisthotonos; the upper extremities are stiff in flexion and adduction, the lower extremities in extension. If standing, the patient falls usually backwards, but the conjugate deviation of head and eyes may bring his face to the ground first. The respiratory muscles and larynx, going into spasm, produce the epileptic "cry", and the respiratory movements being no longer possible the face darkens with the asphyxia, and the sphincters may relax, with the evacuation of bowel or bladder. The protrusor spasm of the tongue and the closing spasm of the jaw may cause the tongue to be bitten. After the tonic spasm has lasted some seconds and perhaps has produced such a degree of asphyxia as seems hardly compatible with survival, it begins to break into a series of sudden shock-like, jerky movements—the clonic spasm—which continue for some seconds, becoming less regular and occurring at longer intervals until, with a final jerk, the muscles become perfectly limp. Meanwhile the relaxation of the respiratory and laryngeal spasm has allowed the respiratory movements to return and to churn up the saliva, often bloodstained, which escapes at the nose and mouth in the form of froth. At the end of the attack there is complete and unrousable loss of consciousness, the pupils are dilated and insensitive to light, the corneal reflexes absent, the knee-jerks absent and the plantar reflexes extensor in type. In a short time the knee-jerks return, the plantar reflexes return to the normal and consciousness returns. Usually the patient is dazed, feels ill, has marked headache and if left to himself soon sleeps heavily for some hours. It must be noted that the general convulsive attack almost always leaves the patient face downwards, so that he has been known to drown in a puddle an inch deep and has been asphyxiated by his own pillow. The latter event is by far the commonest way in which the epileptic meets his death from accident in a fit.

*The epileptic cry.*—There are two quite different sounds that may occur at the commencement of an epileptic attack. The one is a natural, conscious cry of terror at the advent, as in the patient who alternated piercing screams with "It is coming! It is coming!" before the convulsion commenced. It is curious how rarely any memory of such cries or utterances remains with the patient. The other is the epileptic cry proper—a weird, unearthly, hollow sound, produced by inspiratory spasm drawing air over the nearly closed vocal cords. This cry occurs in a minority even of severe cases, for the obvious reason that it is determined by a particular march of the spasm. If the inspiratory spasm occurs before the larynx has gone into spasm or after it is in spasm, there can be no laryngeal noise, but only the commonly witnessed pharyngeal and buccal grunting and gurgling. The spasm must be so timed that the inspiratory spasm must occur as the larynx is closing, and this only obtains in a minority of the cases.

*Tongue-biting.*—Some patients always bite the tongue, others never, and some now and again. The tongue is always bitten at the side and some way from the tip, because it is deviated to one side in the spasm and its thicker part brought between the molar teeth. The same side is usually bitten. The tongue cannot be bitten unless protrusor spasm occurs either before the jaw has gone into tonic spasm or after it has broken into clonic spasm. If any other march of spasm occurs, the tongue escapes. It is remarkable how little scarring occurs even from severe and repeated tongue-biting unless a piece is bitten clean out.

*Incontinence.*—Though common, incontinence is by no means invariable even in severe attacks. More often it is the urine alone that is evacuated, much more seldom the bowel alone, still more rarely both. A rare phenomenon during an epileptic fit is seminal emission.

*Secondary events.*—The degree of asphyxia during the attack may be severe, and blood vessels may give way under the stress, with the production of surface ecchymoses or deep hæmorrhages, including cerebral hæmorrhage. The spasm is powerful and may give rise to much subsequent aching, as if the patient had been beaten all

over. It may dislocate joints, rupture muscles and even break bones. A dislocation once produced in a fit is very liable to recur with subsequent fits.

*Duration of epileptic attacks.*—Two minutes may be given as an outside time-limit for the duration of an individual attack, from its commencement to the end of the active phenomena, and in convulsive attacks to the end of the spasm. Usually the time is much shorter than this, and often is a few seconds only. Sometimes attacks are described as of much longer duration. When analysed, such attacks will be found to be a series of attacks with very short intervals, or slight attacks with post-epileptic functional spasm, or hysterical attacks.

Other varieties of convulsive disorder are commonly encountered either as heralds of a grand mal attack or as the sole expression of the epileptic disturbance.

*SIMPLE JACITATION.*—Simple twitchings of individual muscles or groups of muscles, occurring, now in one part of the body, now in another, are seen in the majority of epileptics at some time or other. They are conspicuous in the convulsions of childhood, where they often constitute the chief clinical feature. They are well known as the "carphology", or "subsultus tendinium" of uræmic and eclamptic attacks, and in the "typhoid state". They may be not infrequently noticed in the epileptic person when he is otherwise well, and engaged perhaps in conversation or other occupation. Gowers emphasised epileptic twitching as a prodroma of an oncoming severe attack; but while in some instances this is undoubtedly true, yet it frequently occurs when no attack follows. It has been called "epileptic myoclonus".

*LOCAL FITS.*—First studied by Hughlings Jackson, these events bear the name of "Jacksonian epilepsy", and this term has unfortunately become coupled with common errors that were no part of Jackson's teaching. These are (1) that some local disease invariably underlies the Jacksonian fit, and (2) that the Jacksonian fit necessarily consists of local motor convulsion. Actually, in many cases naked-eye and microscopic examination may fail to reveal any local lesion, and none such may be present. Also, the Jacksonian fit may consist of phenomena involving any possible cortical function. It may be added that local disease of the brain quite commonly evokes generalised fits indistinguishable from those of idiopathic epilepsy, and conversely that the latter form of epilepsy may express itself in the form of Jacksonian fits.

In local convulsive attacks the common foci of onset are the angle of the mouth, the thumb and index finger, and the great toe, but the spasm may occasionally begin elsewhere. It rarely produces conjugate deviation of the eyes as a primary movement, but usually in association with, and secondary to, deviation of the head. The convulsive movements may remain confined to their place of onset throughout the fit, or may spread widely so as to involve a whole limb, one-half of the body, or the entire musculature. In fits involving the musculature of the right half of the face and tongue, speech is usually lost during the attack and returns shortly after its cessation. Spasm never affects the muscles of one eyeball alone, but the spasm is in terms of conjugate deviation of both eyeballs in one direction. The same rule applies when the neck is affected, for the head is then either rotated to one side or extended or flexed on the chest. With the other bilaterally associated muscles it is different, for the tongue is affected on one side only, as is also the face. The onset is with tonic spasm, which after a little while gives place to broken or clonic spasm, becoming more and more intermittent and finally ceasing. In some cases, but by no means in all, the convulsion leaves varying degrees of weakness in the affected muscles—Todd's paralysis or post-epileptic paralysis—with transient signs of loss of function of the pyramidal system, such as loss of trunk reflexes, increase of jerks and extensor plantar reflexes.

Epileptic spasm usually puts the hand in the position of extension at the interphalangeal joints, and flexion at the metacarpo-phalangeal joints, with flexion at wrist and elbow, and adduction at the shoulder. The feet are dropped and turned, with extension at the knee and hip. Usually the trunk is in opisthotonos.

The sequence of tonic spasm, followed by clonic spasm, though usual in epilepsy, is not invariable. Purely tonic fits may occur with no clonic spasm, the tonic spasm remitting suddenly. Such fits are usually of slight severity and duration. On the other hand, the spasm may be clonic only. The simple jactitation already described may be taken as a simple clonic fit. Local fits, especially of the face and of the hand, may be purely clonic.

*Loss of consciousness in local fits.*—This seems to depend upon the extent of the cortex involved. With narrowly confined fits there may be no evident impairment at all, as in local convulsion of the face or hand, or as in a patient who vividly described a slow visual fit as it was occurring. When the fit spreads, consciousness is usually impaired, and when lost, it is lost late in the fit. For example, it is usual for a convulsion which spreads to one-half of the body to cause some impairment, and if it involves both sides generally consciousness is always lost.

*LOCAL PARALYTIC FITS (simple paralysis).*—This is the rarest of all forms of the epileptic attack. It consists in a sudden inability, relative or complete, to use a limb or one side of the body or the whole voluntary musculature, with no preceding convulsion. There are the usual signs of cerebral paralysis—at first flaccidity with a tendency for the jerks to fail; a few moments later increased jerks, with absent trunk reflexes and extensor plantar reflexes, all of which signs soon disappear. The attack may occur as an isolated phenomenon. More often a slight "minor" attack or a local sensory attack accompanies the onset of the paralysis. Sometimes such an attack may result from local disease of the brain. Such episodes when involving the right face or right side of the body may occasion aphasia, or the aphasia may occur alone as the attack of simple paralysis. Such attacks of simple paralysis without convulsion are well known in uræmia, hyperpæsia and general paralysis of the insane.

*SENSORY EPILEPTIC DISTURBANCES.*—Numerous sudden sensory disturbances may be met with in epilepsy. They may be related to the organs of special sense, to those of common sensibility or to those of visceral sensibility. They may occur as isolated events and so constitute the whole epileptic attack. Often, however, the disturbance of the cortex spreads widely, involving general convulsion and loss of consciousness; but the initial phenomena are remembered by the patient as the "warning" of the attack and have from ancient times been termed "auras", when preceding general convulsion. In reality, they constitute an essential part of the attack as showing the region of the brain in which the disturbance starts, and in every patient who has such "warnings" preceding his severe attacks, the warnings occur at times by themselves without any such sequel.

*Visual fits.*—These may take the form of negative phenomena, such as dimness of vision, complete darkness or hemianopia, or of positive effects, such as flashes of light, scintillating stars or balls of fire, or of both together in the form of blindness with flashes of light. In the last case they may closely resemble the visual phenomena of migraine, and are not infrequently caused by a local lesion of the occipital region. Complex visual hallucinations may occur.

*Auditory fits.*—The hallucinations of sound may be of any nature—hissing, booming and elaborate musical sensations, as of bells, being common. There is usually a sense of coincident deafness of "far away" hearing, which passes off with or soon after the sound.

*Olfactory and gustatory fits.*—These hallucinations are always described as of "flavour", usually unpleasant. Very often, movements of the lips, tongue and jaw, or swallowing movements are present, and the "dreamy state" referred to below may be associated. From the location of the functions of smell and taste in the cortex of the uncinate gyri, and from the common occurrence of fits of this character in lesions of these convolutions, this type of fit is often referred to as the "uncinate fit".

**Sensory fits.**—These hallucinations may have their seat of commencement in any part of the body. They may remain local, but more commonly they spread from the point of origin in terms of the local representations of the body in the cerebral cortex, and usually from the periphery towards the trunk and head, but a sensory fit may spread to the extreme periphery first. For example, commencing in the fingers, it may spread up the arm to the head, or on reaching the shoulder it may invade trunk and leg before ascending to the head. It may be bilateral, and may be confined to the anterior or posterior aspect of the body.

The sensation may be described as "numbness", "tingling", "pins and needles", "vibration", "rushing", "as if the limb were withering", much more rarely actual pain. Sometimes the sensation is indescribable. The sensory attacks have their origin in a local disturbance of the parietal region of the cortex, and may indicate the presence of an organic lesion in that region. They may be accompanied or followed by temporary loss of sensibility, in the form of astereognosis, loss of sense of position or anæsthesia.

Another group of sensory fits for which it is impossible to give any definite cerebral localisation at present, is that of the so-called visceral auras, which are mainly referred to the distribution of the vagus nerve. Such are the very commonly occurring "epigastric" sensation, and sensations of choking, dyspnœa, nausea and cardiac sensations.

Disturbances in the realm of the vestibular nerve are common indications of epilepsy. Sudden giddiness may be the sole indication of epilepsy, and is a common initial event in major attacks. It may be indicative of the sudden fall of blood pressure, or the feeling of rotation may be consequent upon early spasm causing conjugate deviation of the eyes.

**PSYCHO-MOTOR FITS.**—These may take the form of peculiar mental states, of instantaneous onset, remembered afterwards sometimes in exquisite detail, sometimes only in vague character. Emotional conditions of fear or horror, which may cause the patient to attempt with violence to escape from his surroundings—"curative" epilepsy—may occur. Or, the attacks may take the form of a sudden feeling of misery, or an intense sense of personal wrongdoing, a sense of intense familiarity in surroundings which are unfamiliar, a sudden sense of strangeness, as in a patient whose fit was "suddenly seeming to be somewhere else", a sense of euphoria or of intense mental energy, a "dreamy state", often associated with smacking of the lips and champing or swallowing movements, which often has a pleasurable emotional tone. Again, the psychic fit may take the form of a highly complex and detailed hallucination. Other psycho-motor attacks may express themselves as outbursts of uncontrollable rage, and in rare instances the patients make attacks of great ferocity on unoffending individuals and have no recollection of these incidents afterwards.

**MINOR EPILEPSY (*petit mal*).**—The disturbances to which this term is given show considerable variation in degree, but share in common the fact that there is a sudden impairment or loss of consciousness.

**Simple loss of consciousness.**—In this, the commonest of all minor phenomena, there is a simple break in the continuity of consciousness. The train of thought and action is suddenly arrested for a few seconds, and there is a sudden stillness of posture and facial expression which attracts the attention of a witness. The face may show sudden pallor, a vacant expression and curious fixity of the eyes, with large pupils. The patient does not fall, or move or drop anything that he is holding. In a few seconds the attack is over, leaving the patient unable to describe what has happened, perhaps a little confused for some seconds, sometimes emotional and even hysterical. More often he continues what he was about as if nothing had happened. Such attacks sometimes occur very frequently, even hundreds in a day.

**Simple loss of consciousness with falling.**—The patient suddenly falls, without warning, in the extended position, and almost always prone, so that his head reaches the



ground first, and his forehead receives the bruise. He regains consciousness immediately, and picks himself up as if nothing had happened. In another form of this type the head, or the head and trunk, alone are affected; the patient does not fall, but simply drops the head forward.

*Simple loss of consciousness with slight spasm.*—This forms a gradation from the above types to the definitely convulsive seizures. The spasm is seen as conjugate deviation of the eyes, and perhaps of the head also, or it takes the form of laryngeal and respiratory action, giving rise to a groaning noise, or it may involve any part of the musculature.

**CONDITION AFTER ATTACKS.**—The epileptic fit may leave no after-effects whatever, even though it be severe, but this is unusual. On the other hand, even the slightest attacks may cause conspicuous sequels. Sleep and headache are very common, especially following convulsive attacks, and they may be alternative effects, in that if sleep occur there is no headache, but if it be prevented there is severe headache. The post-epileptic paralysis of Todd has already been described, and also the aphasia which may follow right-sided attacks. The mental state is usually affected by the attack, and returns to the normal sometimes quickly, sometimes slowly. Commonly the patient is dull and dazed, speaking at random, unreceptive, irritable, and does not fully recognise his surroundings. Many patients, especially women, weep. During this state of impaired consciousness the patient may pass into a condition of mental automatism, in which various acts are performed in a conscious manner but of which no recollection is afterwards retained. One patient always prepared for bed after her minor attacks, and on one occasion proceeded to undress in the stalls of a theatre. The acts performed during post-epileptic automatism may have no relation to the life and mentality of the patient. He may do spiteful and criminal acts to those he dislikes. This fact has an important bearing as regards the criminal responsibility of the epileptic. These post-epileptic conditions occur commonly after minor attacks, but they may also occur after major fits; they seldom occur when convulsion has been severe.

Vomiting may occur after any type of epileptic fit, but it is most often met with after a convulsive attack. As it occurs during the period of unconsciousness, there is some danger of the vomited material being drawn into the larynx. Though Gowers mentions a case in which this event proved fatal, accidents of this nature are exceedingly rare.

**MENTAL DETERIORATION AND ABERRATION IN EPILEPSY.**—Many epileptics, especially those who have frequent attacks, show signs of mental deterioration, which is often progressive, and which may become severe and end in chronic insanity, while others show no such mental troubles, and some of these fulfil a long life with the highest standard of capacity.

There seems to be no correlation between the type of epilepsy and mental degeneration, though the latter is widely held to be more frequent and more severe when many minor attacks occur.

The tendency to mental failure is greatest in the cases which commence in childhood, and lessens as age increases, but in the epilepsy commencing in the degenerative period of later life, the incidence again increases. In its slighter form there is merely defect of memory, of attention and power of acquisition. In more severe degree there is greater imperfection of intellectual power, weakened capacity for attention and often defective moral control. Mischievous restlessness and irritability may develop into vicious and criminal tendencies with advancing age. Every grade of intellectual defect may be met with to actual imbecility. Paroxysmal outbursts of mental derangement may occur, sometimes transient and immediately following a fit, sometimes without a fit, and sometimes lasting for weeks or months.

**PERIODICITY.**—While some patients may have fits at any time and at all times, yet there is a tendency in the majority for the attacks to occur at particular epochs

and not at others. Epilepsy may be strictly "nocturnal" or "diurnal". It may occur only on rising in the morning, or solely at the menstrual epoch. The fits may come in batches of several in one day, at intervals of many months. A knowledge of the periodicity when present is of great value in the successful treatment of epilepsy.

### SPECIAL VARIETIES OF EPILEPSY

**EPILEPSY FROM LOCAL DISEASE OF THE BRAIN.**—Almost any lesion of the cerebral hemispheres may produce symptomatic epilepsy. But not more than 5 per cent. of all such lesions do this. The convulsions which may occur in cerebral thrombosis, encephalitis and meningitis are examples of epilepsy incident with the onset of an acute lesion. Lesions of the brain in childhood seem to be more commonly associated with epilepsy than when occurring in adult life. Agenetic states of the brain of prenatal origin (cerebral diplegias) are associated with epilepsy in 30 per cent. of the cases, and infantile hemiplegia is followed by epilepsy in about the same proportion. In adults the commonest causes of symptomatic epilepsy are supra-tentorial tumours and cerebral syphilis. Increased intracranial pressure by itself, as, for example, in subtentorial tumours, seldom, if ever, produce fits unless there is associated involvement of the hemispheres as occurs in meningitis, subarachnoid hæmorrhage or hemisphere tumours. Cerebral abscess situated in the hemispheres not uncommonly produces fits.

The fits caused by local lesions may be in every respect identical with and indistinguishable from the usual type of epileptic manifestation, from the slightest momentary minor fit, all through the local sensory and motor fits, to the severe general convulsion of instantaneous onset and immediate loss of consciousness. There are the same auras and the same sequels. It may perhaps be said with relative truth that the splanchnic auras (epigastric, cardiac, etc.) are uncommon, and that there is a greater tendency for consciousness to be lost late.

The minor attack is the least common fit occurring as the result of a local lesion; the general convulsion by far the most common; while the local fit holds an intermediate position, and its nature is often indicative of the position of the lesion.

**TRAUMATIC EPILEPSY.**—Special reference may be made to one of the examples of epilepsy caused by organic cerebral change, namely trauma, on account of the increasing incidence of head injury both in civilian life and as a result of war. It is generally accepted that the underlying pathological change in traumatic epilepsy is the development of a cortical cicatrix although the occurrence or otherwise of epilepsy following such scar formation will be largely determined by the degree of stability of the particular brain affected.

The incidence of traumatic epilepsy is variously estimated by different writers, but it is agreed that the incidence is much higher in penetrating than in closed injuries of the brain. In the case of closed injuries of all severity the estimates range from 4 per cent. to 8 per cent., the liability increasing with the severity of the injury as judged by the duration of unconsciousness. In penetrating wounds of the brain estimates vary from 10 per cent. to 25 per cent., and Symonds suggests that 15 per cent. represents the approximate incidence. The development of epilepsy characteristically follows a considerable latent interval which varies from a few months to many years and averages 2 to 3 years.

In another group of cases, however, the fits seem to coincide with the process of healing, the attacks beginning within a month or two of the injury and ceasing after 1½ or 2 years.

Any form of epileptic disturbance may follow trauma but the generalised convulsion is the most common, and it is not infrequently associated with typical attacks of *petit mal*.

**PKYNOLEPSY.**—This is a form occurring in children, so called because of the great number of the fits which may occur daily. These are of the slight minor type, any sign of spasm being infrequent. It is rare for any major fit to occur. There is no mental impairment whatever, no deterioration of health, and no result is obtained by any form of treatment. The malady invariably ends in spontaneous cure, usually before or at the age of puberty. Its separation from minor epilepsy is of uncertain validity.

**CARDIAC EPILEPSY.**—This is a convenient term for the epilepsy which occurs in Adams-Stokes' disease, and in paroxysmal tachycardia, and for the fits which may occur in congenital heart disease and in some forms of cyanosis. They are probably related to sudden cerebral anoxia.

**VASO-VAGAL ATTACKS.**—Under this misleading title, Gowers described a recurrent paroxysmal symptom-complex with some or all of the following components: a sensation of fullness in the epigastrium; præcordial pain or discomfort; difficulty in breathing; a sense of impending death; a slowness of mental operations but without disturbance of consciousness; a sense of physical fatigue and coldness of face and extremities. These symptoms wax and then wane gradually, and may be present for as long as 4 hours from onset to disappearance.

Gowers stated that he used the term "vaso-vagal" as a purely descriptive one, but without implying any theory of causation. Unfortunately, those who have adopted his terminology have overlooked its lack of foundation. The term has no precise meaning, no sound basis of observation and no proper place in neurological terminology.

**MYOCLONUS EPILEPSY.**—In this group are included: (1) Epilepsy of an ordinary type in which there is much epileptic jactitation of the muscles between the fits; (2) cases of Unverricht's myoclonus in which epilepsy is coincident.

**REFLEX EPILEPSY.**—Numerous cases are on record in which fits could be produced with great regularity by certain specific stimuli. To these the term reflex epilepsy has been applied. The most frequent of such exciting causes is some tactile stimulus to a particular part of the body, especially when unexpected. In another form the stimulus may be a sudden noise or music. Other cases are precipitated by emotion.

**EPILEPSIA PARTIALIS CONTINUA (*focal status epilepticus*).**—Under this name have been described cases of focal epilepsy, usually consisting of clonic spasm, which remain confined to the part of the body in which they originate but which persist with little or no intermission for hours or days at a stretch.

This form of epileptic discharge is most often seen in the face and is probably always associated with local organic disease of the corresponding area of the cerebral cortex.

**STATUS EPILEPTICUS.**—In this condition severe convulsion succeeds severe convulsion at short intervals without any return of consciousness during these intervals. It is as if convulsion recurred as soon as the body recovered sufficiently from the exhaustion produced by the last convulsion. Meanwhile the temperature rises, and may reach a hyperpyrexia. The difficulty in feeding and providing fluids, the severe muscular exertion and the pyrexia add their dangers to those of exhaustion, and the patient is very apt to succumb—usually to a terminal broncho-pneumonia. Status epilepticus must not be confused with frequently recurring fits in which there is some return to consciousness during the intervals, though it frequently develops from such a condition, for the latter is not accompanied by a rising temperature, the fits are more readily subdued, and are not of nearly so severe a prognostic import. If the convulsions of status epilepticus cannot be stopped by treatment, the patient usually dies from sudden collapse, or, the first ceasing, he remains delirious for a while, with rapid heart and high temperature, and dies of broncho-pneumonia. Status epilepticus may be met with in acute lesions of the brain and in chronic lesions such as general paralysis of the insane. It may occur in acute poisoning with lead, bismuth

and absinthe. It may develop suddenly in any type of epilepsy whatsoever, sometimes without apparent cause, sometimes as the result of over-exertion, and excitement, sometimes when medicines which have been regularly administered and which have kept the fits in check are suddenly cut off.

**Diagnosis.**—The recognition of epilepsy requires a working acquaintance with the nature of its many manifestations and especially of the slight forms, little exteriorised, which may be easily overlooked or misinterpreted. The sudden unexpected onset, without cause, the transiency, the recurrence and the circumstances of the moment, are useful aids. If all these clinical features are taken into account a confident diagnosis can almost invariably be made. Epilepsy (idiopathic or symptomatic) is the only condition which causes attacks in sleep, with the exception of the nightmare, and the latter seldom causes difficulty in diagnosis. Again, if an attack occurs soon after waking, there is a very strong presumption that it is epileptic. The electro-encephalogram is seldom helpful in the primary diagnosis but may give useful indications in the differentiation between idiopathic and symptomatic varieties. The water-retention test, which seeks to provoke a fit for diagnostic purposes, is rarely justifiable unless *malinger*ing is strongly suspected.

Syncopal attacks (rapid lowering of blood pressure) can often be distinguished from epilepsy by their slow onset, the gradually increasing pallor or greyness, the distancing of sound, the nausea and flatulence, the presence of an obvious cause, their duration and the absence of any convulsive element.

The hysterical attack has to be distinguished from the convulsion of epilepsy. Hysterical convulsion has not the manner nor the march of epileptic spasm. It never begins with conjugate deviation of head and eyes to one side, there is not the orderly spread of convulsion, and there is never anything but a poor imitation of the sequence of tonic followed by clonic spasms. The movements in the hysterical fit are purposive, spectacular, violent and are liable to be increased by restraint and are rapidly abolished by complete inattention. The hysterical fit never occurs except in the presence of an audience, for it would then be purposeless, and it never occurs during sleep, the tongue is never bitten, though other parts of the body and other people may be. There is no transient abolition of the tendon jerks, nor transient appearance of the Babinski plantar response. The sphincters are never relaxed. Intense converging spasm of the eyes is a common feature of the hysterical attack, but this sign is not met with in epilepsy. When elaborate disorders of behaviour follow slight and rapidly transient epileptic attacks, the distinction between these and purely hysterical attacks is often difficult and sometimes impossible, except after long observation, for the initial epileptic attack may be practically unnoticeable, and the subsequent events may be typical of hysteria and are usually amenable to the same line of treatment. Often some point in the circumstances under which the attack occurs will settle the diagnosis. Any attack having occurred during sleep, or any attack in which the patient has fallen in circumstances of serious danger, as among the traffic of a London street, or any attack occurring when the patient cannot attract the attention of others, establishes the diagnosis of epilepsy. The best plan is to regard all fits as possibly epileptic, and every fit of doubtful type as probably epileptic, until time and circumstance bring definite conviction.

Migraine may sometimes closely simulate epilepsy when sudden paralysis, or sensory auras, or visual hallucinations occur without headache. But while the sensory phenomena of migraine may last for 5 to 30 minutes, those of epilepsy have a duration of seconds only.

Careful search must be made in every case for all the bodily conditions with which symptomatic epilepsy may be associated. Papilloedema, headache and vomiting may reveal increased intracranial pressure from some lesion of the brain; while local paralysis, sensory loss, visual or other defect may indicate a local lesion of the brain, past or present, and this may also be suggested by the nature of a local fit. The

presence of rickets, infantilism, undue adiposity, etc., may indicate the presence of some definite metabolic or endocrine disorder. Renal function and the condition of the blood pressure should always be examined, for even in early infancy fits may be uræmic and in the recurring convulsive attacks associated with chronic nephritis, and with cystic renal disease and arterial hypertension the causal disease is frequently unrecognised. Where syphilis is likely, the reactions in the blood and cerebrospinal fluid should be examined. Lastly, any evidence of chronic intoxication by metals, alcohol, absinth, etc., should be sought for.

Cysticercosis epilepsy should be thought of when the patient has lived abroad. Diagnosis depends upon the palpation of cysts in the tissues, or the shadows in radiographs of calcified cysts in the muscles, particularly those of the shoulders, thighs and calves, or within the skull.

**Prognosis.**—The outlook in epilepsy is so variable that it is difficult to indicate any but the broadest principles in prognosis. Nor can a definite forecast be made in any case until the result of treatment has been watched for some time; for cases apparently favourable may prove rebellious, and those apparently most unfavourable may turn out brilliant successes. Speaking generally, a cheerful outlook is justified in all cases except those in which there is progressive mental deterioration, and in these the outlook is hopeless in proportion to the rapidity of the mental change. Naturally, in those cases which are associated with serious bodily disease, such as brain tumour, renal disease and hypertension, the prognosis involves that of the exciting condition.

The danger to life from the epileptic attack itself, either directly or indirectly, is not great. However severe the fit, it is extremely rare for death to occur, and when this happens it is from turning over and smothering with the wetted pillow or by choking from the aspiration of vomited material. Injury, burning and drowning may cause death, yet the number of epileptics who meet their deaths in this way is so infinitely small as almost to remove the danger of accident from practical perspective. In the rare status epilepticus, however, the danger to life may be very great. Spontaneous cessation of the attacks occurs in a proportion of cases. The convulsive attacks of infancy, which continue for some years after all cause to which they can be attributed has passed away, often cease for ever at the age of 4 to 6 years. Again, after 20 years of age spontaneous cessation is met with.

The probability of cure, arrest or amelioration by treatment may be entertained in all cases where no mental deterioration exists and where no insuperable bodily disease determines the epilepsy, in proportion as the only method of cure—the securing arrest of the attacks for a considerable time by drug treatment—can be adequately administered over a long period. It is greater when periodicity in the occurrence of fits allows these to be anticipated by drug administration. It is much greater when the following out of education, or the continuance of regular employment, allows of a fully occupied and satisfying life, and much less when education is stopped, pleasures and sports forbidden and the patient condemned to social inferiority and ostracism, and to a gloomy, narrow life of frustration because he has a few fits. It is perhaps smallest when severe attacks occur daily or at short intervals and when both major and minor attacks occur in the same subject.

**Treatment.**—*General treatment.*—The general principles for the maintenance of health if good, or for its improvement if poor, should be adopted. Whenever possible, no change whatever should be made from the régime of life of a normal person. In childhood, education, discipline and pleasures and school life should be continued upon strictly normal lines, and the adult should continue with work and occupation. The life of the epileptic should be as regular as possible and physical and emotional strains, changes in occupation and diet should be reduced to a minimum. Continuity of treatment is of great importance and any course adopted should be given a thorough trial before being modified. Frequent changes of doctor should be

avoided. No advantage has accrued from the adoption of special diets, such as the prohibition of meat, the exclusion of salt or the use of purine-free foods, though the production of a low grade of acidosis by a ketogenic diet is occasionally of value in the epilepsy of children. Alcohol seems to be an excitant of the epileptic attack and should be forbidden.

The forbidding of such pastimes as may be fraught with danger should a fit occur, such as swimming, boating, cycling and car driving, may be necessary.

*Marriage and pregnancy.*—The subject of epilepsy sometimes seeks—but rarely heeds—advice as to the expediency of marriage, both in its effects upon himself (or herself) and in respect of any heritable qualities it may possess. Marriage has no necessary effect upon the course of epilepsy, and, as we have seen, direct transmission of the disease is not usual. Therefore the sweeping medical prohibitions once so frequent in these circumstances are not in fact warranted by such knowledge as we possess. Every case must be considered on its merits. It is common, though not constant, for fits to cease in the epileptic woman when pregnant, and in any event the occurrence of fits at this time constitutes no special danger and is not an indication for the artificial termination of pregnancy. On the other hand, the confirmed and serious epileptic is clearly unlikely to be able to discharge adequately the responsibilities of parenthood.

*Institutional treatment.*—In cases where there is low mentality, much mental degeneration or insanity, and cases with frequent fits, where no adequate care and occupation can be provided at home, there is every advantage in a colony, institution or asylum for epileptics. In such patients regular work, discipline and interest often mitigate greatly the burden of the malady.

*Surgical treatment.*—In the present state of our knowledge surgery has no part to play in the treatment of idiopathic epilepsy. Neuro-surgical procedures, such as encephalography and ventriculography, are of great value in establishing or excluding the presence of a space-occupying lesion in doubtful cases and in revealing the presence of cortical atrophy, porencephaly or ventricular dilatation. Such epileptogenic processes as cerebral tumours or abscesses may be amenable to surgical removal and the epilepsy may be relieved thereby. The value of surgery in traumatic epilepsy is more debatable. Foerster and Penfield and others have demonstrated the value of the excision of scarred areas of the cortex in selected cases of traumatic epilepsy but demand as criteria for operation that ventriculography should reveal a definite ventricular distortion in that area of the brain indicated as the starting-point of the discharge by the nature of the fits, and that it should be possible to reproduce an accurate replica of the fit by electrical stimulation of the abnormal area of cortex at the time of operation. In many cases of traumatic epilepsy the cortical scarring plays only a precipitating rôle and there is in addition an inherent instability of the cortex. In such cases excision of the scar affords only temporary relief and the fits soon recur in unaltered frequency.

*Medicinal treatment.*—Further than the measures above described, the treatment of epilepsy is purely medicinal. There are now several groups of drugs which have a remarkable effect in arresting or mitigating the occurrence of the attacks in epilepsy. They seem to have much the same effect, and may conveniently be combined or alternated in the treatment of any given case. Sometimes one group is found to suit an individual patient better than the other. Moderate doses, such as will cause no deterioration in bodily or mental health, even if taken regularly and for years, seem to bring about the best results.

The bromides formerly used universally have been almost completely displaced by the malonyl-urea compounds, of which phenobarbitone (Luminal) and soluble phenobarbitone are examples. These are powerful drugs and must be used with care. Phenobarbitone has certainly the advantage over soluble phenobarbitone in being more prolonged in its action. It is conveniently prescribed in doses of gr.  $\frac{1}{2}$  to  $\frac{1}{2}$

to a child and gr.  $\frac{1}{2}$ , with a maximum dose of gr.  $1\frac{1}{2}$  three times in the day to an adult. In larger doses it is a powerful hypnotic, and in patients who have idiosyncrasy it may produce toxic symptoms. In occasional cases it makes the patients peculiarly quarrelsome.

A more recent introduction is primidone (Mysoline), which promises to be almost as useful an anti-convulsant as phenobarbitone. It is issued in tablets of 0.25 g., of which from 1 to 6 may be taken in the day. The toxicity of primidone is low and by itself it is not strongly hypnotic, but if taken in association with phenobarbitone it may cause excessive drowsiness. Another remedy is phenytoin sodium (Dilantin, Epanutin, Solantoin), which is usually dispensed in capsules of gr.  $1\frac{1}{2}$  (0.1 g.). For adults, 1 or 2 capsules may be given twice or thrice daily, and smaller doses for children in proportion to size. This drug has the merit of being less hypnotic than phenobarbitone, but it is of less general usefulness and far more often produces toxic effects. Of the latter, hypertrophy of the gums is the most characteristic, but rashes and tremor also occur. Phenytoin sodium has its most successful employment in cases in which nocturnal fits are numerous, two capsules being given (to an adult) at bedtime. If it is decided to make a change to phenytoin sodium from some other medication, this should be done gradually over several weeks.

Recently the substance troxidone (Tridione) has been employed in the treatment of *petit mal*. Given in doses of 0.3 g. twice or thrice daily it has a striking effect in a minority of cases. The occurrence of major attacks is a contraindication to its use, and it is liable to give rise to toxic symptoms of which agranulocytosis is the most important. It should therefore only be given under careful observation and when the treatment can be controlled by regular blood examinations.

Many other remedies have been advocated in epilepsy; a few only have stood the test of time and are still in use, both as alternatives and adjuvants to the treatment above given. These may be placed in order of merit as belladonna, digitalis and borax.

Whatever remedy is chosen it is essential if possible to anticipate the occurrence of the fit by the administration of the drug. Thus, if fits are nocturnal only, the remedy is given in a single dose at night, or if diurnal only, in a single dose in the early morning. Again, if, as often happens, the fits occur soon after waking, then the single nightly dose should be used. Or, if the fits occur or are more frequent at the menstrual epoch, they should be anticipated by increased dosage before and during that epoch. With fits that are diurnal and nocturnal, a night and morning dose should be used. Some patients do best on phenobarbitone alone, others on another remedy alone, and others on a combination of drugs, and the best course can only be determined after trial.

**STATUS EPILEPTICUS.**—The treatment of this condition, and that of rapidly repeated fits which not infrequently merges into status epilepticus, is one of urgency and constitutes one of the important neurological emergencies.

The first thing to be done is to check the convulsion, and this is best achieved by inducing a state of light anæsthesia. For this purpose paraldehyde in large doses is perhaps the safest and most effective drug. If it can be administered by mouth,  $\frac{1}{2}$  to 1 oz. should be used in the case of an average adult, or alternatively 1 to 2 oz. may be given per rectum. Subsequently smaller doses should be given every 2 to 3 hours in order to maintain a state of light narcosis, the amounts being judged by the depth of unconsciousness and the occurrence of fits. Alternatively, amylobarbitone sodium (Sodium Amytal) gr.  $7\frac{1}{2}$  given intravenously, which is very effective, may be employed. If fits of great frequency and violence are present at the outset, the situation can usually be temporarily controlled by the light administration of chloroform by inhalation. Morphine gr.  $\frac{1}{4}$  with hyoscine gr.  $\frac{1}{100}$  may be of great value in controlling the restlessness of patients emerging from status, but should be used with great caution owing to their depressant effect on the respiratory centre and

the danger of broncho-pneumonia. Together with the more immediately acting drugs, phenobarbitone (gr. 3) in the soluble form may be given intramuscularly and, if necessary, repeated in 12 hours. Chloral and bromide are usually quite ineffective.

An early opportunity should be taken to promote a vigorous action of the bowel either by the administration of a rapidly acting aperient such as castor oil by mouth or by an enema. Care must be taken to protect the tongue from being bitten and to keep the mouth free from saliva and vomitus. Tongue forceps should be at hand in case the tongue be swallowed during a period of coma, and the patient should never be left alone. As far as possible the chest should be supported on pillows between fits and the patient should be nursed on alternate sides. Where persistent cyanosis is marked, oxygen may be given together with 5 per cent. carbon dioxide where hyperventilation is conspicuous. Adequate fluid should be given, preferably by mouth, but when this is impossible, by subcutaneous, intravenous or rectal drip of 5 per cent. glucose in normal saline. As consciousness returns, a highly nutritious diet should be given in small, frequent meals. Hyperpyrexia may be controlled by frequent sponging or even by immersion in a tepid bath. When consciousness returns, the routine treatment of epilepsy should be resumed. Status epilepticus carries a considerable mortality, and death commonly occurs from broncho-pneumonia or from cardiac failure. Not infrequently status epilepticus is the terminal event in cases of chronic epilepsy.

## NARCOLEPSY

In this remarkable syndrome, originally described by Gelineau and subsequently in greater detail by Adie and Wilson, two quite different kinds of attack occur.

The one is the onset of apparently normal sleep, which comes on especially at time of inattention or when the desire to sleep might normally be expected to occur, as, for example, after meals, in public vehicles or during the performance of tedious duties. The sleep is preceded by a sensation of extreme drowsiness, often amounting to an irresistible desire to sleep. The sleeper is easily roused and is then perfectly normal, but if left undisturbed may remain asleep for many minutes or even an hour or two. Attempts to ward off the attack by voluntary effort lead to an increase in intensity of the craving for sleep until it is satisfied.

The other form of attack consists of a sudden onset of weakness and tonelessness in the voluntary muscles, to which the term *cataplexy* is applied. These cataplectic attacks are almost invariably precipitated by sudden emotion, such as anger, pleasure, surprise or anticipation, and most often of all by events provoking laughter. In a severe attack, when the emotion reaches a certain intensity, the muscles suddenly become limp, the head falls forward, the jaw drops, the eyelids close and the face becomes expressionless, the arms fall to the sides and the legs crumple so that the patient sinks to the ground, an inert mass, speechless, and incapable of the slightest movement, but without any impairment of consciousness. In a second or two the attack passes and the muscles immediately regain their normal condition. Milder attacks may involve any part of the musculature or may consist merely of a momentary feeling of weakness of the knees. Patients can often judge with great accuracy the intensity and nature of the emotion necessary to bring on an attack.

Although, most commonly, the sleep attacks and cataplectic attacks occur under the characteristic circumstances in the same patients, each may occur in isolation. Often the patient complaining of one form of attack will admit to the other upon questioning, though it may have been of rare occurrence and have caused little inconvenience.

In the majority of patients suffering from narcolepsy, examination reveals no evidence of organic disease in the nervous system or elsewhere, and pathological



investigation is equally negative. In such cases the term idiopathic narcolepsy can properly be applied. Males are much more commonly affected than females, and though the attacks may begin at any age a large proportion have their onset between the ages of 10 and 30 and may continue throughout life. In such cases it seems probable that we are dealing with a spasmodic disturbance of function of the nervous system, comparable in many ways to epilepsy, though at present we have no clue to the cause of the disorder.

In rare cases the narcoleptic syndrome may occur as a symptom of organic disease of the nervous system, notably of encephalitis lethargica, tumours of the third ventricle or hypothalamus and cerebral syphilis. This association suggests that the site of the disturbance is in the autonomic centres of the hypothalamus and the floor of the third ventricle.

**Treatment.**—The sleep attacks of narcolepsy are in many cases greatly improved by the regular use of amphetamine sulphate. An initial dose of 10 mg. after breakfast and lunch is often enough, but this may be increased if necessary to 20 mg. b.d. or even 30 mg. b.d. Symptoms of overdosage are sleeplessness, restlessness and tremulousness. Less efficacious, but of undoubted value in some cases, is ephedrine sulphate in doses of gr.  $\frac{1}{2}$  to 1 b.d.

Neither of these drugs is of comparable value in controlling the cataplectic attacks which usually remain resistant, but can often be adequately prevented by the careful avoidance of the emotional stimulus which brings them on.

## MIGRAINE

**Synonyms.**—Hemicrania; Sick Headaches.

**Definition.**—A common malady of which the only essential characteristic is recurring intense headaches, which usually develop on waking in the morning, and which, while often unilateral, may be bi-frontal, occipital or general. The attacks usually date from childhood, but sometimes commence in later life. The headaches are often associated with nausea and vomiting, which has given rise to the designation "sick headaches" or "bilious attacks", and also with peculiar disturbances of vision and with giddiness suggestive of vestibular disturbance. Less common symptoms of the disorder are varieties of slow, sensory auræ, which occur in no other malady, attacks of hemiplegia or monoplegia, or of aphasia, and attacks of ophthalmoplegia. Some of the phenomena may accompany the headaches, but others occur in attacks quite apart from the headaches, and may for that reason give rise to difficulty in diagnosis.

**Ætiology.**—The malady may originate in early childhood, but commonly makes its appearance at about the age of puberty, and tends to persist, with fluctuations in the severity and frequency of attacks, throughout adult and middle life. It often ceases in women at the menopause, and its persistence into old age in either sex is exceptional. *The sexes are equally affected and a history of family incidence is common.* In other cases a family history of such paroxysmal disorders as hay-fever, asthma, urticaria or epilepsy or of psychopathic tendencies may be obtained. Subjects of migraine are commonly of an energetic and intelligent type and many have a meticulous standard of thoroughness and precision almost amounting to an obsession.

Nothing is known with certainty as to the essential cause of migraine. Numerous factors, such as errors of refraction, disorders of digestion and of endocrine function, and psychological disturbances have all been evoked as responsible causes, but it is probable that at most they are never more than precipitating factors in susceptible individuals. There is considerable indirect evidence that the immediate cause of the attack is a paroxysmal variation in the calibre of the cerebral blood vessels, either

spasm or dilatation, or the one followed by the other, but proof is at present lacking.

Precipitating factors are numerous and may be very specific. On the psychological level fatigue, anxiety and frustration play an important part. On the physical plane over-exertion and fatigue, indiscretions or irregularities of food, exposure to excessive light or noise, prolonged eye strain, especially in the presence of an uncorrected error of refraction, commonly figure in the history of migrainous subjects. Women usually have attacks in association with the menstrual periods and often remain entirely free during pregnancy.

**Symptoms.**—The subjects of migraine are usually otherwise quite healthy, and are often robust and strong. Premonitory signs of the attacks are present in some cases, and these may take the form of an unusual feeling of well-being and intellectual acuity, or, on the other hand, of lassitude and depression.

The attack commences most commonly on waking in the morning, when on raising his head from the pillow the patient experiences a sense of giddiness, ocular confusion and nausea, such as is commonly felt at the onset of sea-sickness. It is at this stage of the attack and within a few minutes of its commencement, that the visual phenomena occur if these are present. Often the patient vomits at once, but sometimes vomiting is delayed for hours but may continue throughout the attack with great prostration, sweating and coldness of the extremities. The visual disturbances last but a short time (from 10 to 30 minutes) but leave, as a rule, some confusion of vision and discomfort throughout the attack. The headache follows shortly after these initial symptoms. It is cumulative and throbbing in character and often begins constantly in a localised spot over one eye, or in the temple as a sharp boring pain which gradually spreads, and may involve the neck and arm. The pain may be unilateral, frontal, occipital or quite general, but is usually constant from attack to attack. As the headache increases in severity the face becomes pale and grey, the patient becomes much prostrated and is incapable of mental or physical effort and unable to take food. Light, noise and movement aggravate the pain intolerably and the patient seeks the refuge of his bed in a darkened room. After remaining in this condition for some hours he falls into a deep sleep and wakes next day shaken by his illness, but otherwise well.

The above description covers many attacks of migraine, but many variations occur. The attacks do not always occur on waking; they may come on at any time of the day or at night. They may be rapidly transient, lasting for a few hours only, or they may last for days and give rise to much anxiety in the attempt to provide nourishment and sleep for the patient. It is not uncommon for them to change their character gradually as the patient gets older, and in cases of long standing the patient may complain of a persistent, annoying headache between the attacks. In other cases the headache may be relatively inconspicuous compared with the vomiting and the various sensory disturbance.

**Visual phenomena.**—Considering how very common migraine is, it must be clearly understood that any visual phenomena except slight confusion of vision accompanying the attacks, are rare. They may take the form of general mistiness of vision, floating spots, scotomata, bright stars and colours, hemianopia, double hemianopia with complete blindness, or psychic hallucinations of vision. In connection with scotoma and with hemianopia, the phenomenon of teichopsia may occur as follows: Upon the dark background of the scotoma or hemianopic field, a ball of light appears, which grows larger and becomes dark in the centre. This ring of light breaks at one spot, opens out and takes the form of a series of entering and retreating angles (castellation figure) which become gloriously coloured (fortification spectrum) and which later become fragmented and fade. These visual events usually occur at the very beginning of the attack, before the headache develops, and they are rapidly evanescent, but they may occur as isolated phenomena, when no headache occurs.

**Aphasic attacks** may take the form of confusion of speech, word-blindness, or even

loss of speech-acceptance and exteriorisation. They accompany the headaches and occur at the commencement of the attacks. They are not of common occurrence.

*Sensory aura*.—These are somewhat rare events, but they are pathognomonic of migraine, and may occur quite apart from the headaches. The aura commences upon the periphery of a limb and is likened to that which would be produced by a multitude of cold-footed insects creeping on the skin. It travels very slowly proximally, taking half an hour or more to reach from the fingers to the head, and is very alarming to the patient. It disappears rapidly without further event. It is the only aura with an exceedingly slow spread. Another form of sensory aura occasionally encountered is numbness of the lips and tongue.

*Ophthalmoplegia*.—This is a very rare but most important event. It occurs only at the height of the headache, in severe attacks. Indeed, the patients usually say that the headache, during which the ophthalmoplegia occurred, was the very worst they had ever experienced. It is a partial paralysis of the oculo-motor nerve trunks, most commonly of the sixth nerve alone, but sometimes of the third or fourth nerves, or of a combination of these three. It is generally unilateral, but may occur simultaneously on both sides. Severe diplopia results. It passes off in from a few days to a few weeks. When once it has occurred, it is apt to recur with subsequent attacks. Attacks of this kind have been called ophthalmoplegic migraine, but it should be realised that the ophthalmoplegia and the migraine syndrome are symptomatic of some organic intracranial disease: the nature of this cannot always be discovered by the means at present at our disposal but in many instances it is an aneurysm or angiomatous malformation which may be revealed by arteriography.

*Diagnosis*.—In typical cases the diagnosis of migraine is seldom in doubt. The long history, the familial incidence and the common association of headache with vomiting and various sensory disturbances all contribute to a characteristic clinical picture. When, however, these varied manifestations occur alone considerable difficulty may be experienced.

It is important to remember that tumours of the occipital lobes and intracranial aneurysms may be associated with attacks exactly resembling migraine, and every case should be carefully examined for signs of organic nervous disease, particularly papilloedema or persistent defects in the fields of vision. It is probable that the so-called ophthalmoplegic migraine, in many cases at least, is a symptom-complex distinct from true migraine, and dependent upon a gross intracranial lesion, most often an aneurysm on one of the component vessels of the circle of Willis. Hypertension, with or without chronic renal disease, may be associated with headaches closely resembling migraine, and an examination of the blood pressure and of the urine should never be omitted. Headaches of neurotic origin may closely simulate migraine, particularly when, as is not infrequently the case, they are superimposed upon a background of true migraine. It is exceedingly rare for migraine to recur more often than once in 2 or 3 weeks, or to last more than 2 days in persons without a strong neurotic tendency.

Those who are not familiar with the full range of sensory symptoms that may precede the onset of the headache, and do not realise the severity of the speech disturbances which in some cases accompany them, are apt to take an unduly grave and erroneous view of the history given by a patient who has experienced them. Thus, a diagnosis of epilepsy or of cerebral tumour is not infrequently made. It should, therefore, be remembered that the disturbances of sensation which occur in epileptic attacks are momentary in duration and never persist, as do the migrainous symptoms in question, for many minutes. Again, consciousness is neither blunted nor lost in migraine.

Attacks of migraine consisting wholly of vomiting and sometimes associated with diarrhoea and abdominal discomfort are readily mistaken for abdominal disorders.

*Treatment*.—Few non-fatal disorders are more stubbornly resistant to treatment

than migraine. Many victims suffer from recurring attacks throughout the most valuable years of their lives, to the serious detriment of their work and happiness. In many cases help can be given by attention to general health and physical and mental well-being, for a lowering of these in a migrainous subject seldom fails to evoke an increase in the number and severity of attacks. In others it may be possible to eliminate precipitating factors, whether physical or psychological in nature, but only too often when these are discoverable they are found to be amongst the unalterable features of the patient's environment.

Drugs administered consistently over a long period may be of value in some cases, and of these phenobarbitone, gr.  $\frac{1}{2}$  twice daily or gr. 1 at night, is perhaps the most generally useful. Gower's mixture containing min. 1 of liq. trinitrini, min. 5 of liq. strychninae, min. 10 of tinct. gelsemii, and gr. 10 of sodium bromide administered thrice daily has long enjoyed a favourable reputation, largely from lack of competition. The individual attacks are equally difficult to relieve. Sometimes a full dose of phenazone, acetanilide, phenacetin or aspirin given at the very commencement of an attack will ward it off, but are useless when once the headache is fully developed. Ergotamine tartrate (Femergin) in doses of  $\frac{1}{2}$  to 1 mg. by mouth or injection will sometimes cut short an attack, but is by no means the specific that has been claimed. When attacks are frequent one or two tablets of ergotamine tartrate daily may be used as a prophylactic. Apart from these remedies it remains to keep the patient as comfortable as possible and to induce sleep by the use of ordinary hypnotics and to secure that the patient takes adequate fluids and nourishment during a prolonged attack.

## DISORDERS CHARACTERISED BY INVOLUNTARY MOVEMENTS

### WILSON'S DISEASE (see p. 1484)

#### PARALYSIS AGITANS

**Synonyms.**—Parkinson's Disease; The Shaking Palsy.

**Definition.**—A progressive disease of insidious onset and slow course, usually occurring in the second half of life, and characterised by loss of the normal associated movements and by a peculiar stiffness of the muscles, which give rise to a distinctive facial expression, bodily attitude and gait. The stiffness is accompanied by weakness, and often by rhythmic tremors, which have earned for this malady the name "shaking palsy".

**Ætiology.**—Little is known of the causal factors of this malady. It is essentially a disease of the decline of life, and though in rare instances it is met with as early as the eighteenth year, the maximum incidence is from the fiftieth to the seventieth year. Men suffer twice as frequently as women. Heredity seems to play no part in the causation.

**Pathology.**—No naked-eye changes are to be found other than associated vascular and degenerative changes which are common in senile conditions. The most definite pathological findings are degenerative changes in the cells and fibres of the corpus striatum and its efferent systems. These changes are most marked in the globus pallidus of the lenticular nucleus but occur also in the putamen, the caudate nucleus, the corpus Luysii and the substantia nigra. There is a constant loss of cells, preceded by degenerative changes in those that remain. An associated glial proliferation takes place in the affected regions, together with fibrosis in the smallest arterioles and capillaries. The relationship of these changes to the symptomatology of the disorder

is by no means clear, the more so in view of the fact that in the post-encephalitic cases the principal changes are found in the substantia nigra.

**Symptoms.**—The onset is always insidious, and the paucity of movement and the muscular rigidity are almost always the first signs to appear. This rigidity affects the face, neck and trunk to a greater extent than the limbs, and when the limbs are affected then the proximal muscles present a greater degree of rigidity than do those of the periphery. The oncoming rigidity of the facial muscles does away with the usual play of the emotional movements in facial expression, and the face assumes a fixed, anxious and mask-like expression, with absence of the usual involuntary nictitation. The voice loses its inflexions, and becomes monotonous, from rigidity of the muscles of larynx, tongue and lips; but there is no other defect of articulation. Very striking is the effect of the rigidity of the muscles of the neck, for the patient carries his head and neck in one piece with his trunk as if he were a statue, never inclining or raising it in the customary expressive manner, and if he turns round to look at anything he tends to move the whole trunk round with the head. In looking sharply to one side, the eyes move before the head, whereas, under normal circumstances, the coarse adjustment of this movement is done first by the neck muscles, and the fine adjustment subsequently by the eye muscles. The stiffness of the trunk muscles gives a stooping attitude with the head inclined forwards, while that of the upper extremities causes the shoulders to be rounded, and the arms carried with the elbow semiflexed, and pressed into the sides. The gait is highly characteristic in marked cases since, on account of rigidity of muscles, it is deprived of spring and suppleness the patient, in the characteristic attitude above described, takes small gliding steps, displacing his centre of gravity as little as possible. If, by any circumstance, such as catching the feet against an unevenness of the ground, or a push, the centre of gravity is much displaced, the patient often has a difficulty in regaining it, and in moving to recover his centre of gravity is unable quite to catch it up, and so continues the movement of necessity until he fall or come in contact with some object by which he can arrest himself and restore his balance. This phenomenon is more often seen in advanced cases, and is known as "propulsion", "retropulsion" and "lateripulsion", according as the centre of gravity is displaced and the movement occurs in a forward, backward or sideways direction. Festination is the term used for the quickening of the pace sometimes seen in this attempt to overtake the displaced centre of gravity. In the hand the rigidity is greater in the interosseal muscles, and the hand therefore tends to assume the "interosseal position" with the fingers pressed together and the thumb adducted, the metacarpophalangeal joints being flexed, and the interphalangeal joints extended. From this rigidity of the hand the writing becomes small as well as tremulous, and the patient finds it difficult to write in a straight line. Muscular weakness always accompanies the rigidity and the tremors. It is slight until the late stages of the disease, when it may increase rapidly and render all useful movement impossible. On account of the rigidity and consequent slowness of movement, the patient experiences a sense of weakness which is much greater than the actual weakness shown by the dynamometer. Tremor is present in the majority of cases. It usually commences in the hand and forearm, and is most conspicuous in this situation; but it may be seen in the face, tongue, jaw, neck and feet, while, in rare cases, it may be universal. The nature of the tremor is peculiar, and is highly characteristic. It is a regular rhythmical contraction of the muscles, alternating in the opposing groups with a frequency of from four to six oscillations per second with a range of from an eighth to three-quarters of an inch. Its rhythmic nature, its slowness and its range distinguish it from other varieties of tremor. In the hand the characteristic movement of the tremor is the rolling together of the opposed thumb and fingers, cigarette-rolling, bread-crumbling or drum-tapping movement. There is nearly always in addition a peculiar pronator-supinator tremor. The tremor is increased by excitement and by self-consciousness, and ceases during sleep. A highly char-

acteristic feature of the tremor in about one-half of the cases is that it continues during repose, and is temporarily arrested by the execution of volitional movement. In the other half of the cases, however, the tremor appears or is increased on voluntary exertion, and tends to be less during repose. There seems to be an antagonism between the tremor and the rigidity, for in cases where the rigidity is very conspicuous the tremor is little marked or absent, and conversely, when tremor is universal or is of early onset, rigidity is a less noticeable feature.

Other symptoms of the disease which are very commonly complained of are—(1) difficulty in turning over in bed, which is the obvious result of the rigidity of the trunk muscles; (2) flexion of the toes into the sole of the foot, so that they are trodden on, from spasm of the plantar muscles; (3) pain of a dull aching character in the trunk and limbs, which is presumably produced by the long-continued traction of the rigid muscles upon their attachments; (4) abnormal sensations of heat and cold and (5) hypersensitiveness to changes of temperature—the patient cannot bear to be near a fire nor yet in a cold room. Mental symptoms are conspicuous by their absence, except in the last stages of the malady, when profound asthenia overtakes both mind and body. The constant bodily discomfort, restlessness, sensations of fatigue, which the rigidity and the tremors engender, and the consciousness of a malady which is found only too soon to resist every effort to lessen or arrest it, often result in gloomy and lasting mental depression. Objective sensibility is unimpaired. The special senses and the cranial nerves are not affected. The sphincters and the reflexes are normal. Trophic changes in the periphery of the limbs, thinning and glossiness of the skin, with fluted nails and vasomotor disturbance, are common. *Bed-sore is commonly met with in the late stages of the malady.*

**Diagnosis.**—There are three points which can be surely relied upon to render the diagnosis of paralysis agitans certain in every case, namely—(1) the aspect of the patient when he is walking, when the fixed mournful expression, the stooping attitude with round shoulders, the elbows pressed into the side and the hands carried across the abdomen in the interosseal position, the immobility of the head and neck, and the curious gliding gait which cannot fail immediately to arrest the observer's attention; (2) the rhythmic rolling tremor which is quite unlike any other form of tremor, and which often continues during rest and (3) the absence of any of the signs of disease of the pyramidal system. Difficulty may perhaps be experienced when the aspect is little marked, and the tremor is confined to some unusual situation, such as the face, tongue or neck; but, if the possibility of tremor in any situation being that of paralysis agitans be borne in mind, its rhythmic rolling nature will give the diagnosis. When paralysis agitans is confined to one side of the body, the appearance of the patient may superficially resemble that of hemiplegia; but in these cases the peculiar aspect of paralysis agitans is marked, and the organic signs of hemiplegia, such as the extensor response in the plantar reflex, the increase in the deep reflexes and the absence of the abdominal reflex upon the paretic side are not present. In senile tremor the rhythmic rolling quality is absent, and the aspect is not that of paralysis agitans. In post-hemiplegic tremor the organic signs of hemiplegia are present. Toxic tremor is irregular and never rhythmical, and is (mercurial tremor excepted) a fine tremor. The intention tremor of disseminated sclerosis, cerebellar disease and lesions of the red nucleus are so peculiar, and so widely different from the tremor of paralysis agitans, as to render confusion impossible.

The one clinical condition which may resemble paralysis agitans so closely as to be indistinguishable is the form of Parkinsonism which may appear as a sequela of encephalitis lethargica. In this condition there are similarly placed changes in the basal ganglia brought about by the encephalitic virus. Such post-encephalitic cases commonly originate much earlier in life than paralysis agitans, and there may be a history of the initial disease. The onset is often more rapid and the condition may become arrested, whereas paralysis agitans is invariably relentlessly progressive.

Post-encephalitic cases often manifest other sequelæ of the disease, notably oculogyric crises, post-encephalitic tics, alteration in the pupils or external ocular muscles and changes in temperament. These are absent in paralysis agitans.

**Course and Prognosis.**—Paralysis agitans often begins in one limb, usually the upper, and spreads thence to the corresponding limb of the opposite, or to the other limb of the same side. In the latter case it has approximately a hemiplegic distribution, and it may remain for years much more evident upon one side of the body. The course is slowly progressive with variable rate. In some cases the malady may remain stationary for years, and this is more often seen in middle-aged subjects, before the disease has reached an incapacitating stage. Such arrest in the early stages is not often seen in young subjects, for in the latter the disease seems to take a more continuously downhill course. Real improvement in the symptoms is never seen. A fatal issue may occur in as short a time as 2 years, but this is exceptional, since paralysis agitans has little tendency to shorten life. The average duration is from 10 to 15 years, and since the major incidence of the disease is in the sixth decade of life it will be seen that many of the patients are of average longevity. Death may occur from intercurrent maladies, especially from bronchitis; but more commonly, after the lapse of many years, the patient becomes bedridden from increasing weakness and rigidity, and sinks into a condition of sleepy asthenia which is soon terminated by coma. An unduly high blood pressure is unusual in the subjects of paralysis agitans, and it is noteworthy that they do not suffer from gross cerebral vascular lesions, such as thrombosis or hæmorrhage.

**Treatment.**—All that can be done to arrest or slow down the degenerative process which is responsible for the symptoms is general tonic treatment and the administration of those vitamin B elements which aid the general nourishment of the nervous system. Palliative treatment is almost entirely medicinal. Where there is much rigidity gentle exercise, passive movements and massage are useful, but electrical treatment can do no good. In using the various medicinal remedies which are available, it must be remembered first, that all of them produce their effect for a few hours only, and secondly, that the patient's symptoms cease in any case during sleep. It is therefore important that the patient should take the drugs at such times of the day as to obtain the maximum relief during those periods when he most desires it, and it is useless to take them at night. The most generally useful remedy is benzhexol hydrochloride (Artane), which relieves both the tremor and the rigidity, though in occasional cases by reducing the rigidity it allows the tremor to increase. It is issued in tablets each containing 2 mg. or 5 mg., and small doses should be given until the patient's tolerance of the drug is assured; it can then be increased gradually up to 20 or 30 mg. in the day, until the maximum effect is obtained. The symptoms of intolerance are nausea and occasionally some blurring of vision.

The action of procyclidine hydrochloride (Kemadrin) is similar. Drugs of the belladonna group have long been used—belladonna, hyoscine, stramonium, atropine, and of these hyoscine is in general the most valuable. It may be given in tablets (each gr.  $\frac{1}{32}$ ), or in solution, and the latter has the advantage that the dose is more easily varied (gr.  $\frac{1}{32}$  or  $\frac{1}{64}$  by mouth thrice daily in chloroform water). If quickly absorbed, it may produce feelings of confusion or faintness and should therefore not be taken when the stomach is empty, but only after food. The combination Rabellon contains hyoscine, stramonium and atropine in tablet form.

The progress of the disease is slow and the patient should be encouraged to maintain his activities as long as possible; nothing is to be gained by rest. When the patient is bedridden, great care must be taken with the skin.

Pains may be troublesome and can only be relieved with aspirin and similar analgesics. The immobility of the limbs may cause arthritis in the shoulders, and this should be guarded against by passive movements, and when it occurs treated by the usual appropriate measures.

## CHOREA

**Synonyms.**—St. Vitus' Dance; Sydenham's Chorea; Rheumatic Chorea.

**Definition.**—Chorea is an affection of the nervous system characterised by the occurrence of spontaneous involuntary movements, irregular both in time, in extent and in place of occurrence, and also by muscular weakness, and by a variable degree of psychic disturbance.

**Ætiology.**—The important causal factor of the ordinary variety of chorea is acute or subacute rheumatism. Chorea is much more common among the poorer classes than among the well-to-do. Its incidence is upon nervous highly-strung subjects rather than upon the phlegmatic, and this is probably to be explained by the fact that the rheumatic subject is likely to be nervous and highly strung. Chorea is practically unknown during the first 3 years of life, and is very rare before the fifth year has passed. Common between the ages of 5 to 10 years, it reaches its maximum incidence between 10 and 15 years. After the age of 20 it is rare, except in pregnancy; but a few cases have been reported up to the age of 60 years which have certainly been examples of rheumatic chorea. Females are affected twice as frequently as are males. Heredity concerns the incidence of chorea in two ways: firstly, in the inheritance of the rheumatic tendency, which is the important cause of chorea; and secondly, in the inheritance of the neuropathic tendency, for it is when these two are coincident that chorea is most prone to occur. As early as 1802 rheumatism was regarded as the cause of chorea, and all subsequent investigations have upheld this theory. The family history of a choreic patient generally brings to light the occurrence of acute rheumatism, of cardiac disease and of other rheumatic manifestations among other members of the family. Often the patient has suffered with acute or subacute rheumatism, growing pains, rheumatic erythema, purpura, rheumatic nodules or recurrent sore throat before the appearance of the chorea, and may be found to be already the subject of rheumatic heart disease. A large percentage of those patients who have never shown any sign of the rheumatic state before or during the attack of chorea subsequently suffer with rheumatic symptoms. The British Medical Association Collective Investigation Committee found that rheumatism preceded the chorea in 26 per cent. of the cases, and that in 46 per cent. of the remainder rheumatic signs accompanied the chorea, or appeared subsequently. If to the total of choreic patients who present rheumatic signs at some time or other one adds those with no personal history of rheumatism, but with a family history of rheumatism, it will be found that there are but few cases of chorea in which a personal or family history of rheumatism is absent.

**Psychical disturbances.**—Any emotional disturbance, such as fright, anxiety, depression or overpressure in school, may sometimes act as an immediate determining factor, but much more often these events simply aggravate symptoms which are already present in slight degree.

**Pregnancy.**—The relationship of pregnancy to chorea is very definite. It is generally met with in first pregnancies, and before the age of 25 years, and in most cases the pregnancy appears to be the only immediate cause for the chorea, but a history of rheumatic infection will often be obtained in a careful history. The onset of the chorea is usually between the first and third months of pregnancy. It is liable to recur with subsequent pregnancies.

**Pathology.**—The essential lesion has proved very difficult of detection by microscopical investigation, but according to Greenfield and Wolfsohn it consists in a diffuse meningo-encephalitis affecting mainly the basal ganglia, the cerebral cortex and the pia-arachnoid.

**Symptoms.**—The onset is usually gradual, but it is sometimes abrupt, when emotional disturbance has been the determining cause. The appearance of choreic



movements is often preceded by alterations in the mental and physical condition of the child. She becomes nervous and more impressionable than before. She is increasingly unable to apply her attention. She becomes clumsy in her movements—and lets fall objects which she is holding. Anæmia, apathy and languor and irregularity of appetite are commonly present. At this time, careful observation will discover slight involuntary movements of the face and fingers which are often unilateral in distribution. From day to day the movements become more marked and spread to the limbs and trunk. The face is constantly grimacing, and the hands and arms scarcely cease from turning about, and affection of the legs makes the walking irregular and clumsy. The child can no longer keep still, the respiratory movements become irregular and spasmodic, and the chorea is fully developed. The characteristic symptoms of a well-marked case of chorea are—(1) involuntary movements; (2) weakness of voluntary movements; (3) ataxy or loss of precision of voluntary movement; (4) emotional instability and other psychic disturbances.

1. THE INVOLUNTARY MOVEMENTS are always irregular in time and in the form of the movement. Similar movements are never repeated successively in the same part. Each movement begins rapidly, and ends suddenly, and one frequently sees the involuntary movement complicated by the addition of a voluntary movement to cover the fault. The majority of the movements are complicated, involving several muscles and often more than one joint. In the face, the more simple movements take the form of asymmetrical twitches in the lips, and about the angles of the mouth and orbits. In more severe cases, the strangest grimaces may occur. The tongue is thrust into one cheek, then put out and withdrawn just in time to escape the sudden snap of the open mouth. When asked to show the tongue, the child puts it out rapidly and holds it there by closing the teeth upon it. Smacking of the tongue and palate may often be heard at a distance. Lateral movement of the jaw is common. According to the severity of the case, speech may be difficult, the words being articulated slowly in slurred monosyllables. For the same reason, swallowing may be difficult or impossible in severe cases, and may necessitate nasal feeding. The ocular muscles participate in the involuntary movements only in very severe cases.

In the upper extremities the movements appear first in the hand. The thumb is more restless than the fingers, which are spread and pressed together, flexed and extended, alternately; the wrists twist about irregularly, the forearms are constantly agitated with movements of pronation and supination, flexion and extension; while all possible movements of the shoulder occur. When the upper extremities are outstretched, the hands assume the position of flexion at the wrist and over-extension at all the finger joints in so many of the cases as to make this a characteristic feature of chorea. The lower extremities are less severely affected than is the rest of the body, and here the movements are best seen when the child is lying down. The gait tends to be clumsy and insecure, and in severe cases walking becomes impossible. Alteration of the rhythm of the respiratory movements is conspicuous and is highly characteristic of chorea. The breath is often taken rapidly and held for some time, then let go with a loud sigh. The trunk is often involved, and movements of a writhing nature are characteristic.

So far as the limbs are concerned, the movements may be confined to one side, more commonly the left side, and the condition is then called hemichorea; but the involvement of the face and trunk is always bilateral and is generally equal upon the two sides. In hemichorea, the movements are always of slight severity. Severe chorea is never confined to one side. Choreic movements cease during sleep, and, except in severe cases, can be controlled more or less by voluntary effort; the attempt to write, for example, will generally cause cessation of the movements of the right arm for the time being. They are generally increased by observation, emotion and self-consciousness, but in a few cases it will be found they are worse when the child is alone and unobserved. The violence of the movements of the limbs may cause the

skin over the prominences to ulcerate from friction against their clothing, and the head and limbs may be badly bruised from contact with adjacent objects, and unless the patient be properly protected, wounds may occur, which are liable to infection.

2. **LOSS OF POWER** is shown in the mild cases by incapacity for exertion and undue fatigue. More severe degrees of paresis may accompany or succeed the appearance of the movements. It may be observed that in one limb, or upon one side of the body, the choreic movements are becoming less marked, and that the limbs are becoming progressively weaker. Soon the arm hangs loosely by the side, and the leg is dragged in walking. The degree of choreic paralysis bears no relation to the severity of the movements, for the former may be severe, when the latter are slight and vice versa. Choreic paresis is apt to return with successive attacks of chorea, but not always in the same region.

*Limp chorea (chorea mollis).*—This is a more severe degree of choreic paralysis which may affect the whole musculature but is more often of hemiplegic distribution. It may be preceded by the usual symptoms of chorea. More often the paralysis is the first noticeable symptom, and this develops rapidly in from 24 to 48 hours. The paralysis is characterised by complete flaccidity of the limbs; the child lies upon its back and does not move, and if one of the limbs be raised from the bed and then released, it falls limp and lifeless. The head is no longer held in a natural position, but falls round on to the ear. Careful investigation, however, rarely fails to reveal some slight choreic movements, either in the face or in the fingers. Paretic chorea and chorea mollis run a benign course, and recovery is said to be almost invariable.

3. **INCO-ORDINATION OF VOLUNTARY MOVEMENT** may be the first symptom of chorea to attract attention, and it may precede the appearance of the choreic movements. It may be very obvious when the movements are slight, and it is most noticeable in those of the hand and forearm, which lack precision, and in those of articulation, deglutition and respiration. The involuntary movements that have been described are superimposed upon voluntary movements which they render inco-ordinate, at times interrupting them abruptly and at other times tending to prolong them.

4. **PSYCHICAL DISTURBANCES** are common, some degree of emotional instability, failure of attention and depression being present in most cases, and, generally, in proportion to the severity of the affection. The patient's behaviour changes; she may laugh or weep without sufficient reason; she may become capricious, irritable and obstinate; attention and memory are usually impaired, and less interest is taken in the surroundings. A condition of hebétude may develop. Delirium may occur in acute and grave cases. It is usually violent and loquacious, and resembles other forms of toxic delirium, and it is of serious prognostic import. Visual hallucinations of a terrifying character may occur. Mania is quite exceptional in children, but it is not an uncommon complication in adolescents and adults. The psychical disorders, slight or severe, usually disappear with the chorea, and in all cases the prognosis as regards permanent mental recovery is good.

The pupils are frequently dilated and may be unequal and eccentric, and hippus may be present. Sensibility is not impaired. The sphincters are not affected. The skin reflexes are normal. The deep reflexes are also normal in a large proportion of cases, but often the knee-jerk shows an alteration which is peculiar to chorea. On tapping the patellar tendon, the resulting contraction of the quadriceps is unduly sustained, and the leg remains in a position of extension at the top of its excursion for several tenths of a second; in other cases a pendular knee-jerk is present. In severe cases, the deep reflexes may be diminished and rarely may be absent for months.

**RHEUMATIC MANIFESTATIONS.**—Cardio-vascular changes are common in chorea. In nearly all the cases, careful and repeated examination of the heart will reveal slight dilatation and reduplication of the second sound, often with reduplication of the first sound, and increased rapidity of the pulse. Doubtless these are signs of

myocardial involvement resulting from the rheumatic infection. Irregularity of the pulse may be dependent upon the altered rhythm of respiration. Systolic murmurs are common, and these may be hæmic in nature, or may be the expression of cardiac dilatation, but in the majority of cases they are indicative of endocarditis. Endocarditis is present in 90 per cent. of the fatal cases. At least one-half of all cases present cardiac murmurs, which are suggestive of the presence of endocarditis, while some cases with no cardiac murmur during life are found post mortem to have endocarditis. The mitral valve is commonly affected, lesions of the aortic valve being uncommon. Pericarditis is a frequent associate of endocarditis; only in rare instances does it occur alone. The valvular affections which are met with in chorea may be the result of antecedent rheumatism, or they may develop in the course of the chorea; or while no signs of endocarditis are present during the attack, the patient may shortly afterwards present the signs of organic valvular disease. Cutaneous affections which occur in rheumatism are met with also in chorea, namely, erythema, purpura and subcutaneous nodules. Acute articular rheumatism is comparatively rare, and when it occurs it is usually accompanied by a cessation of the choreic movements. When rheumatic phenomena are present and in the acute mania of chorea, pyrexia is usually present, but uncomplicated chorea is an apyrexial disease.

**RECURRENCE.**—One-third of the subjects of chorea have more than one attack. Females are more prone to a recurrence than males in about the same proportion as they are more liable to original attacks. The average interval between the attacks is 1 year. If, therefore, a patient has remained well for 2 years, it is improbable that a recurrence will take place. The greater the number of choreic attacks, the more likely is the heart to be found affected, and, therefore, cardiac complications are more often met with in recurrences. In a recurrence of chorea the symptoms are usually less severe and their duration shorter than in the original attack.

**Course and Prognosis.**—The disease tends to a spontaneous termination after a variable time, which is usually from 6 weeks to 6 months. The duration rarely falls short of the earlier period. The average duration of cases treated in hospital has been found to be 10 weeks. Cases which last for more than 12 months are not rare, and slight cases with remissions may last several years. The course of the malady is that after a gradual development of symptoms, there is a stationary period during which symptoms are well marked, followed by a period of gradual diminution. In some of the more severe cases of chorea where deglutition is difficult the patient is likely to be insufficiently fed; and this constitutes a grave danger, since in the condition of semi-starvation so induced, the chorea develops apace. In such cases articulation and swallowing become impossible, and the movements become ceaseless, so that both rest and sleep become gravely impaired; the patient wastes rapidly, and is in danger of death from exhaustion unless prompt measures for restoring the depleted nutrition are taken. This is the condition known as "chorea gravis".

The proportion of fatal cases occurring in chorea is less than 2 per cent. Death is most often met with in first attacks, occurring about the age of puberty, and in cases associated with pregnancy. It is very uncommon in young children and in recurrences of chorea.

**Diagnosis.**—The nature of the involuntary movements of chorea is usually so characteristic as to make diagnosis easy, and to avoid any confusion with other maladies which present conspicuous involuntary movements. Nevertheless, occasionally a case of multiple tics in a child does present difficulties, for the movements are not—as is so commonly stated—invariably repetitive. In chorea the involuntary movements may lead to the dropping of objects from the hands. This does not happen in the case of tics. Again, when the choreic subject gives the observer a firm and sustained handclasp, the irregular waxing and waning of the muscular contraction may be felt throughout by the observer. In a case of tics, the contraction is steadily maintained as in the normal subject. In myoclonus, the movements are short and

shock-like, while in athetosis they are slow and writhing. In chorea mollis or hemiplegic chorea the paresis is in itself highly characteristic. It is a flaccid paralysis which is never absolute and usually affects the arm most. There is no pain and no wasting, and while spasticity is absent the deep reflexes are usually preserved.

**Treatment.**—It is well to commence treatment in every case with several days' absolute rest in bed, but in the milder cases this need not be persisted in beyond a few days, though the ordinary periods of rest should be prolonged.

The salicylates are of great value and of these aspirin is the most useful, and it is best combined with equal doses of sodium bromide; gr. 10 of each may be given in mixture thrice daily after meals for a child between the ages of 8 and 14, and aspirin should be continued well into convalescence.

In addition, tonics such as syr. ferri phos. co. (Parrish) and cod-liver oil and malt are valuable especially in the convalescent stage.

Severe cases of chorea call for skilled nursing. The sides of the cot or bed should be well protected by pillows and the patient's hands and elbows covered with pads of cotton wool. An unbreakable feeding-cup is necessary. When swallowing is difficult resort should be made to nasal feeding, especially because of the importance of ample nourishment in this disease. In the worst cases morphine may be required at night.

#### HUNTINGTON'S CHOREA

**Synonym.**—Hereditary Chorea of Adults.

This is a somewhat rare disease, in which symptoms almost identical with those of rheumatic chorea, namely, involuntary spontaneous movements, ataxy, paresis and slow and slurring articulation, gradually appear in adult life, and usually about the age of 40 years, and are accompanied by progressive mental failure, with delusions and suicidal tendency. The choreic movements are seldom severe, but the inco-ordination may be well marked. Maniacal outbursts are not uncommon. The disease always progresses slowly to a fatal termination in from 5 to 30 years, and treatment is entirely unavailing. It is a familial disease, and the transmission is direct from parent to child; but if a generation escape the malady, it seems not to reappear subsequently. Sporadic cases, in which no heredity can be traced, do, however, occur. The sexes are equally affected. Further than the heredity no causal factors are known. The morbid anatomy consists in a slow progressive degeneration of the nerve-cells of the basal ganglia and of the cerebral cortex, with consecutive atrophy of the convolutions, neuroglial overgrowth and meningeal thickening.

#### APOPLECTIFORM CHOREA

This title has been given to rare cases of chorea of sudden onset in elderly subjects. The involuntary movements are usually unilateral, and are often of great severity and large amplitude (hemiballismus).

In cases of this disorder examined after death thrombotic softening or hæmorrhage has been found in the subthalamic region, particularly in the corpus Luysii. The mechanism by which small lesions in this situation give rise to such violent manifestations is not understood, but the occurrence of such cases is obviously of great theoretical importance.

#### SENILE CHOREA

A malady in which typical choreic movements constitute the chief feature is met with in elderly people, and is possibly due to a progressive neuronc degeneration in those regions affected in the other forms of chorea. It differs from Huntington's chorea in the late onset, the absence of heredity and in the absence of mental changes.

## MYOCLONUS

**Synonym.**—Paramyoclonus Multiplex (Friedreich), Myoclonus Epilepsy (Unverricht).

The characteristic symptom of this very rare condition is the occurrence of sudden shock-like contractions of the muscles, which may vary in intensity from simple fibrillary twitching to contraction which causes a violent movement of a limb. The movements are often symmetrical, and are especially incident in the proximal muscles of the limbs.

**Ætiology.**—The malady appears in children usually between the ages of 5 and 15 years, while in adults it commences between the ages of 25 and 40 years. Both sexes are liable to the affection. Many instances, in which several children of the same parents have been affected, have been recorded, and in a few the malady has been transmitted through several generations. There is now good pathological evidence that in some cases the condition is associated with diffuse cerebral lipoidosis, and is related on the one hand to subacute inclusion body encephalitis and on the other to the various forms of cerebro-macular degeneration, while in other cases the peculiar bodies described by Lafora are found in the cells of the brain and also in the liver, heart and possibly other organs.

**Symptoms.**—The movements of myoclonus are simple sudden movements, and may exactly resemble the movement resulting from a single faradic stimulus. Each movement commonly involves a single muscle only, and it may concern no more than a few fibres, resembling then the fibrillary twitching common in progressive muscular atrophy. In other cases, many muscles may be implicated in the shock-like spasms, which may be of so violent a nature as to throw the patient to the ground. The distribution of the contraction is never determined by that of the nerve supply, nor do the muscles contract according to their synergic association. Myoclonic movements are irregular as regards rhythm and range of successive movements. The upper limbs are more affected than the lower, and the proximal parts more than the distal, while the periphery, the hand and foot, often escape. Voluntary muscular effort usually checks the myoclonic movements, but in rare instances it excites or augments the spasm. The electrical excitability of the muscles is unaltered, and there is no muscular wasting, but the mechanical excitability of the muscles is increased, and percussion of a muscle may evoke the spasms. The sphincters are unaffected. The reflexes, both superficial and deep, are normal. Sensory phenomena are absent. Speech may be seriously interfered with when the muscles of jaw, tongue, palate and larynx are implicated, and spontaneous laryngeal and pharyngeal noises may occur. The ocular muscles seem never to be the seat of the movements. Epileptiform convulsions are present in the typical cases.

Characteristic electro-encephalographic changes have been recorded.

**Diagnosis.**—This is not difficult since the simple shock-like movements in symmetrical muscles, without any resemblance to volitional movements and entirely destitute of rhythm, occur in this disease alone.

**Course, Duration and Prognosis.**—Myoclonus, as a rule, is a slowly progressive affection up to a certain stage, and when this is reached it may remain stationary for years, having little tendency to shorten life, death ultimately occurring from some other disease, without any period of freedom from the spasms. Rarely the disease has ended fatally within a few months of the onset, with progressive mental failure and coma.

Recovery may take place spontaneously, but the affection is very prone to recur.

**Treatment.**—Every available measure should be used to improve the general bodily condition so as to bring about a more stable condition of the nervous elements, by improving their nutrition. Sedatives may be tried, but are seldom of value. Myanesin, taken by mouth, relieves or abolishes the twitchings temporarily.

## SPASMODIC TORTICOLLIS

**Definition.**—A disease of the nervous system, characterised by tonic and clonic contraction of the superficial and deep muscles of the neck, causing the head to assume either a position in which it is turned to one side and upwards, or a position of marked retraction (retrocollic spasm). It is more correctly to be regarded as a disturbance of movements than of muscles, and perhaps, physiologically considered, it may be spoken of as a disorder in the carriage of the head. This carriage is a more complex and highly co-ordinated function in the erect posture than in the quadrupedal posture; it is a function peculiar to man, and in this sense is of recent evolutionary development. We may perhaps see in this a factor determining its frequent derangement, as in spasmodic torticollis.

**Ætiology.**—The disease is most frequently met with in middle-aged or elderly subjects, but it may occur at any age from puberty onwards. It is twice as frequent in females as in males. The causation is most obscure. Not infrequently neuropathic heredity, such as epilepsy and insanity, exists, and the patients are often of highly strung, nervous, irritable dispositions. Nervous shock, prolonged anxiety and general ill-health have frequently preceded the onset of symptoms. Less often local strain, or injury and exposure to cold, have been the presumably exciting causes. In a few cases it appears to develop from an occupation neurosis; it developed, for instance, in a tailor who in drawing each stitch had the habit of making a short jerking movement of the head to one side. It occasionally occurs as a symptom of hysteria; but such cases should be carefully separated from those in which there is no hysterical manifestation, as being more susceptible to treatment and having less tendency to recur when once cured. A torticollis movement may occur as a variety of tic. Typical torticollis may occur as the end-result of lethargic encephalitis.

**Pathology.**—No morbid anatomical changes have been found. On account of the involvement of several muscles, effecting special movements, in this disease (as is well instanced by the over-action of the frontalis in retrocollic spasm, for retraction of the head is always normally associated with raising of the eyebrows in the act of looking up), it is probable that torticollis is due to disorder of those centres which direct such associated movements of the affected muscles.

**Symptoms.**—The onset is usually insidious, but in rare cases may be quite sudden, as in the case of a man aged 40 years, who, when walking along a London street, suddenly turned his head at the sound of an accident which shocked him severely; he was unable to turn his head back without using his hands to do so, and he subsequently developed the most severe torticollis. The initial symptom is always spasm, which may be either tonic or clonic, and frequently both forms of spasm are combined in the same case. In the tonic form, the head is retracted and the face turned to one side, usually the left, and owing to the retraction of the head the face is turned upwards. The shoulder on the side to which the head is inclined is usually raised. In severe cases all the muscles of the upper extremity, the scaleni and the face muscles, may become involved. The spasm, except in the earliest stages, always involves muscles of both sides of the neck. Where the bilateral involvement is general and equal, the rotation of the head does not recur, but it becomes strongly retracted, and the condition is then known as retrocollic spasm. Such retrocollic spasm is always accompanied by marked over-action of the frontales, the skin of the forehead being thrown into transverse wrinkles. In the clonic variety there is jerking movement of the same muscles, usually associated with some degree of tonic spasm. The eyes do not follow the movements of the head in the jerkings. The muscle primarily involved is the sterno-mastoid, the action of which is to incline the head forwards and towards the shoulder of the same side, and rotate the face to the opposite side. The next muscle involved is the splenius of the opposite side, which inclines

the head backwards and rotates the face towards its own side, its rotatory action thus coinciding with that of the opposite sterno-mastoid. When the splenii of both sides act together, the head is strongly retracted. Next to be affected are the upper parts of the trapezii and the deep neck muscles, and with further spread of the spasm, any neighbouring muscles of the shoulder and upper extremity may be affected. Sleep causes cessation of the clonic spasm, but not always of the tonic spasm when the case is severe. The spasm is always increased by fatigue and excitement. There is no wasting of the muscles involved, but, on the other hand, they may be even hypertrophied if the spasm has existed for long, and their electrical excitability may be increased. The amount of pain associated with the spasm varies greatly. There may be a slight feeling of cramp only, but usually there is a great deal of aching pain, which may radiate down the arm and into the side of the head, and make life unbearable to the patient. More rarely, sharp neuralgic pains are present.

The course of the disease, which has no tendency to shorten life, is chronic, exacerbations and remissions under treatment being common, and recurrence, after temporary cure, frequent.

**Diagnosis.**—This is usually quite simple. Fixed positions of the head associated with spasm occur in disease of the cervical spine, especially in spinal caries, and are also associated with enlarged lymphatic glands in the neck. The local signs of these conditions, however, are characteristic.

**Treatment.**—Spasmodic torticollis is a most intractable condition, and in many cases temporary alleviation is all that can be secured. It is usually best to begin treatment by rest in bed, the patient lying supine with the head low and between sandbags or pillows. The regular administration of phenobarbitone, or of chloral and bromide may then be tried. Many years ago Bastian claimed good and permanent results from a continuous narcosis lasting 3 weeks and induced by chloral hydrate. Probably a combination of rest as above described, together with massage and resistance exercises, is the most useful line of treatment. In some cases the application of a plaster mould, fixing head and shoulders, and worn for one or more months, or a more easily removed and lighter metal splint will give complete respite from muscular spasm while it is worn, and very occasionally permanent respite after removal. In severe and disabling cases this is well worth trial. Surgical measures (tenotomy, excision of the sterno-mastoid, posterior root section) have all proved disappointing and are not to be recommended. Except in cases of hysterical origin, psychological treatment is without effect.

There is a *congenital form of torticollis* which is of a very different nature. The disease is prenatal and analogous to congenital talipes, the sterno-mastoid alone is affected, and nearly always that of the right side. Such a muscle is frequently ruptured during birth, and this has given rise to the opinion that the birth injury and subsequent hæmatoma of the muscle were responsible for the torticollis. In many of these cases there is marked facial asymmetry, the face being smaller on the side of the affected sterno-mastoid. This association points strongly to some defect in the nerve centres of the medulla. Treatment consists in tenotomy of the contracted muscle.

## THE TICS

**Synonym.**—Habit Spasm.

**Definition.**—A group of maladies characterised by the occurrence of (1) sudden, rapid, twitch-like, involuntary co-ordinated movements, always of the same nature and in the same region; or of (2) sudden psychical phenomena, imperative ideas and explosive utterances; or (3) of a train of deliberate highly co-ordinated actions produced by an imperative idea. Any combination of these phenomena may occur.

The tics are both ætiologically and clinically related to spasmodic torticollis, into

which some of the motor tics gradate. A torticollis movement may occur as a tic, and it may in rare cases pass over into an established torticollis.

The tics may be conveniently divided for clinical purposes into the following groups, between which any combinations may occur :

(1) The clinical picture is made up by the occurrence of sudden twitch-like co-ordinated movements, which resemble reflex or defence movements. The movement is always of the same nature and occurs in the same region, though several different tics may occur in the same patient. The usual region affected is the face, with the pharynx and larynx, the neck and upper extremity. This form occurs chiefly in children, and usually runs a favourable course—Simple Tic.

2. The spasms are more severe and complicated than in simple tic, and imperative ideas and explosive utterances are common and important symptoms. The condition is met with soon after puberty, and more commonly in males—Convulsive Tic.

3. There is no spasm or other motor manifestation, but the psychic tic is expressed by uncontrollable imperative ideas, explosive utterances, arithmomania, etc.—Psychical Tic.

The tics are expressions of unrest and of embarrassment in consciousness in a nervous system which is highly sensitive and not too stable. There is always the desire to relieve the embarrassment by the occurrence of the tic, and a feeling of relief when it has occurred, coupled often with disappointment at the failure of its suppression.

While the more simple forms of motor tic from their pattern suggest strongly that they were originally associated with some peripheral irritation, from the conjunctiva in the case of a blinking tic, from the nose in a case of snuffling tic, and from the larynx in a case of laryngeal tic, and that constant irritation from these regions has set up a habit, yet it cannot be too strongly pointed out that in many cases no such peripheral irritation precedes the onset of tic, and the irritation and cause come from within the nervous system alone.

## 2. SIMPLE TIC

**Synonym.**—Habit Spasm.

This is a common disorder of late childhood, the majority of the cases occurring between the fifth and tenth year. Both sexes are prone to the condition. The onset may be preceded by deterioration of health from any cause, and sometimes fright and emotion bring on the tic. Often the malady arises in perfectly healthy children without assignable cause. The children are usually highly strung and intelligent. It is a rare event to see a dull and backward child with a tic.

**Symptoms.**—The recurring tic appears somewhat suddenly, and may reach its height in a few days. The movements are of the nature of a simple act. They occur suddenly and without warning, and are executed rapidly. Usually the movement is of one kind only; but sometimes several movements coexist. The common site of the spasm is the head, face and neck. Blinking, winking, alternate elevation and depression of the eyebrows, side to side movements of the mouth, tossing the chin in the air, sudden movements of the tongue, palate or larynx, accompanied by an unpleasant fidgiting sound, are of frequent occurrence, while any movement of the head upon the shoulder, torticollis movements, shrugging of the shoulder and any movements of the arm may be met with. Respiratory movements are often associated with those occurring in the tongue and larynx. Tic affecting the legs is much less common. The movements cease during sleep. Generally a variable time of some length separates the individual movements, but in severe cases these may follow one another almost unceasingly. They are increased by excitement and by observation, and can usually be controlled by the will, but only for a limited time.

**Diagnosis.**—The movement of tic is so peculiar that it cannot be confused with



any other spontaneous, involuntary movement. It is the same movement, repeated with very rapid execution, in the same place. It is short and sharp, like a twitch. In chorea the movements are slow compared with those of tic, and are irregular in nature, in time and in place.

**Prognosis.**—Most cases of simple tic recover, whether they are treated or not. They recover much more quickly under treatment, and 2 or 3 months suffices in most cases to see the end of them. The longer a tic lasts, the more difficult it is to cure. In the rarest cases only does a tic of this nature persist or merge into one of the more severe forms.

**Treatment.**—A scrutiny of the general health should be made, and any defects attended to. Matters of hygiene, diet, education, exercise and pleasure should be correct and normal. Observation and remarks upon the child's defects, and anything tending to increase self-consciousness should be avoided. The confidence of the child should be gained if possible, and any source of mental worry, or grief, or annoyance should be ascertained and corrected. Restraint and discipline should be kindly taught, and an orderly life followed in which the child is happy, and in which his time is fully and congenially employed.

## 2. CONVULSIVE TIC

In this malady, which was first described by Gilles de la Tourette, and which bears his name, the same movements as are met with in simple tic occur; but they are more severe and more widely spread, and they may involve the whole body in spasm at one time. In addition, there are psychic tics, which cause irresistible impulses, among which are explosive utterances, repetition of words, sounds and gestures, and also imperative ideas.

**Ætiology.**—The stigmata of physical and mental degeneracy are rarely absent, neuropathic and sometimes direct heredity is often present. The malady is said to be more common in males, and is met with more often in France than in England—where it is a rare disorder. The symptoms appear usually between the ages of 10 and 15 years, and commonly follow physical or mental shocks or acute illness of any kind.

**Symptoms.**—The spasmodic movements resemble at first those of simple tic in their nature and rapidity, and favour the same sites; but they are not restricted to the repetition of the same movement, but successive movements may vary widely in position and extent and sometimes involve the whole musculature of the body. The great variety of facial grimaces, head jerking, grotesque attitudes and ridiculous pantomime which may occur in this affection lead commonly to the belief that the patient is shamming. The tic is not continual as in the simple form. It occurs in the form of bouts in which the same pantomime is reproduced. These are often excited by observation and emotion. They can often be controlled, but with much fatiguing effort on the part of the patient, who becomes so worn out with half-successful efforts to control them that he ceases to make the attempt. Between the attacks the patient seems quite normal. The psychic phenomena are the same as in psychical tic, about to be described, and the treatment of the two conditions is identical.

## 3. PSYCHICAL TIC

In this condition there is no muscular spasm; but the sudden event takes the form of explosive utterances, imperative ideas and impulsive acts. This condition often occurs as a part of convulsive tic. The exclamatory tic consists of some sound or word or group of either, which is habitually uttered, with complete irrelevancy of time, place or sense. Sometimes the words are of an obscene nature and cause the greatest distress to the patient. The utterances may be single, or may be repeated

over and over in rapid succession. Echolalia, which is an uncontrollable impulse to repeat sounds heard, or to repeat words which the patient or others have just spoken, may be met with. The great characteristic of the condition is that though the patient desires above all other things to prevent their occurrence he cannot do so by any effort of will. Other symptoms that are commonly met with in this condition are imperative ideas and impulsive acts of all sorts, and in general the symptoms of a severe obsessional state.

**Diagnosis.**—Both in the convulsive and psychical tics the diagnosis is placed beyond doubt, both by the nature of the movements and by the peculiarity of the psychic disturbance.

**Prognosis.**—*Permanent recovery has occurred from both these conditions; but such an event is rare. Most of the cases follow a downward course despite treatment, and many end in suicide or insanity.*

**Treatment.**—General tonic treatment, with change of circumstance and healthy pursuits and congenial intellectual and physical occupation are the most likely to benefit. The psychiatric treatment is that of the underlying obsessional state.

## OCCUPATION NEUROSES

**Synonyms.**—Craft Palsy; Occupation Palsy; Occupation Cramp.

**Definition.**—*A peculiar malady determined by the habitual use of one set of muscles for the constant repetition of an act of short range, to the exclusion of acts of wider range and acts involving a different set of muscles. The symptoms are: (1) local pain in the muscles concerned; (2) local spasm of the muscles; (3) loss of volitional control of the range and nature of the movements and (4) weakness of the movements. These symptoms may occur separately or together.*

**Ætiology.**—The variety of names by which this group of disorders has been known reflects the uncertainty and change in views as to its ætiology and pathogenesis. Certain facts are, however, generally agreed. (1) The disorder is apt to arise in any occupation involving rapid, repetitive movements of short range by a small portion of the body, especially the hand. Such movements figure prominently in the occupations of manual writers, typists, telegraphists, musicians, seamstresses and many others. The movements concerned are always acquired, and necessitate a high degree of precision and co-ordination, but in the course of time become so automatic that in health they are carried out without attention and almost subconsciously while the performer's thoughts are concentrated on other aspects of his work. (2) They involve the rapid, repetitive action of small groups of muscles which may thus be supposed to be subject to especial fatigue. In many such occupations from 5 to 10 repetitive movements a second may be executed. (3) No structural change in the cerebral cortex, nervous system or muscles has ever been demonstrated. (4) In the vast majority of cases the disability initially concerns only one set of stereotyped movements and the affected parts function normally in other activities even though these involve movements of comparable rapidity and skill. Thus, the subject of writer's cramp is able to use the hand normally for shaving, eating or even for playing the piano. In severe and intractable cases, however, other similar co-ordinated movements of the hand may gradually be drawn into the ambit of the disorder, especially if they concern the patient's definitive occupation. (5) The first manifestations of the disorder are likely to make their appearance when the individual is called upon to exceed a certain level of performance, or after any physical or psychological event which may lower the patient's normal level of efficiency. (6) The more searching the enquiry, the greater is the number of these cases that are found to show evidence of predisposition towards psychological instability. In a study of telegraphist's cramp in 1927 this was estimated to be as high as 75 per cent. (7) Faulty training in the

use of the instrument, *e.g.* the pen, and bad design in machinery, *e.g.* certain varieties of Morse transmitters, predispose to the disorder in operatives concerned.

Opinion has gradually moved away from the original conception that the disorder was due to structural change or uncomplicated physical fatigue towards the view that it is primarily psychogenic. Causative factors are no doubt numerous and often multiple, and both physical and psychological in nature, but in their summation they result in the breakdown of the smooth execution of a stereotyped movement, and ultimately lead to the setting up of a faulty habit closely akin to a stammer or a tic.

**Symptoms.**—These are of two orders, namely: subjective, consisting of discomfort, pain and the sense of fatigue; and objective, comprising muscular spasm and the abnormalities of movement arising from it and from the effort to avoid both pain and spasm. In some subjects pain, in others spasm predominates.

The onset is gradual. In the case of writer's cramp the movements of the pen become inexplicably difficult and tend to be irregular, the strokes extending too high or too low. The subject then finds himself grasping the pen with excessive force, and the correct adjustment of the finger ends becomes hard and apt to fail, the index slipping off the penholder. This he tries to correct by a still firmer grasp. The hand then begins to ache, and feels heavy and tired. With the passage of time all these symptoms increase, and the writing becomes more irregular and the nib is driven more firmly into the paper which it penetrates, the ink spluttering over the sheet. Some tremor may develop in the limb. As the condition grows worse, the cramp appears more and more readily when writing is started, so that even taking the pen in the hand may evoke cramp. At the same time, other fine and repetitive movements of the hand may be performed with normal ease and facility. The pain which in varying degree accompanies the cramp tends as the affection grows worse to spread from the small hand muscles up the limb until the whole arm and shoulder ache. With variations dependant upon the details of the movements involved, comparable disturbances are seen in the other varieties of the disorder.

**Diagnosis.**—From what has been said of the character of the symptoms in these forms of cramp, of the mode of their production by a particular movement-complex, and of their occurrence in the absence of signs of organic nervous disease, it seems reasonable to state that errors of diagnosis should not occur.

Nevertheless, errors are not infrequent and consist in the diagnosing of writer's or of telegraphist's cramp when in fact some organic affection is present. Paralysis agitans, with little or no tremor, and post-encephalitic Parkinsonism provide fruitful sources of error. In the clinical picture thus presented, the initial symptoms may involve the right arm and hand, and at first consist in a difficulty in the normally rapid and free performance of fine movements. Not unnaturally the handwriting may be affected early. It becomes slow in performance, spidery and progressively smaller, and the effort to continue writing may be irksome and even painful. The total clinical picture in such a case is made up of such small deviations from the normal that the inexperienced or careless observer may miss them and may note no more than the patient himself has noted; namely, that it has become difficult and uncomfortable to write. Amongst other organic conditions which may be encountered under the erroneous diagnosis of writer's or telegraphist's cramp may be included cervical rib, any organic nervous affection which impairs fine hand movements, arthritis and painful affections of muscles. The general principle which underlies accuracy of diagnosis here as elsewhere is careful and systematic clinical examination.

**Course and Prognosis.**—In a young subject, who shows signs of the malady during training or soon thereafter, the outlook is hopeless with regard to continuance of the occupation, and the progress is from bad to worse. In older subjects the course varies greatly. Some cases recover completely and permanently, even though they continue with the occupation. In others—and this class is much larger than is usually supposed—the condition of cramp becomes stationary, and persists though not in

disabling fashion. In a third and numerous group it progresses to incapacity, and tends to reappear with every change of occupation. In a few cases the patients become incapacitated for all the finer movements of both hands. The prognosis is usually serious; but a correct forecast can only be made from the history and progress of each individual case.

**Treatment.**—The responsibility and costliness which the Compensation Act entails upon employers are slowly enough but surely leading to the abandonment of those instruments, the manipulation of which may produce cramp. Good teaching of unconstrained methods of manipulation and encouragement of ambidexterity in all the occupations concerned are important prophylactic measures. Long hours and the speeding-up of work should be avoided. After long absence from work, the work should be gradually resumed and not recommenced at full pressure. When the malady appears, rest and change of work afterwards are absolutely essential. Long-continued rest, be it remembered, cuts both ways for, as has been pointed out above, resumption after long rest is actually a cause of cramp, for long unemployment decreases the stability and the aptitude of the mechanism.

General treatment consists of the removal, when possible, of adverse factors in the patient's environment, such as uncomfortable working conditions, poor light, excessive noise and sources of personal friction. Full attention should be given to all aspects of the subject's physical well-being.

Psychological treatment may play a valuable part in relieving the underlying anxiety and tension, and in enabling the individual to make a better adaptation to his surroundings, and whenever necessary in giving guidance as to a change in occupation. Careful selection of personnel in occupations liable to the disorder is of great value in eliminating those with special predisposition to this form of breakdown.

When attention has been given to these factors re-education of the movements themselves can profitably be attempted, particularly in the variety of the disorder most often encountered in general practice—namely, writer's cramp. A specially large pen or pencil should be used, and held loosely and comfortably in the natural writing posture. At first the patient should practise drawing straight lines from left to right with easy movements of the forearm. Next, while the same basic movements are maintained, the lines should be made wavy by simultaneous movements of the wrist. Then the waves should be regularly interrupted so that they become series of pot-hooks, m's and n's. From this by gradual stages the smooth execution of other letters may be achieved.

## LOCAL LESIONS OF THE SPINAL CORD

### INTRODUCTION

For lesions of the spinal cord the general rule applies that examination of the nervous system enables us to determine the nervous structures which are affected and also the site of a lesion, but in order to determine the nature of the lesion we are dependent on information obtained from other sources, namely, (1) the history, (2) the general examination of the patient and (3) special tests.

There are many morbid affections in which the spinal cord is damaged only in a short portion of its extent, and it may be of the greatest importance to determine the exact site of the lesion.

The functions of the motor and sensory tracts are usually to a greater or less degree interrupted by the lesion, and it is possible by examination of these functions to determine the somatic level below which muscular weakness, spasticity and reflex disturbances exist, and below which sensory functions are impaired. By these means

the level of the lesion can be determined approximately. Secondly, the motor, sensory and reflex functions of the individual segments of the cord are known, and from this knowledge it is possible to determine more precisely in which segments of the cord function is abolished or impaired, and therefore at what precise level the lesion is situated. Myelography (p. 1533) may confirm the site of the lesion and gives additional information in very many cases.

#### MOTOR TRACT DISTURBANCES—SPASTIC PARAPLEGIA

*Motor symptoms.*—Interruption of the pyramidal tracts produces spastic weakness in parts below the lesion, which, when fully developed, constitutes the picture of spastic paraplegia. The clinical features are: (1) Diminution of voluntary power; (2) alterations in the amount and distribution of muscle tone, and in the attitude of the limbs; (3) changes in the tendon and skin reflexes and (4) the occurrence of certain involuntary and reflex movements.

The phenomena of spastic paraplegia have been analysed by Walshe as follows: it is essential to remember that the muscles of the lower limb are divided into two distinct groups, namely, the flexors and the extensors, and that the muscles which dorsiflex the foot and toes are physiologically flexors, while the corresponding plantar flexors are extensors. In all that follows these important muscles will be grouped according to this nomenclature.

1. Loss of voluntary power varies from slight weakness of one group of muscles to complete paralysis of both limbs, and depends on the degree of damage to the pyramidal tracts. It usually begins in the distal segments of the limb, and is greater in the flexors than in the extensors. Dorsiflexion is the earliest and remains the most severely impaired movement.

2. The tone in all the muscles increases early, and is greatest in the extensors. Hence an early symptom is generally stiffness of the limbs, especially a difficulty in flexing them. If the limbs are handled passively, the resistance to flexion is found to be greater than to extension. It is greatest at the beginning of a passive movement and decreases suddenly in a way that has given rise to the expression "clasp-knife rigidity". As power diminishes spasticity increases, until at length the limbs are held constantly in an attitude of complete extension. This combination of weakness and spasticity with extended lower limbs is known as "paraplegia in extension".

As the damage to the cord increases, and when certain extra-pyramidal motor tracts are affected, the extensor muscles gradually lose their excessive tone for which connections with the brain-stem through these extra-pyramidal tracts are essential, while the tone in the flexor muscles, which depends on a reflex arc which is purely spinal, is retained. The result is that the knee- and ankle-jerks, which indicate tone in extensor muscles, are lost while the reflexes from flexor muscles (hamstring-jerks) persist. At the same time, in some cases, the limbs are gradually drawn up by the unopposed action of the flexors. This combination of weakness and spasticity with flexed lower limbs is known as "paraplegia in flexion". At first, the flexed position is occasional—flexor-spasms; later, it becomes constant, but is still due entirely to excess of tone in the flexors; and ultimately, contractures occur in the muscles, and the deformity becomes permanent.

3. Exaggeration of the tendon reflexes is a constant early sign of spastic paraplegia. The abdominal reflexes below the level of the lesion and the cremasteric reflexes are lost early. The normal plantar reflex is also lost, and is replaced by a different kind of reflex—Babinski's sign, the "extensor" plantar response.

4. While the limbs are still rigid in extension, the commonest involuntary movement is a spontaneous clonus of the extensor muscles, in which the whole limb trembles, as it does when ankle clonus is elicited in a case with marked spasticity. In the later stages, when the extensor muscles are beginning to lose their tone, a new

kind of movement appears, in which the limbs are drawn up suddenly from time to time by an involuntary contraction of the flexor muscles—flexor spasms. Further, by appropriate stimulation many reflex movements can be produced in the paralysed limbs. The most important of these is the “flexion reflex of the lower limb”. This is elicited most easily by stimulating the outer border of the sole by firm pressure or a pin-prick, and in its complete form consists in flexion of the hip and knee, dorsiflexion of the foot, and an upward movement—so-called extension but physiological flexion—of the great toe. When the damage to the motor tracts is slight, when the limbs are rigid in extension and the movement of flexion is prevented by the hyper-tonus of the extensors, or when almost all reflex activity has disappeared, the reflex appears in its minimal form. A part of this minimal response is an “extension” of the great toe. The normal “flexor” plantar response is obtained from the sole alone. The pathological reflex, of which the “extensor” response is a part, may be obtained not only from the sole, but when well developed by stimulating the skin and deeper structures on any part of the lower limb. In the light of this the nature of many reflexes which have been described as isolated signs of pyramidal tract disease, *e.g.* the “extensor” plantar response, Oppenheim's and Gordon's signs, and many others, become clear. In all of them a stimulus is applied to some part of the lower limb, and the response is a flexion reflex, whose most obvious component is “extension” of the great toe. It is unfortunate that the term “extensor response” is commonly used to describe a movement which is physiologically one of flexion.

#### SENSORY TRACT DISTURBANCES

The level of the lesion may be determined approximately by ascertaining the highest point at which sensation is impaired, but in general, for reasons which will be given, the exact site of the lesion is usually several segments higher than the level determined by this method. When the two sides of the cord are affected unequally the anaesthesia is confined to one side or extends higher on one side than on the other. In many instances reliance has to be placed on the disturbances of pain and temperature sensation and it must be borne in mind (1) that the spino-thalamic tract in the antero-lateral column of the cord is concerned with pain and temperature sensation on the opposite half of the body, and (2) that the fibres crossing the cord to join it do so with different degrees of obliquity at different parts of the cord. In the lumbosacral enlargement the pain and temperature fibres cross slowly and in fact clinical experience suggests that they have not taken up their new position until they reach the twelfth dorsal segment. In the mid-dorsal region the decussation of pain and temperature fibres is complete one segment above the point of entry of the root by which they reach the cord. At higher levels crossing again takes place more slowly, until in the upper cervical region impulses which enter together in one root ascend through five or six segments before all of them reach the opposite side. At all levels pain crosses most quickly, then cold, then heat, and touch slowest of all.

When the posterior columns of the cord are involved in the lesion, loss of sense of position occurs in the feet and legs with resulting ataxia. Disturbances of posterior column sensation cannot be used for localisation in the dorsal portion of the cord, but in the cervical portion the disturbances of postural sense in the different fingers may be of localising value.

#### BROWN-SÉQUARD SYNDROME

When a lesion affects one half of a segment of the spinal cord it interrupts (1) the pyramidal tract conveying motor impulses for the lower limb on the same side, and (2) the spino-thalamic tract conveying pain and temperature impulses from the opposite side of the body below the level of the lesion, and (3) the posterior column conveying sense of position impulses from the lower limb on the same side as the

lesion. Consequently a local lesion affecting one half of the cord produces a syndrome, described by Brown-Séquard, consisting of loss of power (with spasticity) on one side, and loss of pain and temperature appreciation on the other side, below the level of the lesion; and, if the posterior column is involved (and it often is not), loss of sense of position on the same side as the weakness.

The Brown-Séquard syndrome most commonly results from lesions in the thoracic portion of the cord. Occasionally it occurs with lesions in the cervical portion, and then the upper limbs as well as the lower may be involved. It does not occur with lesions in the lumbar or sacral cord, because, as has already been mentioned, the pain and temperature fibres have not crossed in these portions, and, consequently, with lumbar and sacral unilateral lesions all the sensory loss is on the same side as the weakness.

### SEGMENTAL DIAGNOSIS

*Motor localisation.*—Each segment of the cord contains groups of anterior horn cells for several muscles, and most muscles receive nerve fibres from more than one root; but as each muscle seems to have one main root of supply, the weakness, wasting and loss of tone vary in distribution with the segment affected. The muscles which suffer most when the corresponding segment is damaged are named hereunder:

*C<sub>1</sub>*. Supraspinatus, infraspinatus. *C<sub>2</sub>*. Biceps, deltoid, brachialis, supinator longus. *C<sub>3</sub>*. Pronators of forearm. *C<sub>4</sub>*. Triceps, extensors of wrist and fingers. *C<sub>5</sub>*. Flexors of wrist and fingers. *D<sub>1</sub>*. Small muscles of the hand. *D<sub>2-10</sub>*. Intercostal muscles. *D<sub>7-12</sub>*. Muscles of the abdominal wall. *L<sub>2-3</sub>*. Adductors of thigh. *L<sub>4</sub>*. Abductors of thigh, extensors of knee. *L<sub>5</sub>*. Hamstrings—Anterior tibial muscles. *S<sub>1</sub>*. Glutei—calf muscles. *S<sub>1</sub>*. Anterior tibial muscles—peronei—small muscles of foot.

Wasting of the muscles in an intercostal space is a valuable guide, as the muscles of each space are innervated from one segment alone. If the lesion is at the level of the ninth dorsal segment the rectus abdominis is weakened below a point about an inch above the umbilicus. In such a case, when an attempt is made to raise the head against the resistance of a hand placed on the forehead when the patient is in the supine position, the upper part contracts and the umbilicus is drawn upwards (excursion of the umbilicus). If the lesion is at the twelfth dorsal segment the entire rectus contracts, but the iliac regions bulge, owing to weakness of the lower part of the oblique muscles.

*Localisation by changes in the reflexes.*—Above the lesion, the reflexes are normal; at its level, they are diminished or lost; below it, the skin reflexes are diminished or lost, and the tendon reflexes are exaggerated. The segments on which important reflexes depend are:

*C<sub>5</sub>*. Biceps- and supinator-jerks. *C<sub>6</sub>*. Pronator-jerks. *C<sub>7</sub>*. Triceps-jerks. *D<sub>7-12</sub>*. Abdominal reflexes. *L<sub>1</sub>*. Cremaster reflexes. *L<sub>2-4</sub>*. Knee-jerks. *S<sub>1</sub>*. Ankle-jerks. *S<sub>1</sub>*. Plantar reflexes.

In lesions involving the fifth cervical segment of the cord, such as may be found in syringomyelia and in injuries associated with dislocation of the cervical spine, Babinski has recorded that the supinator jerk may be abolished and replaced by finger flexion when the lower end of the radius is tapped. This is known as "inversion of the radial reflex", and is a useful localising sign of lesions of the segment in question.

*Sensory localisation.*—The sensory areas supplied by each segment of the cord are shown in the diagrams on p. 1531. "Root pains" in the distribution of one or more of these areas form a fairly sure guide to the affected segment. There may also be sensory loss or impairment over the same areas, and this may be continuous below with the sensory loss which is the result of interference with the sensory tracts, or there may be an interval corresponding to the distribution of one or several

segments between the "root loss" at the affected site and the upper limit of the "tract loss". In many other cases there is a state of hyperalgesia in the segmental areas corresponding to the segment just above the lesion or to the affected segment itself if the lesion be a relatively slight one.

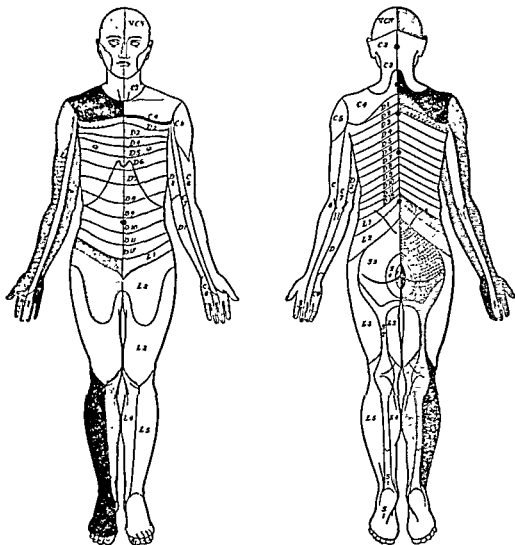


FIG. 3.—Diagram of cutaneous areas of posterior nerve roots.

#### DISTURBANCES OF THE BLADDER AND RECTUM

Emptying of the bladder is essentially a reflex function, but in the normal state the reflex is voluntarily controlled, being inhibited or initiated at will. The detrusor musculature of the bladder wall is innervated by para-sympathetic fibres from the second and third sacral segments of the spinal cord through the vesical plexus. The sphincter musculature is also innervated by the sacral nerves as well as by sympathetic fibres coming from a higher level, namely, from the first and second lumbar segments, with contributions from the third and fourth. The emptying reflex is excited



by an appropriate degree of pressure within the bladder and it evokes a co-ordinated activity combining contraction of the detrusor with relaxation of the sphincter. Voluntary control over this reflex is exerted through the upper motor neurones, and as long as one pyramidal tract is functioning perfectly, control of the bladder remains normal. When the function of both pyramidal tracts is impaired by a spinal lesion above the lumbar region, voluntary inhibition and voluntary initiation of the bladder-emptying reflex become imperfect. If spinal reflex activity below the level of the lesion is greatly exaggerated, as, for instance, in many cases of disseminated sclerosis, the bladder-emptying reflex is hyper-active and with the impaired control the patient is unable to inhibit it and precipitancy of micturition results. In other instances the patient is unable to initiate the reflex when he wishes and may be able to pass urine only after long delay. While one or other form of disturbance usually predominates, they are not mutually exclusive and both may occur on different occasions in the same patient. Delay in micturition may go on to retention as a progressive spinal lesion becomes more complete.

With sudden or rapidly occurring tract lesions above the lumbar region, associated as they are with depression of spinal reflex activity, retention of urine is the rule. As soon as the bladder becomes distended retention is followed by overflow incontinence, and it should be an invariable rule in all cases of incontinence to feel for a distended bladder in the abdomen. At a later stage in many such cases spinal reflex activity increases and reflex emptying of the bladder may then occur at intervals. The bladder may act spontaneously or the reflex may be initiated by pressure on the lower abdomen or by other means. Such reflex micturition is a useful aid in the management of a case of complete paraplegia, but it should be realised that emptying of the bladder by this means is always incomplete and leaves a considerable amount of residual urine.

With lesions in the upper lumbar region of the cord, the vesical sphincter is paralysed and dribbling incontinence results. Lesions in the second and third sacral segments or in the corresponding spinal roots interrupt the arc of the emptying reflex and so cause retention, with a flaccid condition of the bladder wall. Lesions in the *conus medullaris*, where there is a reflex controlling centre, produce the same effect.

Control of the rectum is in nearly every respect similar to that of the bladder. Incontinence of faeces usually occurs only after aperients have been taken: retention expresses itself as constipation and may be relieved by regular enemata.

#### SWEATING

With severe lesions of the spinal cord, sweating is excessive on the paralysed parts of the body. If not evident it may be excited by cutaneous stimuli or by the injection of a small dose of pilocarpine (gr.  $\frac{1}{4}$ ), and the level of a spinal lesion may be determined by this means by an observer who is familiar with the cutaneous segmental distribution.

#### SURFACE ANATOMY

If the cord is to be exposed at the level of the affected segments their relation to the spinous processes of the vertebræ must be known. The segmental localisation of a lesion having been obtained, the desired segment can be found as follows: in the cervical region of the cord, deduct one from the number of the segment—the sixth cervical segment is at the level of the fifth cervical spine; in the upper half of the thoracic cord, deduct two—the fifth thoracic segment is at the level of the third thoracic spine; and down to the first lumbar segment, deduct three—the first lumbar segment is at the level of the tenth thoracic spine. The remaining segments of the cord are shorter and so are farther separated from their corresponding vertebræ. The third lumbar segment is approximately at the level of the eleventh dorsal spine,

and the first sacral segment at the level of the twelfth. The cord terminates just above the level of the first lumbar spine.

#### LOCALISATION BY MYELOGRAPHY

When the existence of a compressive lesion of the cord or its exact site is in doubt, great help may be obtained by injecting into the thecal canal a fluid substance which is opaque to radiography. If 1 or 2 ml. of Myodil or other opaque medium be injected through the occipito-atlantoid ligament into the cisterna magna of the sub-arachnoid space, it falls rapidly to the site of obstruction, where it is arrested, wholly or partially, and can be seen on the radiographic screen or film, in relation to the vertebrae. A safer procedure is to inject the Myodil by lumbar puncture and then, making use of a tilting X-ray table, to tilt the patient so that the oil runs towards his head. Even when the lesion is as high as the cervical region, this manoeuvre is satisfactory, though some discomfort may be caused to the patient by prolonged tilting. The oil will run more rapidly within the theca if it is heated to just above body temperature by immersion of the phial in warm water for 15 to 20 minutes before injection.

#### GENERAL MANAGEMENT OF PARAPLEGIA

In all cases of severe paraplegia from spinal cord lesion in which sensory and sphincter functions are also impaired or lost, whatever the nature of the lesion, there are certain general principles of treatment. The patient should be nursed on a fracture bed, with an air, water or foam rubber mattress. The back should be attended to 4-hourly, first washed with soap and water, then carefully dried, rubbed with surgical spirit or Eau-de-Cologne, and powdered. These measures harden the skin and make it less likely to break down under the constant pressure of the body-weight. The patient's position should be changed at intervals of not more than 3 hours and he should be made to lie on his face for at least 6 hours in 24 in order to prevent the development of sacral bed-sores. When there is incontinence of urine, as far as possible care should be taken to prevent the skin from becoming wet and sodden, and the toilet of the anus after defaecation should be careful and thorough. There are various remedies for the sacral or trochanteric bed-sore when it develops. Separation may be hastened by wet dressing of eusol, or sometimes by fomentations, though the latter should be used with caution. The ulcer is packed with eusol gauze, or with an ointment of zinc oxide and castor oil. When it is clean and healing begins, it may sometimes be hastened by dressings of gauze soaked in red lotion. The heels should also be carefully watched for the appearance of the hæmorrhagic blisters which herald the development of a sore. Rings for the heels may avert them, and air rings for the sacrum may also be needed.

*Rehabilitation of the paraplegic.*—Experience gained during the War of 1939-1945 has gone far to improve the lot of paraplegics suffering from irreparable but solitary lesions of the spinal cord, particularly young subjects with traumatic lesions.

Bed-sores, even of large dimensions, can be caused to heal by active treatment, as described by Guttman. Supra-pubic cystotomy and tidal drainage of the bladder may gradually be replaced by the development of satisfactory automatic emptying, which permits the use of a urinal. Contractures and deformities can be prevented, or where necessary corrected. Physiotherapy and training directed to the healthy muscles may enable the patient to replace to a great extent the functions of the paralysed parts, as well as overcoming the gravitational effects in the circulation, which are a conspicuous feature of thoracic cord lesions.

Finally, occupational therapy, both prevocational and vocational, in specialised spinal centres and mental readjustment can enable these patients to a remarkable degree to resume their places as active members of the community.

## TUMOURS OF THE SPINAL CORD

**Synonym.**—Intramedullary Tumours.

**Ætiology and Pathology.**—Tumours of the spinal cord while uncommon, are not rare, and are encountered at all ages. According to Kernohan's statistics the ependymoma, a tumour arising from the cells of the ependyma of the central canal, is the commonest type, forming about half of the total number. Tumours of this variety are demarcated from the nervous tissue of the cord, and although centrally placed are capable of surgical removal. They arise most frequently in the cervico-thoracic region and in the filum terminale. Various types of gliomata form the remainder of the total, the glioblastoma being the most common; all the tumours of this group are of an invasive character, devoid of any definite demarcation, and therefore incapable of being removed by operation without gross damage being done to the cord. In addition to the tumours arising from the tissues of the cord medulloblastomata and oligodendrogliomata may be found on the surface of the cord as seedling metastases from cerebral and especially cerebellar tumours. Various types of hæmangioma are also found.

**Symptoms.**—In the case of any patient presenting the signs of a local lesion of the spinal cord of gradual onset the possibility of an intramedullary tumour should be kept in mind.

The symptoms often start unilaterally, with weakness and stiffness of one leg, and at a slightly later stage a partial Brown-Séquard syndrome is not uncommon. At all stages dissociated sensory disturbances are common on account of different degrees of involvement of sensory tracts. Root pains are unusual, but local muscular wasting, corresponding to one or several consecutive segments, is frequently present. Sphincter disturbances occur at a relatively early stage.

The cerebrospinal fluid contains a moderate excess of protein, and some excess of globulin. Queckenstedt's test does not indicate any blockage in the spinal theca until the tumour has reached such a size that it occupies most of the width of the theca. Unless the tumour is at an advanced stage, there may be no obstruction to the passage of Myodil, and even at a late stage the obstruction may be only partial. The expanding mass within the spinal theca may cause thinning of the pedicles of several consecutive vertebrae, which may be apparent in the radiograph, and in consequence of the thinning the interpeduncular distance on each affected vertebra is increased.

**Diagnosis.**—This has to be made from (1) other forms of spinal cord disease which produce paraplegia of gradual onset, and (2) compression of the cord from without. Of the former, disseminated sclerosis is usually the most difficult to exclude, and is the disease to which the symptoms of spinal tumour are most often wrongly attributed. The diagnosis of disseminated sclerosis is rarely justified unless there is evidence of several lesions in the central nervous system, and if after careful examination of the whole nervous system all the signs and symptoms can be attributed to a single spinal lesion, the probability of tumour is greatly increased. Secondly, with tumour, the exacerbations and remissions of disseminated sclerosis do not occur. Finally, in a case of tumour the cerebrospinal fluid may show a considerable increase of protein; a moderate increase, however (·06 per cent. or less), does not help in the differentiation. It should also be borne in mind that the spinal fluid in an active case of disseminated sclerosis occasionally gives a "paretic" type of curve with Lange's colloidal gold test, which does not occur in the case of tumour. Cases of supposed disseminated sclerosis beginning after the age of 45, especially in males, should be regarded with the greatest suspicion. The diagnosis may be particularly difficult in cases of hæmangioma of the cord, because in many of these there is evidence of two spinal lesions.

Localised spinal syphilis may also closely simulate intramedullary tumour, but such cases are quickly recognised if the Wassermann reaction is performed on the cerebrospinal fluid and blood as a routine measure.

The diagnosis between intramedullary tumour and compression of the cord from without (e.g. by a meningeal tumour, or a neurofibroma) cannot usually be made with confidence on clinical grounds. Search should first be made for evidence of those conditions which are known to cause compression. Queckenstedt's test may, of course, indicate obstruction in the theca, but in many cases at the stage at which diagnosis is called for it gives an indefinite result, and radiographic investigation with Myodil is then required. If this reveals no obstruction, or if the picture obtained indicates a fusiform expansion of the cord with a little of the oil passing down at the sides of it, the diagnosis of intramedullary tumour may be accepted. In many cases the final diagnosis is made only by exploratory operation.

**Treatment.**—Many ependymomas have been successfully removed by skilled neuro-surgeons, the cord having been incised between the posterior columns. If exploratory operation reveals a glioma or evidence of a hæmangioma, surgery can do no more to benefit the patient, and the treatment thereafter is that of paraplegia in general. Radiotherapy is ineffective.

## COMPRESSION OF THE SPINAL CORD

In compression, the lumen of the spinal canal is reduced in a small part of its length and the spinal cord is injured at this point, either directly by pressure or indirectly by interference with its blood supply. Nearly all the extramedullary lesions of the cord come under this heading. Except in cases of collapse of a vertebral body such as may occur in malignant disease, compression is in general a slow process, although in a number of cases the symptoms come on rather abruptly. A sudden process, such as fracture-dislocation of the spine, causes laceration rather than compression of the cord.

Clinically, compression is characterised by a combination of two sets of phenomena, namely, local or root symptoms in the regions supplied by the roots arising from the cord at the level of the lesion; and remote or cord symptoms due to interruption of the conducting paths in the white matter. Obstruction of the spinal theca may be inferred if Queckenstedt's test (see p. 1378) is positive. In addition, complete or partial obstruction is associated with an increase of protein in the fluid below the obstruction, and Froin's syndrome (see p. 1379) may be present. In most cases the fluid shows a slight degree of xanthochromia. Radiographic examination after injection of Myodil into the theca (see p. 1533) confirms or reveals the site of the obstruction, and the outline of the filling defect may give a valuable clue to its nature.

Compression of the spinal cord may be the result of (1) conditions arising within the theca, the most important of these being meningeal tumours, neurofibromata and arachnoiditis; and (2) lesions compressing the theca and subsequently the cord. Of the latter, the most important are vertebral diseases, especially tuberculous disease of the spine and secondary carcinoma; also common is a protruding intervertebral disc; and rarer causes are extra-theal abscess, Hodgkin's disease, Paget's and other forms of bone disease.

### I. INTRATHECAL COMPRESSION

#### MENINGEAL TUMOURS

Though fibroma and sarcoma are occasionally found, for practical purposes the "meningioma", or endothelioma of the dura, is the only common tumour arising from the spinal meninges.

**Ætiology and Pathology.**—The meningioma is a firm, oval, pinkish tumour of smooth or nodular outline. When impregnated with calcareous deposits the term "psammoma" was applied to it, and it may become so calcified as to be discernible on a radiograph of the vertebral column. The incidence of these tumours is mainly between 30 and 60 years of age, and they affect women much more often than men. Their common site is in the thoracic region and they usually lie posterior to the spinal cord.

**Symptoms.**—Pain of root distribution and of variable severity is usually the first symptom. It is aggravated, typically, by coughing, sneezing or straining. This is followed after some time by spastic paralysis of slow onset and steady uninterrupted progress, affecting first one leg and then the other, the combination and especially the course of these symptoms being almost pathognomonic. Sensory signs of similar slow course accompany the motor signs, or follow them after a brief interval. The sense of position may be the first to be disturbed, and give rise to unsteadiness in walking and standing. By the time the patient comes under observation the cerebrospinal fluid shows considerable increase in its protein content and in the globulin fraction, and Queckenstedt's test is positive. If the tumour is in the cervical region, as is unusual, all the foregoing changes are less intense.

Radiographic examination may reveal an outline of the tumour at the level determined clinically, or, more often, it shows some change in the shape of the pedicles of the vertebral arches, or an increase of the interpeduncular distance. Myodil introduced into the theca is held up, and its border in contact with the obstruction displays the outlines of the surface of the tumour.

**Diagnosis.**—With such manifestations the diagnosis of meningioma is most probable, but the diagnosis from other forms of intrathecal obstruction is not certain until the tumour is seen at operation. The diagnosis from extra-theal compression is usually easier. With spinal caries root pains are rarely so severe, signs of bone disease are rarely absent, and the paralysis is usually bilateral from the beginning and is severe by the time sensory loss develops. The distinction from vertebral new-growth is generally made or confirmed by radiographic examination, but may for a time be impossible when bone symptoms and radiographic signs are absent.

**Course and Prognosis.**—The growth is often extremely slow. Root symptoms may precede paralysis by months or even years, and the weakness may increase gradually for several years before walking becomes impossible. In the absence of operation it progresses eventually to complete motor, sensory and sphincter paralysis, possibly with paraplegia in flexion. Most patients with simple tumours come to operation during the second year after the onset of the first symptom. The prognosis for recovery of power after removal of the tumour depends in part on the duration of the weakness in the lower limbs. Complete recovery may be expected if it has not lasted more than a year, and if sphincter control has not been lost. Recovery from severe paralysis takes from 5 to 9 months. When the paralysis is of longer duration, recovery, though gratifying, is rarely complete. Nevertheless, full return of power has been seen after 3 years of severe paralysis.

**Treatment.**—This is obviously surgical. The mortality after operation for the removal of simple tumours is low in skilled hands. During the recovery stage following removal of the tumour, the treatment after the operation wound has healed is that of spastic paraplegia in general (p. 1533).

#### NEUROFIBROMATA

**Ætiology and Pathology.**—Neurofibromata within the spinal theca affect both sexes and occur mostly in early middle life. They arise on the spinal nerve roots, and may be solitary or multiple. In cases of neurofibromatosis the occurrence of small neurofibromata on many of the lower spinal roots is the rule, although they

may not give rise to severe symptoms. A neurofibroma may be situated partly within and partly outside the vertebral canal, the constriction at the intervertebral foramen giving the tumour a dumb-bell shape. Histologically the intrathecal neurofibroma has a structure similar to that of the acoustic neuroma (see p. 1382).

**Symptoms.**—A neurofibroma compressing the spinal cord is apt to give rise to unilateral symptoms, and to the Brown-Séquard syndrome. Root pains may be severe, and in some cases there are spasms of intense pain on the opposite side of the body below the level of the tumour resulting from irritation of the spino-thalamic tract by the growth.

**Diagnosis.**—The unilateral nature of the spinal signs may suggest the nature of the tumour. Also, neurofibromata cause a great increase of protein in the cerebrospinal fluid; findings above 1 per cent. are common in the lumbar fluid, and even in the fluid above the tumour the protein content is raised. The fluid withdrawn at lumbar puncture may be yellow. Queckenstedt's test and examination with Myodil disclose complete or partial obstruction of the theca. Radiographic examination of the spine shows in many cases enlargement of the intervertebral foramen through which the affected nerve root emerges, and the Myodil picture may show the lateral situation of the obstructing mass.

**Prognosis and Treatment.**—For the solitary neurofibroma these are similar to those of a spinal meningioma. When multiple neurofibromata are present the prognosis is less favourable, although the removal of a single tumour may completely relieve the spinal compression.

#### ARACHNOIDITIS

**Synonym.**—Meningitis Serosa Circumscripta.

**Ætiology.**—As a result of a low-grade inflammation of the arachnoid membrane, adhesions occur within it and give rise to cystic formations containing cerebrospinal fluid, or the membrane, thickened and fibrous, may become bound down on to the spinal cord. Such arachnoiditis follows injury (perhaps as a reaction to hæmorrhage), or is a consequence of generalised infectious diseases, or it may follow meningitis.

**Symptoms.**—In the course of a year or several years, the cyst or contracting membrane may cause slowly increasing pressure on the cord. Root pains are seldom pronounced, but muscular wasting may occur, corresponding to the site of the maximal local incidence of the arachnoiditis. The tract signs are usually limited to gradually *increasing spasticity of the lower limbs, but sensory changes, with a definite level*, may develop. Pressure measurements at the time of lumbar puncture may reveal complete or partial obstruction of the theca, and the Myodil picture may show an appearance of guttering, the opaque fluid being broken into droplets among the arachnoid adhesions.

**Prognosis and Treatment.**—In the case of a cyst its removal by operation may bring about great improvement in the patient's clinical condition. The sites of adhesion may be difficult to see, and if the cyst be opened inadvertently during operation, the only evidence of its former presence is flattening of the cord and of the nerve-roots at the level of the expected lesion. Sometimes the position of the cyst can be *inferred* from the absence of normal pulsation below that level. When the membranes are punctured in this position, fluid escapes under pressure and the pulsations reappear. Later, symptoms may recur, or, in spite of operation they may progress as a result of the adhesive process.

#### 2. EXTRATHECAL COMPRESSION

With extrathecal compression, the pressure on the spinal cord is apt to be more uniform, and the manifestations have in consequence a greater tendency to be equal

on the two sides, especially in the lower limbs. This is, however, no more than a rule of thumb and there are many exceptions to it. As long as the compression is relatively slight, motor tracts are more affected than sensory, and consequently with the more slowly progressive conditions, weakness and spasticity of the lower limbs may precede sensory disturbances by a long period.

#### TUBERCULOUS DISEASE OF THE SPINE

**Synonyms.**—Spinal Caries; Pott's Disease.

This disease is the most frequent cause of slow compression. It occurs most often in children, but is common in adults, and may begin late in life. Signs of injury to the cord develop in about 1 case in 20, and are usually preceded by obvious deformity of the spine, but in many cases they appear before disease of the bone is suspected. Rarely paralysis comes on for the first time in an adult who has had a curvature since childhood.

The cord may be damaged by direct pressure of displaced bone, but more commonly by an abscess beneath the periosteum of the diseased vertebrae. In almost all cases the injury is indirect, and results from œdema of the cord, arising from interference with its blood supply by tuberculous granulation tissue, which forms on the outer surface of the dura mater and fills the epidural space (pachymeningitis externa). The functions of the cord may be temporarily deranged for long periods by this œdema, without permanent damage to the nervous tissues; hence, when the disease is cured, the œdema subsides and the cord recovers. In cases of greater severity necrosis of the nervous structures follows thrombosis of the vessels, or prolonged pressure causes atrophy of nerve roots, and complete recovery is impossible.

**Diagnosis.**—When spastic paraplegia develops in a patient who is known to suffer from tuberculosis of the spine, the cause is obvious; but when it precedes the appearance of signs of bone disease, the diagnosis is difficult. In all cases of compression the spine should be examined repeatedly for deformity, tenderness and limitation of movement. If tenderness is found constantly in the same place, and the nervous symptoms are compatible with disease of the underlying segments, disease of the bones is almost certain. In young persons disease of the spine is usually caries, and in adults also caries is not uncommon, but tumours of the spine and aneurysm should be excluded. Severe root pains are rare in spinal caries but are the rule in vertebral new-growth. A radiograph will usually demonstrate the presence and nature of the bone disease.

**Course and Prognosis.**—The course of the bone disease does not always run parallel with the paralysis, and either may alter in severity independently, but if the caries undergoes cure the paralysis usually diminishes. Considering the severity of the paralysis, the prognosis is favourable and astonishing recoveries occur. The outlook is best in young people with disease in the dorsal region. Many recover completely, but more often, especially in adults, recovery, though considerable, is imperfect. So long as the lower limbs remain spastic in the extended position together with exaggerated tendon reflexes the prognosis for complete recovery of power is good; but if the limbs become flexed, if they become flaccid, if the knee- and ankle-jerks are lost, if sensory loss is severe, or if there is wasting in the limbs following damage to lower motor neurones, the outlook is bad. Some patients live for years with severe paralysis, but life is constantly endangered by sepsis from bed-sores, ascending infections of the urinary tract, chest complications and tuberculous disease in other parts.

**Treatment.**—This is to be directed towards curing the bone disease in the hope that cure of the paralysis will follow, and it usually does so. Complete rest on the back and fixation of the spine for many months is the routine treatment and recovery commonly takes about 2 years. Streptomycin and isoniazid should be administered.

as in other forms of tuberculosis. The general condition of the patient is to be improved by fresh air, a liberal diet, cod-liver oil and iron, and great care is to be taken to prevent bed-sores, cystitis and deformities of the limbs. Laminectomy is in general contraindicated, and operative intervention of any kind should only be undertaken by a surgeon who has special experience of this disease. After the bony disease has healed, fixation of the spine by Allbee's operation or a modification thereof is called for in a few cases.

### TUMOURS OF THE VERTEBRAL COLUMN

Vertebral tumours are about twice as common as all the other forms of extra-medullary tumours together, and almost all of them are malignant. Carcinoma is always secondary, and is a frequent and distressing complication of cancer elsewhere. A very small primary carcinoma, *e.g.* of the breast, lung, thyroid or prostate, may produce extensive disease of the vertebræ. Evidence of compression may appear before the existence of the primary growth is suspected, but, on the other hand, such may occur several years after complete removal of the primary growth and may even be the first evidence of a recurrence. Sarcoma, though the commonest form of primary growth, is relatively rare and it begins in the bone or periosteum of the bodies or laminæ. Primary sarcomata are sometimes multiple. Secondary sarcoma arises by metastasis from sarcoma elsewhere, or by direct extension from a growth in neighbouring soft parts, *e.g.* of tumours in the mediastinal and retroperitoneal spaces.

The growth of vertebral tumours is usually rapid, and extensive portions of the spinal column may be completely destroyed. The cord is compressed by the growth itself, by displaced bone, or by a process of the growth which invades the spinal canal through an intervertebral foramen. As a rule, the dura mater sets bounds to its inward extension. Benign tumours of the spine are rare. They usually grow forwards, but occasionally an osteoma, or an exostosis, produces signs of compression.

**Symptoms.**—In most cases these are typical of spinal compression. Root pains are usually severe and may be agonising, but occasionally they are absent. Not infrequently the onset of paraplegia is rapid, paralysis developing in the course of 24 or 48 hours. No deformity of the spine is ordinarily apparent, but local tenderness is usual, and radiographic examination reveals bony disease at a level corresponding to it. Lumbar puncture reveals the signs of thecal obstruction.

**Diagnosis.**—When root pains occur in a patient with malignant disease, or from whom a malignant growth has been removed, the diagnosis of secondary growth in the vertebral column is most probable, even though radiographic examination fails at first to reveal any deposits in the vertebral bones. When pains are the first symptom, mistakes are easily made because their root origin is not recognised. Diminished sensibility in the painful area indicates the nature of the pain, and this directs attention to the spine, where tenderness or deformity is discovered. As most vertebral tumours are secondary, the next step is to examine the parts where carcinoma is common, remembering that a small primary growth, *e.g.* in the breast, lung, thyroid or prostate, may give rise to widespread metastases in the bones. In the absence of a history or signs of new-growth in other parts, the diagnosis is founded on the combination of local tenderness or deformity and rigidity of the spine with root or cord symptoms. The severity of the root pains, and their great aggravation by movement, are characteristic.

**Course and Prognosis.**—When sarcoma or carcinoma spreads to the vertebræ from surrounding parts, the duration of the disease is measured in weeks or months, and death is due to the primary condition. In primary sarcoma, and in some cases of carcinoma of the vertebræ, life may be prolonged for a year or two, and death is due rather to complications of the cord disease—bed-sores, cystitis, etc.



**Treatment.**—In many cases of malignant vertebral disease the clinical effects of compression are relieved by extension of the spine, the patient being kept flat in bed with an underlying fracture board. If the paraplegia improves, a plaster spinal jacket can be applied and the patient may begin to get up again. In favourable cases radiotherapy may then be considered. When root pains lead to the discovery of a secondary deposit in the spine in a case in which the primary growth has been removed and there is no evidence of secondary growths elsewhere in the body, radiotherapy should be employed; paraplegia is prevented, the pains are relieved and life is prolonged. In slowly growing primary growths of the vertebrae, laminectomy is indicated in order to relieve pressure, or to prevent pain by cutting sensory roots, or dividing the antero-lateral columns of the spinal cord. The operation is merely palliative but is often followed by considerable temporary recovery.

#### PROTRUDING INTERVERTEBRAL DISK (CERVICAL AND DORSAL)

The protrusion of an intervertebral disk in the cervical or dorsal region is much less common than in the lower lumbar region. The mechanism by which it occurs is the same at all levels; as a result of trauma the cartilaginous annular portion of the disk is ruptured, and the semi-solid nucleus pulposus is then gradually extruded. In most cases the mass is protruded backwards into the vertebral canal, and causes compression of the theca. In the cervical region the degree of compression of the cord which ensues is seldom severe.

The clinical history of the case is that of spastic paraplegia coming on gradually some months after an accident. Progress of the paraplegia is usually slow, and after a time one arm or both arms may become spastic and may show a little muscular wasting. At this stage the condition in most instances becomes stationary. Sensory impairment is seldom demonstrable, but there is usually a zone of hyperalgesia corresponding to the segment just above the level of the lesion. Mild root pains across the shoulders are likely to be attributed to rheumatism. In some cases, however, root pains are the principal manifestation and may be ascribed to brachial neuritis.

Unless there is a close association with a definite accident the diagnosis is always a matter of great difficulty and only occasionally can it be made with confidence. The spinal theca in the cervical region is wide and the degree of obstruction is not sufficient to give a positive result with Queckenstedt's test. After injection of Myodil the hold-up is at best partial, but in favourable cases a filling defect is revealed on the radiograph. While the symptoms are progressing the differentiation from an intramedullary tumour of the cervical enlargement may be impossible, but the history of an accident, and the persistent absence of objective sensory loss, should raise a strong suspicion of a disk lesion, and the eventual arrest of the progress excludes the presence of a tumour. From disseminated sclerosis the diagnosis may be equally difficult, but if it be recognised that all the manifestations are attributable to a single spinal lesion it is unjustifiable to postulate disseminated lesions, and moreover many of the patients concerned are above the age at which disseminated sclerosis is likely to begin.

Some of the cases have been relieved by surgical treatment, and it is only by operation that the diagnosis can be established with certainty. Failing operation, the sufferers remain permanently disabled, but a moderate degree of spontaneous improvement is not unknown. Collars of different types are often prescribed to immobilise the neck and take some of the weight of the head off the cervical vertebrae, but it is doubtful whether the effects obtained compensate for the inconvenience or discomfort.

#### INJURIES OF THE SPINAL CORD

**Ætiology.**—The spinal cord is a delicate structure. Injuries of it occur in the first place in association with fractures and dislocations of the spinal column. The

cord is usually lacerated, and its fibres are torn and its circulation interfered with so that compression, if present at all, plays little part in causing the persisting symptoms and its relief brings about no amelioration. Dislocation of the axis, however, provides possible exceptions to this rule. Transverse lesions of the cord may also result from gunshot wounds. Secondly, disruption of fibres, and laceration of other elements and minute hemorrhages occur within a localised extent of the cervical cord as a result of acute flexion of the neck. The damage is probably the result of the sudden traction exerted on the cord, as flexion of the neck causes the cord to be pulled upwards. When the muscles of the neck are relaxed, a very moderate degree of violence may cause the head to fall forward, producing sudden flexion of the neck and damage to the cord. With greater violence there may be accompanying dislocation or fracture of the cervical vertebrae, but in the typical case the spinal cord is not compressed. Sudden extension of the neck, as in diving accidents, also may cause severe injury of the cord, with or without vertebral dislocation or fracture.

Fracture-dislocation of the vertebral column is most common in the region of the fifth and sixth cervical vertebrae and in the lower dorsal region. Crush fractures of vertebral bodies due to force transmitted longitudinally, as when a patient falls from a height and lands on his feet, usually affect the first lumbar or one of the adjacent vertebrae, and the corresponding lumbar spinal roots or the roots of the cauda equina may be damaged. The roots, being peripheral nerves, are generally believed to have greater power of recovery than the structures within the cord itself.

Fractures of the vertebral arches, pedicles or spines may be caused, particularly by gunshot wounds, and in association with them the spinal cord may be injured in greater or less degree.

**Symptoms.**—A sudden transverse lesion of the spinal cord gives rise at first to a condition of "spinal shock", in which most of the automatic functions of that part of the cord below the level of the lesion are temporarily abolished. If this occurs at a high level, death is usually immediate, but if not, flaccid paralysis of all four limbs results. If the lesion is in the dorsal region the immediate result is a state of acute flaccid paraplegia, with retention of urine due to flaccid paralysis of the bladder wall (detrusor urinæ); in severe cases, all the tendon reflexes and the plantar and abdominal reflexes are at first absent, and there is complete loss of sensory appreciation below the level of the lesion. In some cases the degree of spinal shock is less and the abolition of spinal function is partial.

With the traction injuries of the cervical cord there is seldom the same degree of spinal shock, but temporary paralysis may be considerable; sensory loss is usually partial, and some or all of the reflexes are preserved. Retention of urine is in most instances a matter of a few hours. Paralysis of the hands, with relative sparing of the upper arms, is not infrequent in these cases. As the fifth cervical segment is often involved in the lesion, the supinator jerk, which depends on this segment, is often abolished, but the flexion reflexes remain, and tapping of the supinator tendon produces reflex flexion of the fingers. This is called "inversion of the supinator reflex". The fibres of the cervical sympathetic (as they descend in the cord to emerge with the first dorsal root) are often involved in the lesion, and in consequence there may be contraction of the pupil and a slight degree of ptosis of the upper eyelid on one or both sides. At a later stage, when the lower limbs have largely recovered, wasting becomes apparent in the hands and forearms, and the case presents a superficial resemblance to one of amyotrophic lateral sclerosis, but the history of accident, the presence of sensory disturbances and such features as the absence of the supinator jerks and signs of disturbance of the sympathetic nervous system should help to make the distinction (see p. 1556).

**Course and Prognosis.**—In incomplete and mild cases, as spinal shock passes off, the reflexes begin to return. Retention of urine persists for a variable time, and if not prevented by catheterisation, overflow incontinence ensues. The Babinski reflex

appears, and is coupled after a time with withdrawal reflexes of the lower limbs. Later, the tendon reflexes return and a variable degree of sensory and motor recovery may take place. In severe cases this does not happen and the condition remains one of complete physiological interruption of the cord at the site of the lesion. After an interval the lower limbs may become the seat of frequent flexor spasms, and a state of paraplegia in flexion may follow. Any stimulus applied below the level of the lesion may then give rise to violent flexion spasms in the legs, contraction of the abdominal wall and extrusion of urine from the bladder—the "mass reflex" of Head and Riddoch. In the great majority of those cases in which the cord is completely divided, the paralysed muscles remain entirely inert and the only evidence of reflex activity is the development of automatic function of the bladder.

In severe cases, the outlook is always extremely grave. With high cervical lesions, death, if not immediate, may occur within a few hours from respiratory paralysis. With lesions at lower levels death is liable to take place within a few weeks or months, from bed-sores or infection of the urinary tract. The cases of less severe injuries of the cervical spine usually make good recoveries. Wasting and weakness may be left in the hands, and sensory disturbances, particularly of a subjective nature, may persist and affect one side of the body or both sides.

**Treatment.**—Cervical dislocation should be reduced under general anaesthesia, and subsequently a plaster collar should be applied to the neck in order to prevent undue mobility until the damaged ligaments have healed. In cases of cervical fracture, a collar should also be applied, because further displacement may occur during sleep or under other conditions of muscular relaxation.

In cases of fracture of the spinal column with injury of the cord, open operation is usually contraindicated. Fracture of the vertebral arches, on the other hand, may call for operation and the removal of bony fragments from the spinal canal. Pressure on spinal roots is usually relieved by the Watson Jones method of treating spinal fractures.

The further treatment of injuries of the spinal cord is that of acute paraplegia (see p. 1533), and in no condition is the most careful nursing and skilled medical supervision more urgently called for. In general the retention of urine is best treated by immediate supra-pubic cystotomy, but if the nursing conditions are ideal and there is good prospect of recovery, tidal drainage through an indwelling catheter may be preferable. The bowels are best controlled by regular enemata.

## ACUTE TRANSVERSE MYELITIS

**Ætiology.**—The condition is rare during childhood, and mostly occurs during the first half of adult life. The sexes are affected equally. In most cases the cause cannot be determined. While a number are syphilitic, syphilis has long ceased to be the most frequent cause.

**Pathology.**—The cord appears healthy except in a short portion of its length comprising one or two segments. The lesion is most frequently situated in the lower half of the dorsal region, and at its site the cord shows intense signs of disease and may be wholly or partly diffuent. In some microscopic sections of the affected segments no normal spinal tissue may be found, and in others, though elements are spared in an irregular fashion, nearly every portion exhibits some pathological change. The adjoining segments are affected in lesser degree, and elsewhere the cord is healthy. Unless all the elements are necrotic there is evidence of inflammatory reaction in the diseased portions. There is no evidence of primary arterial or venous thrombosis, but intense congestion of vessels and minute points of hæmorrhage may be present. In the syphilitic cases there is intense cellular infiltration within the affected portion

of the cord and in the meninges around it, and some small vessels may be thrombosed, but the lesion does not appear to be primarily thrombotic (see p. 1469).

**Symptoms.**—In the non-syphilitic cases, there may be malaise and a slightly raised temperature and sometimes pain of "root" type at the level of the lesion for a few days before the onset of paralysis. These symptoms are followed by weakness of one or both legs, and paralysis may be complete from the waist down within 24 or 48 hours; in other cases, it is complete in an hour or two; in others, though remaining incomplete, it may reach its full intensity in that time; while in still other cases, the onset is "apoplectic", i.e. the patient feeling some weakness, sits down, and within a few minutes is completely paraplegic.

In the syphilitic cases, pain in the back frequently precedes the onset by several hours or a day or two.

If the patient is seen soon after the onset he usually shows complete motor and sensory paralysis from the waist down, with flaccidity of the muscles and loss of reflexes; retention of urine is present and may have gone on to overflow incontinence. If some power of voluntary movement or some sensation is preserved, some of the reflexes usually persist too. There may be from the first a zone of hyperæsthesia at the upper limit of the paralysis, and later a "girdle sensation" may develop at this site. While the limbs are flaccid and sensation is absent, bed-sores may develop with great rapidity, and in the paralysed bladder intense cystitis may occur. The patient may die in the acute stage as the result of these complications. More often sensation and the reflexes return after a few weeks, and in course of time spasticity develops in the limbs, with a variable amount of voluntary power. There may be a partial Brown-Séquard syndrome. Remarkable recovery may occur in the course of many months, but even then considerable disability usually persists. In other cases there is no return of power, and the bedridden patient succumbs in a few months to intercurrent disease.

**Diagnosis.**—The Wassermann reaction, both in the blood and in the spinal fluid, should always be done, with the knowledge that the latter may give a negative result in syphilitic cases, even when cellular increase is present. Queckenstedt's test should also be done at the time of lumbar puncture, in order to exclude conditions of thecal block. Poliomyelitis is excluded by the presence of severe sensory loss. It may not be possible to make the differential diagnosis from hæmorrhage into the substance of the cord, but the latter is usually associated with more pain and, after the first acute stage is over, with a syringomyelic type of sensory loss. Angioma of the cord usually gives rise to less acute paralysis coming on with less constitutional disturbance.

**Treatment.**—The treatment consists of good nursing, with the most careful attention to the bladder. After the constitutional disturbance of the early days has passed, massage and passive movements should be given to the paralysed limbs.

In the syphilitic cases a full anti-syphilitic régime should be started as soon as possible (see pp. 223, 1458).

## LOCAL VASCULAR LESIONS OF THE SPINAL CORD

Hæmorrhage into the spinal cord is uncommon apart from pre-existing vascular abnormalities. When it occurs it produces signs of an acute segmental lesion, followed, as a rule, by those of more general hæmatomyelia (see p. 1549).

Local arterial thrombosis is usually due to syphilitic arteritis.

In old people who are the subjects of severe atheroma, transient partial paraplegia occasionally occurs, most of the symptoms passing off within 24 hours or less. The mechanism of its causation is not fully understood.

There is some reason to think that venous thrombosis in the cord may give rise

to local lesions involving a greater or less degree of paraplegia, and the residual paraplegia following local extrathecal infective conditions has been attributed to this cause.

Vascular abnormalities resulting from congenital malformation of blood vessels are not very uncommon in the spinal cord. The most usual type is a racemose venous angioma, situated partly within the cord and partly on its posterior surface. These lesions are almost always in the lower half of the cord. Pain of root type affecting the lower limbs and recurring in acute episodes is a salient clinical feature. It may be followed, or even preceded, by wasting and weakness of one or both legs, and sphincter disturbance is usually present during the acute episodes. The reflex findings are often anomalous.

The diagnosis is seldom made until the angioma is exposed at operation.

The superficial vessels should on no account be interfered with, and surgical intervention must be limited to such symptomatic measures as dividing a posterior nerve root for the relief of pain.

## SPINA BIFIDA

The most common developmental abnormality of the spinal cord results from a failure of the neural tube to close perfectly and to separate completely from the surface ectoderm. In consequence of the failure of separation, the mesodermal tissues in which the vertebral arches develop cannot close over the posterior surface of the developing cord at the affected site, and spina bifida ensues. Spina bifida is thus usually associated with some abnormality in the cord itself, and its significance as a clinical finding is that it is a pointer to a local fault of development in the cord.

Spina bifida is not uncommon, and in 90 per cent. of cases affects the lumbosacral region and in about 5 per cent. the lower cervical region. There may or may not be some abnormality of the skin over the affected vertebral arches, or there may be a frank meningocele. Hydrocephalus may be associated. Severe degrees of malformation of the spinal cord are incompatible with life.

**Symptoms.**—Weakness of the lower limbs may be present from birth or from an early age, and may increase, or it may be first complained of about puberty, when the vertebral column elongates and the spinal cord, which in these cases is often adherent at its lower end, becomes pulled upon. The ankle-jerks and possibly also the knee-jerks may be absent, and the muscles of the legs poorly developed and the feet hollow. Congenital talipes may be present. Control over the sphincters of bladder and anus is often imperfect, the former being the more frequently and conspicuously affected. Trophic changes may occur on the feet, and there may be areas of anæsthesia on the feet and on the buttocks. Sometimes the sensory loss is of a dissociated type.

**Diagnosis.**—If the symptoms have been present in some degree since childhood, the diagnosis is usually easy and is confirmed by radiographic examination. When symptoms appear at puberty or later, and there is no external abnormality, spina bifida may not be thought of, but if tumour is suspected radiographic investigation is likely to be undertaken and a bony abnormality is revealed which is in keeping with the clinical findings.

**Prognosis.**—In the less severe cases the symptoms become stationary, and are consistent with a normal duration of life. In the more severe cases which live beyond infancy, the patients become bedridden and succumb at a relatively early age.

**Treatment.**—In most cases, because of the malformation of the cord, no improvement can be expected from operation. Treatment should otherwise be symptomatic, and enuresis should be treated with full doses of belladonna.

## OTHER DISEASES OF THE SPINAL CORD

## SYRINGOMYELIA

**Synonym.**—Status Dysraphicus.

**Definition.**—A chronic disease characterised by the formation in the spinal cord and brain-stem of long cavities with surrounding gliosis. To the disease in the brain-stem the term syringobulbia is often applied.

**Ætiology.**—In most cases the disease begins to cause symptoms during the period of growth, and it is rare for their appearance to be delayed beyond the age of 30. Both sexes may be affected and males are more prone to suffer than females. There is considerable indirect evidence that the disease depends upon a congenital abnormality, and other somatic abnormalities may be present in the same patient. Cavitation in the spinal cord may also occur in association with intramedullary tumours, with spinal vascular disease, with pachymeningitis cervicalis and with hæmangiomas of the spinal cord.

**Pathology.**—At necropsy the cord is enlarged, and cross section reveals a cavity filled with clear or yellowish fluid. It extends up and down for many segments, and the lower cervical and upper thoracic segments are the most frequently and the most severely affected. The cavitation is most marked in the posterior half of the cord and appears to arise at the base of one of the posterior horns, or in the middle line behind the central canal. The cavity does not represent a dilated central canal, for this can often be found separate from it, though the two usually communicate. More than one cavity may be present. It is surrounded by glial tissue which is relatively acellular and often peculiarly translucent. The blood vessels frequently show degenerative changes, and the fluid within the cavity may give evidence of old or recent hæmorrhage. The cavity is so placed that it interrupts the crossing neurones which convey pain and temperature sensations. As it enlarges, the anterior horns of grey matter become involved in its surrounding gliosis and the cells degenerate. Ascending and descending tracts are affected either by pressure as a result of distension of the cavity with fluid, or by the glial process. The posterior columns always survive longest.

In the medulla the disease affects particularly the floor of the fourth ventricle in the region of the hypoglossal nucleus and tends to extend as a slit antero-laterally to a position just anterior to the descending nucleus of the trigeminal nerve. In its course it may destroy the motor nucleus of the vagus and glosso-pharyngeal nerves or emerging fibres of these nerves. The slit interrupts (1) the internal arcuate fibres passing from the cuneate and gracile nuclei to the mesial fillet, and (2) the fibres from the descending nucleus of the vestibular nerve to the posterior longitudinal bundle. The development of this lesion thus (1) renders complete sensory loss which was previously of the typical dissociated type, and (2) causes or increases nystagmus. If the slit reaches far enough it also interrupts some or all of the fibres passing from the descending trigeminal nucleus to the fillet of the opposite side, and so (3) causes dissociated sensory loss on the face on the side of the lesion. The disease may extend up into the pons and, in rare instances, higher.

**Symptoms.**—*Disturbances of sensibility.*—By far the most constant and characteristic feature of syringomyelia is a sensory loss of a peculiar kind which was named by Charcot "the dissociated sensory loss". This is a loss of sensibility to painful impressions and to thermal stimuli, while sensibility to touch, to vibration, to position, to passive movement and to the appreciation of location upon the skin, remain relatively or entirely intact. In other words, those forms of sensibility which travel by a path crossing in the commissures of the spinal cord are lost, because the lesion of syringomyelia destroys especially the region of the commissures, while these

forms of sensibility which travel by paths which are uncrossed in the spinal cord are not affected.

The destruction of the commissures in the lower cervical and upper dorsal regions produces the dissociated sensory loss symmetrically over the thorax and upper extremities, the distribution varying with the extent of the lesion. Only rarely does the symmetrical sensory loss extend below the thorax, for the reason that the spinal lesion does not often extend below the mid-dorsal region. Occasionally the sensory loss varies in depth, extent and symmetry of distribution according to the completeness, extent and symmetry of the lesion. Thus, in early and slight cases, the sensory disturbance may not amount to more than a relative loss of pain and temperature confined to the hands and ulnar borders of the forearms, while in an advanced case there is usually complete inability to appreciate painful and thermal stimuli over an area which would be covered by a sleeved jacket. The area often extends later over the neck and the face. Combinations of the "sleeved jacket" sensory loss with hemianalgesia and hemithermanæsthesia often occur in cases where both the spinal lesion and the medullary lesion are present. The dissociated sensory loss makes its advent insidiously, and is often unnoticed by the patient and discovered for the first time on medical examination. Or it may appeal to the patient, who on bathing finds that he appreciates heat and cold upon some parts of the skin and not on others. Not infrequently he finds that he injures himself or burns himself without noticing it at the time.

Subjective sensibility is not often affected, and for the most part syringomyelia may be described as a painless disease; but there are very notable exceptions. Sensations of heat and cold, dull fixed pains, lasting neuralgic pains, and lightning pains resembling those of tabes, may occur. These pains are confined to the regions which are the seat of the other symptoms.

*Muscular atrophy.*—This is met with in considerably more than half the cases. Though usually bilateral, it is often not symmetrical, and may be entirely confined to one side. The intrinsic muscles of the hands, and the muscles of the ulnar side of the forearms are first and most affected in the ordinary run of cases. The atrophy is often here confined, but it may extend up the arm, though it is unusual for the whole upper limb to be affected. Sometimes the shoulder muscles are first affected, and again the scapulo-thoracic and humero-thoracic muscles may be early involved. The upper intercostals and that section of the muscles which supports the spine supplied from the upper six dorsal segments suffer, but the scalenes seem generally to escape. The muscular atrophy is strictly limited and is apt to become complete in the muscles affected. Fibrillation is not usually present. The lesions of the medulla may involve the motor nuclei of the cranial nerves. Wasting of the tongue on one or both sides is not uncommon, and its discovery in a young subject should always arouse suspicions of the presence of syringomyelia. Unilateral paralysis of the palate, pharynx and all the muscles of the larynx upon the affected side may occur from involvement of the nucleus ambiguus. Similarly, but in much rarer cases, atrophic paralysis of the face, of the trigeminal muscles, of the sternomastoid and trapezius may occur from unilateral involvement of the corresponding motor nuclei. Nystagmus is almost a constant feature.

Contractures resulting from the muscular atrophy are commonly seen in the hands, and the deformity resulting tends towards the "claw-hand" type, but hardly reaches the degree seen in ulnar nerve paralysis, and is often much modified by trophic and vasomotor changes, and by the results of injuries and whitlows.

*Other motor symptoms.*—The lower extremities almost invariably escape so far as atrophy of muscles is concerned but usually present a slight spasticity, with the signs of involvement of the crossed pyramidal tracts. This does not often produce much disability. In cases, however, where the lesions involve the lateral region of the cord, either by direct extension or by the pressure of distended cavities, severe spastic

paraplegia may result. And again, in very rare cases, such pressure may lead to total avascularisation and total transverse lesion of the spinal cord with the appearance of a complete flaccid paraplegia with incontinence, total sensory loss and absent deep reflexes.

Sphincter trouble is usually absent, or slight and occasional; but in cases in which paraplegia is severe any degree may occur.

The skin reflexes of the trunk are diminished or absent and the plantar reflexes are of the extensor type, according to the degree of pyramidal involvement. Some degree of pes cavus is often present. The knee-jerks and ankle-jerks are increased, while the arm-jerks, even in the absence of muscular wasting, are characteristically absent.

Spinal curvature is present in many cases. It consists essentially in a kyphosis or kypho-scoliosis of the upper dorsal region, with a compensating lordosis and lateral curve in the lumbar region. The upper convexity is to the left, because of the major use of the right hand. It is dependent upon paralysis of the trunk muscles, from involvement of the anterior horns in the upper dorsal region, and, in addition, dystrophic changes in the bones may be factors in its production. It is more marked the earlier it commences during the period of growth, and in cases in which heavy manual occupation has been followed.

*Trophic and vasomotor disturbances.*—Thickening of the bones or a condition of osteoporosis and brittleness may be met with. More often Charcot's arthropathy occurs. It differs in no way from the similar condition in tabes dorsalis, but being confined to the joints of the analgesic region it affects those of the upper extremity. The most characteristic of the trophic changes consists in thickening of the subcutaneous tissue and of the skin itself, which is seen in the hands. The fingers become thick and swollen, and lose their natural outline, the tips become blunted and the knuckle-folds thick and coarse, and vasomotor disturbance renders them unduly red, or even blue. They have been termed "sausage-like" fingers, and often stand out in contrast to the wasting of the intrinsic muscles of the hand. A similar condition affecting the whole hand is common, and was termed by Charcot the "fleshy hand" or "main succulente". The analgesic condition of the hands and the thermanæsthesia present expose them unduly to injuries and, since the injuries are likely to be unnoticed or disregarded, septic infection arises easily, and the results of injuries, burns and whitlows are frequently seen, giving rise to further deformity from scars, or loss of the terminal phalanges.

Considering that the efferent neurones of the cervical sympathetic system have their origin in the brain-stem, and their exit from the spinal cord in the upper dorsal segments, thus traversing the whole of the region usually affected by the lesion of syringomyelia, the frequency with which *paralysis of the cervical sympathetic* occurs is easily understood. It may be complete or incomplete, unilateral or bilateral, and is recognised by smallness of the pupil, narrowing of the palpebral aperture (sympathetic ptosis) and a peculiar flatness of expression on the side of the face affected, with decrease or loss of sweating. These signs are much more obvious when unilateral than when bilateral, for, in the absence of the contrast which a normal side of the face gives, they are often overlooked when bilateral.

*Morvan's disease.*—This is a condition of great rarity, in which a chronic peripheral neuritis is combined with syringomyelia, with consequent very severe effects upon the extremities. There is absolute loss of all forms of sensibility in the hands and in some cases also in the feet, together with atrophy of the intrinsic muscles. The cause of this complication of syringomyelia is unknown.

*Diagnosis.*—Syringomyelia has to be differentiated, in its early stages, from those diseases which cause slowly progressive muscular atrophy in the upper extremities, and, in its later stages, from other lesions of the central region of the spinal cord. Those cases in which the lesions are chiefly in the ponto-medullary region must be distinguished from other slowly oncoming lesions of the brain-stem.



The age of onset, during the later years of childhood and the earlier years of adult life, is important, and during this period slowly developing paralysis with sensory loss, and with or without muscular atrophy should always suggest the possibility of syringomyelia. Other causes, which may produce this system group, and which may be confused with syringomyelia, are local lesions of the brachial plexus, and, especially, the lesion produced by the presence of cervical ribs, root lesions, lesions of the central grey matter of the spinal cord, especially central tumours of the spinal cord, and hæmatomyelia. That the peculiar sensory changes of syringomyelia are usually the first signs of that disease is important; but this rule has many exceptions, both as to the nature of the sensory changes and as to their time of appearance. When sensory changes are not an early sign the diagnosis has to be made from such diseases as progressive muscular atrophy, peroneal atrophy and myotonia atrophica.

Local lesions of the peripheral nerves produce signs which are confined to the distribution of the nerve involved; the sensory loss is to all forms of sensibility, and the condition is ordinarily unilateral. While these features are sufficient to distinguish such lesions from syringomyelia in nearly all cases, nevertheless in certain rare instances of syringomyelia the sensory loss and the muscular atrophy may be so narrowly confined to the distribution of the ulnar nerve as to cause close resemblance between the two conditions. Any sensory loss over the trunk, or signs outside the distribution of the peripheral nerve, will, if present, clearly divide the two conditions.

Cervical ribs may produce slowly progressive atrophy of muscles, pains and sensory loss, very difficult to distinguish from those resulting from syringomyelia. The diagnosis in these cases is beset with peculiar difficulties, for so frequently do cervical ribs produce no nervous symptoms at all that their presence, when demonstrated, does not argue that they are the cause of the symptoms. Again, cervical ribs are among the commonest of the developmental peculiarities which are so frequently seen in the subjects of syringomyelia. Slow muscular atrophy and slowly oncoming sensory loss and perhaps pain characterise both syringomyelia and cervical rib paralysis, and the distribution may be unilateral or bilateral in either condition; but it is only when the manifestations are strictly confined to the upper extremities and neck that difficulty arises. The slightest physical sign outside of this region at once turns the diagnosis in favour of syringomyelia, and of these signs cervical sympathetic paralysis, sensory loss on the trunk and alteration of the abdominal and plantar reflexes are the most important. A very careful search must be made for any such signs, and the patient observed over a considerable time before a certain diagnosis is made.

Lesions of the central grey matter of the spinal cord may produce a symptom-complex, closely resembling that of syringomyelia. Central tumours of the spinal cord, when of slow growth, are hardly distinguishable, inasmuch as the lesion of syringomyelia is in reality a central tumour of the cord. The majority of central tumours, however, are of more rapid development, and speedily produce severe paraplegia.

Progressive muscular atrophy in its early stages may cause difficulty in diagnosis, since the muscular atrophy in syringomyelia may occasionally precede the appearance of any sensory loss or may be well marked when the sensory loss is slight. In this connection, widely distributed fibrillation is of great importance in indicating a diagnosis of progressive muscular atrophy, particularly if it be seen in muscles not conspicuously wasted. In peroneal atrophy the atrophy of the intrinsic hand muscles is always preceded by a more extensive atrophy of the muscles below the knee, which are rarely atrophied in syringomyelia.

Syringomyelia of the brain-stem (syringobulbia) may be distinguished from other lesions of this region by its insidious onset and the special tendency to the involvement of the lateral region of the medulla, so giving rise to a unilateral paralysis of palate, pharynx and larynx with hemianalgesia and hemithermanæsthesia on part

of the face and even on the opposite half of the body. Often some signs of cervical syringomyelia coexist; but the medullary lesion may exist alone, and it cannot be too prominently borne in mind that any very slowly progressive lesion of the brain-stem of insidious onset may be of the nature of syringomyelia.

**Course and Duration.**—The malady, commencing insidiously, progresses very slowly, and often ceases to progress for periods which may amount to many years. The tendency to the destruction of life is not great; but when rapid extension of the physical signs, and especially of paralysis and muscular atrophy of the upper extremities and respiratory muscles, occurs, the end is likely to come quickly. Signs of great distension of the cavities, such as pain and rigidity of the neck, and also severe and increasing paraplegia, with sensory loss of all forms of sensibility below the level of the lesion, point to a rapidly fatal termination. In rare instances acute exacerbations of the manifestations occur, and are followed by partial remissions. Such episodes are due to hæmorrhage into the syringomyelic cavity, and when death has occurred in the course of one of them, the cavity has been found filled with blood.

It is not unusual to meet with well-marked cases in which the signs develop and increase during late childhood and early adult life, and then remain more or less in a stationary condition, allowing an occupation to be followed until well after middle life has been reached; but with the advent of the degenerative period of life, from 45 years onwards, there is often a slow increase of the disability which puts an end to useful capacity. The patients succumb to intercurrent disease, and few reach the age of 60 years.

**Prognosis.**—Recovery never occurs; but arrest of the disease for long periods is frequent. Those disabilities, which are the result of pressure or distension, may abate spontaneously or as the result of treatment, and in arrested cases training may bring about lessening of the disability. Increasing symptoms, especially if the increase be rapid, are always a cause for anxiety, and increasing involvement of the respiratory muscles is the gravest of events.

**Treatment.**—In the vast majority of cases nothing can be done to retard the slow but relentless progress of the disease and treatment is therefore symptomatic. Radiotherapy has been used and occasionally diminishes the spontaneous pains. Rarely the presence of a dilated cystic cord may justify surgical operation and evacuation of the cyst.

## HÆMATOMYELIA

**Synonym.**—Spontaneous Hæmatomyelia.

**Ætiology and Pathology.**—Hæmatomyelia, or hæmorrhage into the spinal cord sufficient to cause symptoms is a rare disease. It appears to arise almost exclusively when there is some abnormality of the spinal vessels, and in particular some variety of angioma; excessively rarely it is associated with syphilitic disease of the spinal arteries, and equally rarely with hæmophilia. Hæmorrhage may occur into a syringomyelic cavity. The hæmorrhage is nearly always centrally situated, and shows a strong tendency to spread longitudinally and may extend over many segments.

Males are affected far more often than females, and the main incidence is in the first half of adult life.

The clinical effects resulting from trauma of the cervical cord have in the past often been attributed to hæmatomyelia, and may be due to this cause, but it is now known that in the majority of such cases no significant hæmatomyelia is present.

**Symptoms.**—Prodromal symptoms may occur in the form of local weakness or transitory sensory disturbances. In most cases the actual onset is sudden, and the symptoms attain a considerable severity in the course of a few minutes, but they may continue to increase for an hour or two.

The symptoms vary according to the site and the extent of the extravasation. In the majority of cases at first there is paraplegia, with more or less complete motor and sensory paralysis up to the level of the lesion, and usually with pain at the upper limit of the disturbance. As the hæmorrhage extends longitudinally these manifestations are quickly followed by a syringomyelic type of sensory loss.

Sometimes, but not usually, blood is found in the cerebrospinal fluid.

**Diagnosis.**—The diagnosis of primary hæmatomyelia rests upon the sudden onset, the rapid development of symptoms, which soon come to a standstill, and the physical signs of a central lesion of the spinal cord. The distinction has to be made from acute myelitis. Acute myelitis, though rapid in onset, rarely shows the sudden development of symptoms seen in hæmatomyelia, and the sensory loss which accompanies it is not of the syringomyelic type. Prodromata often precede the onset in both conditions.

**Prognosis.**—Hæmorrhage in the cervical region may be rapidly fatal from respiratory paralysis. In the non-fatal cases a variable degree of recovery occurs, and in many a syringomyelic type of dissociated sensory impairment ensues, the intensity of the loss being usually less than in syringomyelia.

**Treatment.**—The general treatment is that of any severe spinal cord lesion with paraplegia. Absolute rest is essential. When there is evidence that a syphilitic lesion of the spinal arteries is in question, the treatment is that of spinal syphilis. Angioma and other malformations of the spinal vessels are not amenable to surgical intervention.

## SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

**Definition.**—A progressive disease associated with pernicious anæmia, in which the white matter of the spinal cord degenerates, the incidence of the lesions being particularly on the posterior and the lateral columns.

**Ætiology.**—It has now been determined that when subacute combined degeneration occurs pernicious anæmia is always present in some degree, but the degree of anæmia is extremely variable. The spinal affection is evidently not the result of the anæmia, but the spinal disease and the blood disease are both due to the absence of an essential factor now identified as cyanocobalamin (Vitamin B<sub>12</sub>); both are associated with complete gastric achylia.

As in the case of pernicious anæmia, familial incidence has been recorded. First met with in the third decade of life, the malady in former times became increasingly frequent until a maximum incidence occurring in the sixth decade, while cases commencing in the seventh decade were not uncommon. Owing to the earlier recognition and adequate treatment of pernicious anæmia the condition is becoming increasingly rare in this country.

The cases seen are often atypical and may occur in patients with Addisonian anæmia in whom the treatment has been inadequate. The sexes are equally affected.

**Pathology.**—The pathological and clinical features of the disease were established in a classical paper by Russell, Batten and Collier published in 1900. The essential lesion is degeneration of the myelin sheaths and subsequent degeneration of the axis cylinders in the posterior and lateral columns. Similar degenerative changes are found in the peripheral nerves. The myelin swells and later disintegrates. This change first occurs in the lower dorsal region of the cord, and is first seen in the centre of both posterior columns, and soon afterwards in the centre of either lateral column, as small areas of a darker and more translucent appearance than the normal white matter. It is only at an early stage of the disease that the anatomical picture is strictly one of posterior and lateral degenerations, for soon after, spots of degeneration appear on either side of the anterior median fissure and in other parts of the antero-lateral columns. The degenerated areas increase in size centrifugally,

coalesce with one another, reach the surface of the cord and eventually involve the whole of the white matter of the cord as seen in transverse section, with the exception of the narrow zone of short internuncial fibres which everywhere clothe the grey matter. Occasionally the disease is confined to the posterior columns.

From its starting-point in the lower dorsal region the degeneration spreads upwards and downwards in the white columns of the spinal cord, by means of the occurrence of small isolated spots of degeneration in the posterior, lateral and anterolateral columns, which increase in size and thus join the area previously degenerated. The degeneration tends to extend upwards indefinitely, and in severe and advanced cases has been found in the pyramidal tract as high as the internal capsule.

The lesions of the white columns entail the usual secondary degeneration, both ascending and descending; but these occur late, and are often much less obvious than might be expected from the severity of the local lesions. The destruction of the axons by the local lesions also causes a series of retrograde changes in the corresponding nerve-cells, and tigrolysis, vacuolation, shrinking and neurophagy may be conspicuous, especially in the cells of Clarke's column and in the cells of Betz, which give origin to the pyramidal fibres. There is never any inflammatory exudate, and a peculiar feature is the absence in untreated cases of any glial proliferation.

When degeneration in the peripheral nerves is severe the muscles are conspicuously wasted in the later stages, and the muscle fibres show great diminution in size and poor striation. There is not any considerable increase of the muscle nuclei, and little or no fibrosis is found.

*The blood.*—Usually the blood shows a hyperchromic anæmia of varying severity; the hæmoglobin ranges from 35 to 75 per cent., the lower of these figures being common; the colour index is above the normal and may be as high as 1.6. Macrocytosis is present. Anisocytosis, poikilocytosis and polychromasia are common. Normoblasts are often numerous and megaloblasts may be found in numbers. In a few instances, anæmia has been absent throughout, the hæmoglobin content and the cytology being normal; this has occurred chiefly in cases which have run an acute and fatal course in a few months. Sternal puncture shows a megaloblastic marrow. A relative lymphocytosis is almost always present, and may reach as much as 55 per cent. *This change occurs early and is helpful in the confirmation of the diagnosis of the nervous disease.* Achlorhydria is always present in the stomach, even after the administration of histamine.

A careful investigation of the blood-changes at various stages of the disease and of the post-mortem findings in a large series of cases has proved beyond any possible doubt that the blood-changes in subacute combined degeneration are identical with those met with in the various stages of pernicious anæmia. The cerebrospinal fluid is normal.

*Symptoms.*—(1) *Nervous.*—In a large majority of instances the symptoms appear insidiously and without any recognised exciting cause. Sometimes the onset is more rapid and may be preceded by gastro-intestinal symptoms, or the patient may go to bed for a few days with an attack of "influenza" and on getting up again may be grossly unsteady.

The first nervous symptom is usually numbness or tingling in the feet, and if the patient is asked he will usually admit that he has a slight sensation of the same kind in the fingers. Less often the sensation in the feet is one of swelling, or coldness, or as if walking on cotton wool; and in a few cases unsteadiness in walking is at first the only complaint. Very soon weakness in the legs is experienced, and the numbness gradually spreads farther up, and the patient begins to feel unsteady in walking.

Examination at this time reveals a slight degree of weakness in movement of the toes or in dorsiflexion of the feet, diminution or absence of the ankle-jerk, probably an extensor plantar reflex, and a variable degree of sensory loss; the latter is usually

most marked for vibration and for sense of position in the toes and then for light touch. There may be some tenderness of the feet or calves. Romberg's sign is positive. The superficial sensory loss is at first only over the feet, then it spreads up to cover a "sock" area, and later has a "stocking" distribution, pain and temperature impairment meanwhile being added to it. Loss of deep sensation however generally predominates, and unsteadiness may be very pronounced at a time when other signs are slight or absent. At the stage we are referring to there are usually no objective disturbances in the upper limbs, although intense numbness in the hands may be complained of.

If the condition is allowed to progress, either the signs of peripheral nerve disease or those of spinal cord disease may predominate. In the former case the knee-jerks become diminished and the ankle-jerks lost, the muscles below the knees become paralysed and flaccid and eventually waste, deep sensory loss is severe, and there is loss of all forms of superficial sensation over a "stocking" area. The paralysed muscles become very tender, flexion spasms may set in and every movement is agonising. In the upper limbs a variable degree of sensory loss may develop with astereognosis in the hands and loss of superficial sensation over a "glove" area. The signs of spinal cord disease predominate, the legs tend to become spastic, the knee-jerks are exaggerated but the ankle-jerks are usually weak and the plantar reflexes are strongly extensor. Sensory loss is less marked as a rule than when the signs of peripheral disease predominate, but deep sensation is always greatly impaired, and as time goes on there is considerable loss of pain and temperature appreciation, extending over the lower limbs and to a gradually higher level on the trunk. In the arms the tendon jerks may be increased. Except in advanced cases sphincter disturbances are slight.

The cranial nerve functions are usually unaffected, but optic atrophy is an important complication which occurs in a small percentage of cases, and the visual disturbances due to it may be the first symptom. Slight nystagmus is common.

Mental changes occur in a small proportion of cases, at a time when the degree of anaemia is not sufficient to account for them. Apathy, mild dementia and confusional psychosis with impaired memory and disorientation are the commonest types of disturbance.

(2) *Anaemia*.—Although anaemia is one of the most characteristic features of subacute combined degeneration, since it is found in every case of long duration at some time or other and, moreover, it is sufficiently striking as at once to suggest the diagnosis in at least two-thirds of all the patients when they first come under observation for nervous symptoms, yet it may be absent throughout the course of the disease in a rapid case, and its appearance may be delayed until several years after the disease of the nervous system is manifest. The anaemia in almost every case is identical in every respect with pernicious anaemia. Of those cases in which the blood picture is not typical, nearly all show megalocytosis, with a relative lymphocytosis and a high colour index, as do early cases of pernicious anaemia, and it may be said with certainty that the longer the patient survives, the greater the likelihood of typical pernicious anaemia developing. The spleen has been found to be enlarged in many cases, and the marrow of the bones is typical of pernicious anaemia, as may be also the iron reaction in the liver and the changes in the myocardium and other muscles. As in pernicious anaemia, the tongue is clean and glazed, and this occurs so regularly that any appearance of furring of the tongue may justly be said to exclude the diagnosis of this disease; a history of soreness of the tongue is obtained, if enquired for, in more than half the cases. Fractional test meals show an absolute achlorhydria as in pernicious anaemia. The colour of the skin is often peculiar and striking, even when anaemia is not severe, and is best described as "biscuit coloured". A bright malar flush upon this yellowish biscuit-coloured background gives a characteristic

and vivid facial aspect in the earlier stages of many of the cases. The manifestations common to all anæmic states, breathlessness, headache, cardiac and venous murmurs and œdema, are commonly present, but hæmorrhages are infrequent. Syncopal attacks may occur. Attacks of diarrhœa are common, but, on the other hand, constipation may be obstinate. Irregular pyrexia is almost invariably present at some period in the course of the disease, and this quite apart from fever-producing complications, such as cystitis and bed-sores. In the later stages progressive emaciation is constant, and if life be prolonged it becomes extreme.

**Diagnosis.**—In the early stages of the disease, when peripheral paræsthesiæ dominate the picture, the condition has to be distinguished from peripheral neuritis and occasionally from peripheral arterial disease. In the well-developed stages of the disease, its recognition presents no great difficulty. Attention is quickly attracted by the conspicuous anæmia and biscuit-coloured skin. Following a period of slight paraplegia, the steadily increasing paralysis of the lower extremities, producing complete and lasting helplessness, the characteristic distribution of the sensory loss, the irregular pyrexia, the anæmia and the relatively late onset of sphincter trouble serve to separate this disease from other forms of paraplegia. The change from the spastic to the flaccid type of paraplegia with loss of the deep reflexes and persistence of the extensor response, which occurs in some of the cases in the late stages, is highly characteristic.

In the earliest stages and before the appearance of any definite evidence of organic spinal disease, there may be such disability as to suggest hysterical paraplegia or ataxia, and only the examination of the blood may expose the real disease. When there is evidence of organic spinal disease, it is especially from disseminated sclerosis, spinal tumour, tabes dorsalis and polyneuritis that the diagnosis has to be made. The preponderance of peripheral subjective sensations and the anæmic appearance should always suggest a diagnosis of subacute combined degeneration. Slight spastic ataxia is the common clinical picture of subacute combined degeneration, of disseminated sclerosis and of spinal tumour. The presence of objective peripheral sensory loss is in favour of subacute combined degeneration, whereas diplopia, nystagmus, transient amblyopia and intention tremor are strongly in favour of disseminated sclerosis. Spinal tumour is especially distinguished by a sharp line of sensory loss, transverse to the axis of the body, which does not spread up from below in slow fashion.

When subacute combined degeneration commences with flaccid ataxia and loss of deep reflexes, the distinction must be made from tabes dorsalis. The extensor plantar reflex, which is almost always present in the former disease and which is rare in early tabes, the different distribution of the sensory loss in the two diseases, the loss of power and associated anæmia in subacute combined degeneration, and the results of the examination of the blood and cerebrospinal fluid for syphilitic reactions and of the latter fluid for lymphocytosis, are important aids in the differential diagnosis.

It is also necessary to bear in mind the strikingly close resemblance the disease we are considering may bear to polyneuritis. The differentiation may in the early stages depend chiefly, if not wholly, upon the examination of the blood and the result of a fractional test meal. But, sooner or later, the appearance of an extensor response will indicate the presence of a cord lesion. On the other hand, in the spastic type, the presence of muscular tenderness in the legs is a strong indication in favour of subacute combined degeneration.

**Course and Prognosis.**—Before the days of effective treatment the duration of the disease varied within wide limits. In some the progress was rapidly downhill, survival being a matter of months from the first recognition of the symptoms; in others the disease remained for several years in a relatively mild stage, and partial remissions were common, but once the patient became bedridden the survival period was usually short.

With the advent of liver therapy for pernicious anæmia the outlook for subacute combined degeneration was not at first greatly changed, but with more potent liver preparations and the development of an adequate technique of treatment, improvement and, later, cure soon became apparent. For the case that comes under intensive treatment before the patient has become quite unable to walk, functional cure usually takes about 6 months to a year. Some reflex abnormalities, which mean nothing to the patient, may still persist for a time or permanently. Some authorities believe that cases of the flaccid type, in which the element of peripheral neuritis predominates, respond better to treatment than do those that are more spastic, the disease in the latter being chiefly in the spinal cord. No such generalisation can however be made, and in cases of the latter type the extensor plantar reflex, usually the most persistent sign of spasticity, may disappear. Advanced cases of both types may fail to show much response to treatment. But no case, however advanced when first recognised, should be deprived of full treatment on this ground, and the most surprising recoveries are sometimes seen. If treatment is stopped relapse occurs sooner or later, and with renewed treatment recovery again ensues, but it is doubtful whether this process can be frequently repeated, on account of the probability of gliosis in the spinal cord.

**Treatment.**—Whatever the degree of anæmia present, intensive replacement treatment is essential. Cyanocobalamin (Vitamin B<sub>12</sub>) has now, for practical purposes, superseded the various forms of liver concentrates. For the first month this should be given in doses of 100 microgrammes on alternate days. Thereafter the dosage may be very gradually reduced provided that the blood picture is satisfactory and the ultimate maintenance dose may be as little as 100 microgrammes monthly. The blood-count should be brought up as quickly as possible to five and a half million red cells per cubic millimetre, and kept at that level. The more advanced the stage of the disease the more prolonged will need to be the period of intensive treatment and the more severe the residual disability is likely to be.

Any suppurative condition of the body should be energetically treated. Every care should be taken to prevent bed-sores and cystitis. When present these are often amenable to treatment in the early stages of the disease and also in less acute cases, but in the later stages and in the more acute cases they are inevitable and the bodily vitality is too low for any reparative process to take place. Pains are relieved by such analgesics as aspirin, acetanilide, amidopyrine and phenazone. Flexor spasms are among the most troublesome of the symptoms, since their frequent occurrence denies sleep to the patient and they are most important factors in the occurrence of bed-sores. The remedy which seems to have most effect in checking these spasms is barbitone.

## PROGRESSIVE MUSCULAR ATROPHY

**Synonyms.**—Motor Neurone Disease; Amyotrophic Lateral Sclerosis.

**Definition.**—It is usual to describe together a large group of cases in which progressive wasting of the musculature of the body and a moderate degree of spasticity are associated with, and evidently secondary to, widespread degenerative changes in the central nervous system, the chief incidence of which is on the lower and upper motor neurones. Clinically the cases are capable of great variety, according to the sites of the initial wasting and the degree of spasticity, but they are nearly all comprised by three clinical types. In the first and most common type, the wasting begins in the upper limbs, and the lower limbs become spastic but do not waste. This variety was called by Charcot *amyotrophic lateral sclerosis*. In the second type, the wasting commences in the muscles innervated from the medulla and pons, and the names *progressive bulbar paralysis* and *labio-glosso-pharyngeal paralysis* are applied to it. In the third type, the wasting begins in or quickly spreads to the lower limbs and no

spasticity develops: this is called the *purely atrophic type*. Transitions between these types may be met with, and the first two are frequently combined.

**Ætiology.**—The disease is rare before the age of 25, but occurs at all ages thereafter, attaining its maximum incidence between 30 and 45. Males are affected much more frequently than females. No causal factors have been discovered. The pathological findings are most in accord with the suggestion that the malady is due to a deficiency of some element essential to the nutrition of the spinal cord, in the same sense that subacute combined degeneration and pellagra are the results of such deficiencies. The question of the relation of trauma to the causation of progressive muscular atrophy admits of no decisive answer. In occasional instances the onset follows more or less closely on an injury, but we know of no pathological process whereby a peripheral injury can set up a diffuse degenerative process within the central nervous system. Injury of the cervical portion of the spinal cord may produce a syndrome embracing wasting in the upper limbs and spasticity in the lower limbs (see p. 1541), thus superficially resembling amyotrophic lateral sclerosis, but there is not sufficient evidence that trauma can cause the progressive and ultimately fatal malady of which true amyotrophic lateral sclerosis is the most common clinical variety (see Diagnosis, p. 1560).

In rare instances progressive muscular atrophy has been described in the subjects of old acute anterior poliomyelitis. Certain cases of syphilitic amyotrophy (see p. 1470) present clinically a close resemblance to amyotrophic lateral sclerosis.

**Pathology.**—While in the less advanced cases the degenerative changes are almost limited to the anterior horn cells and the pyramidal tracts, in the most advanced they affect almost all the structures of the cord with two striking exceptions, namely, the fibres of the posterior columns, and the fine fibres passing forward in the grey matter. It will be noted that the former fibres and probably the latter also have their cell bodies outside the central nervous system. The latter probably subserve reflexes; their preservation seems to be constant in amyotrophic lateral sclerosis and not in other forms of progressive muscular atrophy, and it is probably to be correlated with the preservation of the tendon reflexes in the wasting muscles which is a peculiar and striking clinical feature of amyotrophic lateral sclerosis.

To the naked eye, a cross-section of the spinal cord may show some diminution in size of the ventral horns. The essential lesion is a primary degeneration of the cells in the ventral horns of the spinal cord and in the homologous motor nuclei of the brain-stem, namely, the hypoglossal, facial, trigeminal and oculo-motor nuclei. Coupled with the degeneration of the lower motor neurones is a degeneration of the upper motor neurones of the pyramidal system. In the ventral horn cells the degeneration is evidenced by a gradual shrinking in size of the cells, which lose their dendrites and become oval or spherical in shape. The Nissl bodies slowly disappear, and only in rare and rapid cases is definite chromatolysis seen. The nuclei dwindle and become irregular and distorted.

The dorsal and lateral horns are almost invariably intact, but degenerative changes are sometimes seen in the cells of Clarke's column. The affection of the motor nuclei of the brain-stem in the bulbar cases is in every way similar to that of the ventral horns. The degeneration of the motor nerves which take origin from the degenerate ventral horn cells, often proceeds *pari passu* with the degeneration of the cells, but in some cases this is conspicuously not so.

The affected muscles are soft and toneless, and the muscle fibres are found irregularly degenerated, bundles of normal and of degenerating fibres being found side by side until the atrophy is complete. The characteristic change is shrinkage of the affected fibre to a calibre much less than normal. As is usual in all slow tissue degenerations, fibrosis and local arterial disease accompany the atrophy of the muscle fibres.

The pyramidal neurones (cells of Betz), which characterise the precentral cortex, undergo a degeneration very similar to that of the ventral horn cells, but with this



difference, that the earliest structural changes are found in the most distal part of the pyramidal fibres. The degeneration of the upper motor neurones never proceeds to the complete destruction of anything like all the pyramidal fibres. Degenerative changes are constantly present also in the anterior columns of the spinal cord.

The pathological picture, therefore, of progressive muscular atrophy is a widely scattered degeneration of nervous elements, not confined to the motor systems, though these are predominantly affected.

**Symptoms.**—The onset is in most cases very gradual, but it may be more rapid, and severe incapacity may result in the course of a few months. In rarer cases, a severe degree of paralysis may develop in the course of a few days, and in such cases it is not uncommon to see the most remarkable temporary improvement. The nature of the onset, as a rule, indicates the course which the malady will pursue. A very slow onset is followed by a very slowly advancing disease, often interrupted by long stationary periods, whereas the more rapid the commencement, the quicker will be the advance and the sooner will a fatal issue occur. Accompanying and sometimes preceding the onset, and not infrequently conspicuous during the early states of the disease, are certain sensory symptoms which, from the confusion in diagnosis they may cause and from the scant attention which has been paid them in descriptions of the malady hitherto, deserve emphasis. These symptoms are confined to the regions where the wasting first appears, and consist in a subjective feeling of stiffness and uselessness, much increased when the limb or the body is cold. Or there may be dull aching pains, intermittent neuralgic pains which may be severe, or a sensation of coldness or numbness which may be intense. Painful cramp in the muscles which are about to be affected is comparatively common. The attention of the patient may be first drawn to his malady by the altered appearance produced by the atrophy, and this is more common when the commencement is in the hands, where the subcutaneous tissue is thin and the region constantly in view. More often the disability consequent upon the weakness is noticed first; this is always the case where the commencement is in the bulbar muscles, and usually also where the muscles of the legs, proximal muscles of the arms and trunk muscles are first involved. Lastly, the fibrillation may be so marked as first to attract notice.

The *muscular wasting*, which constitutes the most characteristic feature of the disease, may commence in any group of the skeletal muscles whatsoever. It may be first manifest in such rare situations as the facial muscles, intercostal muscles, muscles of the back and abdominal muscles. The commonest situation is in the muscles of the upper limb, where the distal (intrinsic muscles of the hand) or the proximal muscles (deltoids, spinati, etc.) are first affected in about an equal number of cases. In the hand, the muscles of the thenar eminence are the first to waste, and this is followed by atrophy of the hypothenars, of the lumbricals and of the interossei with the usual flattening of the palm, exposure of the flexor tendons in the palm from loss of the bulk of the lumbricals, hollowing of the interosseal spaces and a tendency to the "claw" attitude of the hand. This *main en griffe* is never so marked in this disease as in paralysis of the ulnar nerve, syringomyelia, etc., because the wasting soon affects the long flexors of the fingers, and, moreover, contractures of the affected muscles are not marked in progressive muscular atrophy. When the upper arm is primarily affected the wasting is usually first seen in the deltoids, whence it spreads upwards, involving the spinati and the muscles attaching arm to scapula, and arm and scapula to trunk. Among these muscles some tend to escape the atrophy relatively, or to be affected much later than others, and these are the triceps, the latissimus dorsi, the lower half of the pectoralis major, the levator anguli scapulæ and especially the upper half of the trapezius, which for this reason was called "*ultimum moriens*" by Duchenne. In the limbs the wasting always commences in one limb, but soon spreads to the corresponding limb of the opposite side and tends ultimately to become symmetrical.

The type of muscular wasting which is characteristic of amyotrophic lateral sclerosis and present less often in other forms of progressive muscular atrophy is that which was called by Gowers "*tonic atrophy*". It might be expected that when *degeneration began in a group of anterior horn cells, the corresponding muscles would gradually lose their tendon reflexes and become inexcitable. But in amyotrophic lateral sclerosis, while the muscles waste, their tendon-jerks become and remain exaggerated, and the wasting muscles, though they hang flabbily on the limbs, become hyperexcitable to percussion and they show spontaneous contractions of groups of fibres, known as fibrillary twitchings or fibrillation or fasciculation (see p. 1559).*

In other forms of progressive muscular atrophy, the wasting muscles are more liable to lose their tendon-jerks, they may be inexcitable to percussion of the muscle bellies, and they show less, if any, fibrillation.

Accompanying the muscular wasting there is usually considerable wasting of the *subcutaneous tissues and the skin becomes very loose, and the reduced and separated muscles stand out when they are voluntarily contracted. In some cases the subcutaneous tissue does not waste and may even be increased (especially in the lower limbs), and then the muscular wasting may be masked for a long time even till paralysis becomes complete. There may be an appearance of vasomotor paralysis—redness, blueness and some swelling of the periphery—but this seems to occur much more as the result of the continual pendent position of the hands and of the absence of muscular activity which normally aids the circulation than as the result of any definite vasomotor palsy.*

While, in the most usual type of case, muscular wasting is going on in the upper limbs, slight signs of spasticity gradually develop in the lower limbs. The knee-jerks and ankle-jerks become exaggerated, and after a time the plantar reflexes become "*extensor*". There is not often a severe degree of spasticity and sometimes palpable spasticity is absent, although the reflex signs of pyramidal disease are present. The parts which become spastic do not, in general, develop any wasting.

Spasticity from the upper motor neurone disease may develop in the lower extremities before there are any signs elsewhere of atrophic paralysis due to the lower motor neurone lesion, and such cases present the physical signs of a primary lateral sclerosis. It must, therefore, be borne in mind that a case presenting such features in an adult may eventually prove to be one of amyotrophic lateral sclerosis.

In some cases of progressive muscular atrophy no abnormal clinical signs are found in the lower limbs, but, post mortem, degeneration of the pyramidal tracts is evident.

Next in order of frequency to initial wasting in the upper extremities comes the incidence of the disease upon the muscles concerned in facial expression, articulation, mastication and deglutition, and in lesser degree upon the muscles of phonation. The disease may be confined to these muscles throughout the whole of its course. From the widely different clinical picture resulting, and from the fact that all these muscles are supplied from the brain-stem and upper two segments of the spinal cord, this form of the disease has borne the name of *progressive bulbar paralysis, or labio-glosso-pharyngeal paralysis*. The wasting commences in the intrinsic muscles of the tongue and spreads thence to the orbicularis oris, to the extrinsic muscles of the tongue, pharynx and larynx, to the muscles of mastication and, eventually, but in less degree, to the facial muscles generally; but only in rare cases are the oculomotor muscles affected.

The intrinsic muscles of the palate, the constrictors of the pharynx, the intrinsic muscles of the larynx and the muscle of the œsophagus are little affected. This seems at first an anomalous and astonishing fact, considering how great and important are the troubles with deglutition in bulbar paralysis. But the anomaly disappears at once when one considers that the muscles which are concerned with buccal deglutition are

the muscles of the tongue, those forming the floor of the mouth, including the mylohyoid and the digastric, the muscles which raise and lower the jaw, and those of the lips. Further, the muscles which are most important in pharyngeal deglutition are those which raise and lower the hyoid bone and larynx as a whole, and these are the stylohyoid and stylopharyngeus, the palatoglossus and palatopharyngeus, the geniohyoid, thyrohyoid, sternohyoid, sternothyroid and omohyoid. All these muscles are early and severely affected in bulbar paralysis; and when they fail, the intrinsic muscles of the palate are unable to shut off the naso-pharynx, the constrictors of the pharynx are entirely unable to perform the act of deglutition, and the intrinsic muscles of the larynx—though phonation is never lost—are unable, since the larynx is unfixed by the extrinsic muscles, to modulate the tone of the voice. The very active pharyngeal reflex and the difficulty in using the laryngoscope on account of spasm of the pharynx in the subjects of this disease, are very good clinical evidence that the pharyngeal constrictors are not affected.

The earliest physical sign of bulbar paralysis is the loss of the finer movements which are essential for correct articulation, and consequently a slurring dysarthria develops and increases, and the consonants become less and less distinct until they are inaudible. The failure of the palate to close upon the posterior pharyngeal wall begets a nasal element in the voice. Later, the patient becomes unable to interrupt his blast at any of the stop positions, and his utterance becomes a long, moaning, monotonous, inarticulate sound. His phonation remains, but he cannot alter its pitch nor divide it into parts of speech, except by taking a fresh breath. The orbicularis oris is early affected, and the lips lose their firmness and become thin, and as they weaken, the unopposed retractors of the angles produce a wide, straight mouth, both at rest and in emotional action. Whistling and pursing up the lips become impossible, and ultimately there is much dribbling of saliva, for this can neither be retained by the lips nor swallowed. The tongue shows fine fibrillation, and as it wastes it loses its point, becomes rounded, and is protruded with difficulty. Its surface becomes dimpled and faceted; in the end it consists solely of the covering mucous membrane, the glands and the fibrous tissue, and lies motionless in the floor of the mouth, resembling a crinkled mushroom. The muscles of mastication all become affected. The bite becomes feeble and the mouth cannot be opened against resistance. In the late stages the jaw drops and the mouth is constantly open. The combined weakness of tongue and buccinators makes it very difficult for the patient to keep his food between his teeth in mastication, and often he aids his disability by digital pressure upon the cheeks. Nasal regurgitation is not uncommon. The difficulty in swallowing is greatest with fluids, for these require quick action, and is next greatest with lumpy solids, for these necessitate powerful action. It is least with food of a porridge-like consistency, and this should be carefully borne in mind in feeding the patients.

The other muscles of the face are affected later and to a much less severe degree than is the orbicularis oris. It is as if there were a physiological selection on the part of the disease for the nervous mechanism subserving mastication and deglutition. Still in the majority of cases there is bilateral general facial weakness and wasting which, with the peculiar mouth and dropping jaw, produce a characteristic facies which can be instantly recognised. If the upper facial muscles are tested by raising the eyelid with the finger against resistance, invariably they will be found to be weak. Only in very rare cases does the atrophy extend to the oculo-motor muscles. As in the paralysis of the limbs, so also in bulbar paralysis, concomitant signs of both upper motor neurone and of lower motor neurone lesion may exist. When such tonic atrophy of the bulbar muscles is present, the symptomatology and clinical appearance are the same as have been above described for the simple atrophic form, with the exception that the jaw-jerk and the other muscle-jerks of the bulbar region, which are absent in the latter condition, are brisk in the tonic-atrophic form. And,

further, it must be remembered that the additional element of spastic paralysis adds greatly to the degree of the paralysis as a whole.

In less common cases of progressive bulbar paralysis the upper motor neurone lesion alone is in evidence, and the bulbar paralysis is purely spastic. Here the symptomatology as regards articulation, deglutition, etc., is the same, and the facial aspect identical with that of the simple atrophic and tonic-atrophic forms. The muscle-jerks are brisk. The appearance of the tongue, however, is quite different; it is smooth, narrow, stiff and drawn into a narrow compass by the spasm of the muscles composing it. It appears too small for so large a mouth. There is no fibrillation, and the muscles are nowhere wasted.

The muscles of the back of the neck, the splenius, complexus, etc., are not uncommonly the first muscles to be affected with the wasting of progressive muscular atrophy. There is increasing difficulty in extending the head, which drops forward, causing a characteristic attitude, which is associated with a constant overaction of the frontales which raise the brows to clear the line of vision when the head is dropped forward, so giving rise to a permanently furrowed brow. The loss of substance in the muscles of the back of the neck, together with the dropping forward of the head, causes the lower cervical and upper dorsal spines to stand out in undue prominence, and to give an appearance approximating to that of an angular curvature.

Primary affection of the lower extremities is much less common than that of the upper extremities, bulbar region or neck muscles. The anterior tibial and peroneal muscles are usually attacked first, and less commonly the quadriceps. The clinical type is that of flaccid atrophy in most of the cases. Tonic atrophy, which is so common in the upper limbs and in the bulbar region, is rare in the legs.

Wherever the site of commencement of progressive muscular atrophy may be, it invariably spreads to other regions, sometimes slowly and with periods of arrest which may last for years, sometimes with remarkable rapidity. The manner of spread is usually in terms of the contiguity of the affected elements in the nervous system; but it is sometimes in terms of the physiological association of the muscles, as is commonly seen in the bulbar forms of the malady. When the disease is definitely installed the appearance of fibrillation, in any muscles otherwise unaffected, is a sure sign that atrophy will shortly commence in those muscles.

According to the method of advance shown by the disease, cases of progressive muscular atrophy fall into two groups which it is important to distinguish. In the first group, the atrophy spreads locally and slowly and remains confined to one region of the body during most of the course of the malady. These cases are always of the simple atrophic type, and they usually survive a long time. Such cases, however, tend to become general just before the end. In contrast with the local type of the affection is the group in which the manifestations, commencing locally, spread within a comparatively short time to many parts of the body, or even become universal. The spread may be very rapid, and the end may occur in a few months, or it may be slower; but it is unusual for any of the cases forming this group to survive for more than 2 years. This group comprises (1) the generalised cases of simple flaccid atrophy; (2) all the cases of amyotrophic lateral sclerosis and (3) most of the bulbar cases.

*Fibrillation* is a most important symptom of the disease, and is an associate of the muscular atrophy. It precedes the wasting of the fibres, and is a sure herald of the advent of wasting in this disease. It ceases to occur when the muscle is completely wasted, and is not seen when the atrophy is not progressing. On account of the importance of fibrillation as a diagnostic sign of progressive muscular atrophy it is important here to consider those other conditions in which it is met with clinically. It occurs in syringomyelia and in peroneal atrophy, but only when the muscular atrophy is progressing, and, therefore, it is only an occasional symptom in either disease. It is often very marked in cases of interstitial neuritis (sciatica, etc.). It

occurs in a most magnified and conspicuous form in certain conditions of gastro-enteritis, and is presumably due to an intoxication, and to this form of fibrillation the term "myokimia" has been applied. It is not met with in polyneuritis, poliomyelitis, myopathy, nor in the common gross lesions of nerve trunks, nerve roots or spinal cord.

The *electrical reactions* of the affected muscles vary according to the degree of degeneration. Since normal and degenerate fibres are stimulated side by side in the affected muscle, there will be some lowering of the response to faradism with a tendency to a polar change. This is known as the "mixed reaction" and it is common to all diseases in which muscle degenerates fibre by fibre. Faradic excitability lessens as more of the muscle fibres degenerate, and when degeneration is complete all electrical excitability is lost. In tonic atrophy the excitability of the affected muscles to direct mechanical stimuli, such as percussion, is increased so long as any living muscle remains.

*Contractures* are conspicuous by their absence in this disease, which is thus strongly contrasted with peroneal atrophy and some other muscular atrophies. If the atrophy becomes complete in a whole limb the end-result is that the limb is flail-like and without contracture.

*Mental alterations* are constantly present in the cases in which the bulbar region is affected. Emotional instability and hyperexcitability are the usual change. The patient is easily excited to tears or to laughter by trivial causes, and when so excited cannot control his expression of emotion. He himself feels little joy or grief during the paroxysms of laughing or crying.

*Sphincters*.—In the majority of the cases these are not affected, but every now and then dysuria in any of its forms occurs, and it may occur early in the course of the malady, and it may be severe. Loss of sexual power is very common.

*Reflexes*.—The reflexes are modified in this disease, on the one hand by spasticity, when this is present, and, on the other, by the muscular atrophy which may prevent response in the affected muscles. The pharyngeal reflex in bulbar cases is usually brisk, notwithstanding the statement to the contrary, which most writers upon this subject have recorded; but the response is not the normal response, involving all the muscles concerned in deglutition, for these are atrophied and paralysed; it is confined to the constrictors of the pharynx and the muscles of the palate, with the feeble co-operation of such of the somatic bulbar muscles as are still able to act. The plantar reflexes are usually of the extensor type when the legs are spastic; but this does not always obtain. Similarly, the abdominal reflexes do not disappear so constantly or so early as is the case in disseminated sclerosis, for example, and they may persist when the legs are markedly spastic and extensor plantar responses have appeared. In cases of tonic atrophy the tendon reflexes are everywhere increased, even in regions where the atrophy is severe, and in this type of the malady they never disappear. The same increase of the muscle-jerks occurs in the purely spastic cases. In simple atrophic cases the tendon-jerks disappear *pari passu* with the wasting of the muscles.

*Cerebrospinal fluid*.—The cerebrospinal fluid is always quite normal by all the tests at present in vogue. It does not usually contain more than one cell per c.mm., and no change has been detected in its chemical constitution.

*Diagnosis*.—The malady has to be distinguished from the many conditions in which progressive weakness and wasting of the muscles occur, from those in which muscular wasting and spasticity are conspicuous clinical features, and lastly from other diseases, in which bulbar symptoms are early evidenced. Injury of the cervical enlargement of the spinal cord gives rise to a limited degree of wasting in the upper limbs, and spasticity of greater or less intensity in the lower limbs (see p. 1541). The wasting in the upper limbs becomes apparent some weeks after the injury and affects the muscles corresponding to the injured segments of the cord, which are

commonly those of the forearms and hands. But weakness of these muscles and the spastic weakness of the legs are maximal immediately after the injury, and power usually shows an improvement during the succeeding weeks or months, whereas in progressive muscular atrophy the weakness, wasting and spasticity come on insidiously and progress steadily. It must be realised that, although bony injury is commonly present, injury of the cervical cord may occur without any fracture or dislocation of the cervical spine. Furthermore, a moderate degree of weakness of the limbs may escape observation while the patient is in bed after an accident, or they may be ascribed to other causes, and so the signs resembling amyotrophic lateral sclerosis may not be discovered until several weeks after the occurrence of the lesion responsible for them. Inversion of the supinator jerk (see p. 1541) is a common sign in cases of injury of the cervical enlargement, but rarely, if ever, occurs in progressive muscular atrophy. Syphilitic amyotrophy (p. 1470) may be indistinguishable from progressive muscular atrophy except by the results of the Wassermann reactions in the cerebrospinal fluid and blood. Peroneal muscular atrophy very closely resembles progressive muscular atrophy, in that slow wasting and fibrillation of the muscles are the chief clinical features. The points which distinguish the two conditions are that peroneal atrophy is often a familial disease, and is apt to commence in childhood when it is unusual for progressive muscular atrophy to begin. The location of the atrophy is peculiar, and when well marked in the periphery of all four limbs, as is common in this disease, cannot be confused with progressive muscular atrophy since the latter disease never has this distribution. Syringomyelia is easily distinguishable by the early and striking loss of pain and temperature sensibility. Cervical rib not uncommonly produces atrophy of the intrinsic muscles of the hand, and, though this is usually confined to one hand, it may be bilateral. Further, it is exceptional for the atrophy to involve all the small hand muscles simultaneously, or equally. It picks out the opponens pollicis first and most severely, and is not uniform for all the hand muscles, as in progressive muscular atrophy. Pain in the distribution of the eighth cervical and first dorsal roots, and some loss of sensibility, may be present. The atrophy remains local, and is never accompanied by fibrillation. The abnormal rib is easily discoverable on radiographic examination. It must be borne in mind that cervical ribs are not uncommon, and that their presence does not necessarily prove the cause of atrophy of the hand muscles, for cervical ribs may be present in the subjects of progressive muscular atrophy, syringomyelia or any other disease.

The diagnosis of progressive muscular atrophy from the primary muscular dystrophies seldom causes serious difficulty. The latter occur, in general, at a much earlier age and several members of a family may be affected; the incidence of the wasting is almost invariably on the proximal muscles, the weakness is out of proportion to the apparent wasting, fibrillation is absent, and the progress of the disease is very much slower than that of progressive muscular atrophy. Dystrophia myotonica is at once separated from progressive muscular atrophy by the myotonus, when this latter symptom is present. When myotonus is absent, the characteristic wasting of the sternomastoids and of the muscles of the thighs, the age of the subject, and sometimes the presence of cataract should suggest the diagnosis. Arthritic muscular atrophy occurs in the regions of joints which show easily recognisable disease. Fibrillation does not occur, nor are there alterations in the electrical excitability of the wasted muscles.

Lesions of peripheral nerve trunks may be diagnosed by the history of a local cause, by the discovery of a palpable local lesion upon the course of the nerve, and by the confinement of the atrophy to the distribution of one particular nerve, while pain and sensory loss often occur in that same distribution.

Lesions of the nerve roots, and especially those produced by pachymeningitis and by neoplasm in the vertebræ may cause signs and symptoms so closely resembling those of the more rapid forms of progressive muscular atrophy, as to render correct

diagnosis very difficult. Such a lesion in the cervical region, for example, may give rise to wasting of the hand and forearm muscles, and a spastic condition of the legs, resembling exactly a condition of amyotrophic lateral sclerosis, without deformity or rigidity of the spine, and without pain or sensory loss. In such cases of difficulty the course of a little time will bring the advent of the conclusive symptoms of a local pressure lesion. It is important in this connection to remember that pressure upon the spinal cord results in hyperalbuminosis of the cerebrospinal fluid, and if the lesion causing the pressure is syphilitic there is likely also to be lymphocytosis in that fluid, neither of which conditions is found in progressive muscular atrophy.

Diagnosis is most difficult in those cases where spasticity in the limbs is the first sign of progressive muscular atrophy, and where such spasticity precedes the appearance of any muscular atrophy by a long time. If it be clearly borne in mind that spastic paralysis may be the earliest and for a time the only sign of progressive muscular atrophy, and that among the many diseases of the nervous system which commence with the same clinical picture of spastic paralysis a certain diagnosis cannot be made until further distinguishing signs appear, error will be avoided. The importance of the examination of the cerebrospinal fluid in doubtful cases cannot be too strongly emphasised.

**Course and Prognosis.**—The nature of the disease is to progress, and to extend its area of invasion until a fatal issue is reached. The progress may be rapid, and the end may be reached in a few months, or it may be slow, and several years may elapse before death occurs. The local types of progressive muscular atrophy of slow onset are the most gradual in their development, and these are often characterised by periods of arrest in the progress of the disease. The generalised simple atrophic type of the disease is the most rapid, especially when it commences with severe initial flaccid paralysis without atrophy.

In the bulbar types of the disease, and in the common type of amyotrophic lateral sclerosis, the course is, for the most, steadily progressive. Every type will show, however, upon occasion, exacerbations and remissions, and the exacerbations are the most important, and in the bulbar types may bring about the end in a few hours. Of particular interest are rapid extensions of a flaccid paralysis, which may occur in a few hours, and which resemble, and indeed are identical with, onset of the disease with initial flaccid paralysis without atrophy, which has been already described. Whatever type of the disease be present, it tends in the end to spread and to become general.

Involvement of the respiratory muscles or severe bulbar symptoms, and the pulmonary complications which may accompany either condition, may bring about the fatal issue. It is usual however for death to occur in a manner which is common to so many degenerative nervous diseases; a rapid increase of the paralysis is associated with an increasing lethargy, which soon deepens into a rapidly fatal coma. It is uncommon for death to occur from intercurrent maladies. The average tenure of existence after definite signs are present is under 1 year in the generalised flaccid type, and it may be as short as 2 months. Bulbar symptoms are not generally survived for more than 12 months. Localised cases of simple atrophy may live for many years. Some of the patients in whom a positive Wassermann reaction is found improve, and the disease is sometimes arrested by antisyphilitic treatment.

The progressive character of the disease renders the prognosis grave in every case. There are some cases occurring in middle life, which resemble cases of progressive muscular atrophy of local distribution and slow course, which become finally arrested or even recover; the true nature of such cases is doubtful, but it is probable that they are allied to polyneuritis.

In amyotrophic lateral sclerosis the average duration of life is seldom more than 3 years from the onset. When bulbar symptoms are present the average duration is under 2 years. In the generalised cases the average duration is under 1 year. Widely

spread fibrillation in muscles, which are neither weak nor wasted, is the constant herald of generalisation, and renders the immediate prognosis serious. In cases where syphilis is present the prognosis is more favourable, and there is even a possibility of arrest and improvement if energetic treatment of the associated condition is provided. Rapid extension of the weakness, the advent of bulbar symptoms, involvement of all the respiratory muscles, and especially general asthenia and drowsiness are the signs which usher in the fatal result.

**Treatment.**—This malady seems to be entirely uninfluenced by any treatment that has hitherto been adopted. At one time dramatic claims were made in respect of vitamin E (tocopherol acetate), given in doses of 3 mg. thrice daily. This was said to arrest wasting and weakness and in early cases to effect rapid improvement. These claims, however, have proved illusory. It remains, therefore, to secure favourable conditions of life for the patient, and to maintain the general health in as perfect a state as possible. Massage and passive movements are useful as giving bodily comfort to the patient, and satisfying him that something is being done for him. In bulbar cases, the dysphagia must be aided by avoiding liquids and solids, and by serving all the articles of diet in pultaceous form. Salivation, which is so troublesome in this condition, may be greatly helped by the administration of hyoscine or belladonna by the mouth.

## PERONEAL MUSCULAR ATROPHY

**Synonyms.**—Charcot-Marie-Tooth Type of Muscular Atrophy, Neuritic Type of Muscular Atrophy.

**Definition.**—This is an absolutely distinct and peculiar form of muscular atrophy, with a frequent tendency to occur in several members of the same family. It usually commences in mid-childhood, and after progressing for some 20 years or less, comes to a final arrest. The atrophy always commences in the intrinsic muscles of the feet, and is throughout strictly distal in distribution. The muscles of the face and trunk and the proximal muscles of the limbs are never affected. The atrophy leaves a *peculiar elastic fibrosis in the affected muscles, so that the incapacity caused by this disease is much less than in any other form of muscular atrophy of like degree.* Sensibility is often slightly affected, and there may be deep sensory loss. The essential morbid anatomy is a primary neurone atrophy of the anterior horn cells and of some of the afferent neurones in Clarke's column.

**Ætiology.**—The disease usually commences between the fifth and tenth years of childhood, but it may appear as late as the fourth decade of life. Males and females are both affected. Heredity plays an important part in the incidence, although isolated sporadic cases are not uncommon. It may exhibit every type of inheritance. The malady often occurs in families, and has been traced through five generations; it may skip a generation and then reappear.

**Pathology.**—The anterior horn cells of the affected regions show a slowly progressive atrophy and disappearance, with corresponding atrophy of fibres in the peripheral nerves. The cells of Clarke's column show signs of degeneration, as do also some of the fibres of the posterior columns of the spinal cord, and especially those of the postero-lateral column. Slight degeneration in some of the fibres of the pyramidal tracts is usually found. The affected muscles show a simple atrophy of the muscle fibres, indistinguishable from that seen when a motor nerve is divided. There is a simple shrinking of the fibres, which stain progressively and more and more deeply with hæmatoxylin, lose their striation, and finally disappear. Secondary fibrotic changes accompany the atrophy, together with sclerosis of the arteries of the muscle.

**Symptoms.**—Muscular atrophy dominates the clinical picture of this malady.



It is strictly distal in distribution, and this feature will serve to distinguish peroneal atrophy from any other form of muscular atrophy. This is to say it does not affect one particular muscle, but the distal ends of all the muscles below a certain level on the limb, leaving the proximal ends of the muscles normal, and it advances up the limb inch by inch, the separation of the wasted portion of the muscle from the normal portion being always transverse to its length. In other words, the muscle fibres seem to waste in terms of the length of the spinal axons which supply them. The wasting commences always in the intrinsic muscles of the feet, and hollowness of the instep and thinness of the feet, together with retraction of the toes and the difficulty which the pes cavus so produced entails in fitting boots, first draw attention to the disease. As the process advances, the lower segments of the anterior tibial, peroneal and calf muscles become affected, and the limb is subsequently involved until the lower third of the thigh is reached, at which stage the disease is invariably arrested. This slow spread of the atrophy from the distal towards the proximal portion of the limb, gives rise to a unique and characteristic feature in the appearance of the legs at the several stages of the disease. As an example, the complete atrophy of all the muscles below the middle and a well-developed musculature in the upper half of the leg, give rise to the inverted "fat bottle" calf. When the atrophy has involved the lower third of the thigh, the lower end of the femur, bare of muscle and covered only by skin and tendons, contrasts strongly with the well-developed muscles of the upper thigh, and causes the thigh to resemble an inverted champagne bottle.

Some years after the atrophy has become marked in the lower extremities, and in the usual run of cases just before the age of puberty, the intrinsic muscles of the hands, and first those of the thenar and hypothenar groups, begin to waste, and this wasting may extend as high as the middle of the forearm. It must be borne in mind that the disease may become arrested at any period of its spread, and especially that the upper extremities often escape altogether. With the exception of the lower part of the thighs, the proximal segments of the limbs do not become involved, and the muscles of the head, neck and trunk remain unaffected.

The affected regions of the muscles waste absolutely, and leave a very elastic fibrous tissue. The electrical excitability in the wasted regions becomes first lowered and then lost, and, in the earlier stages, may show a mixed reaction, in which there is lowering of excitability to faradism, with a tendency to an inverted polar reaction. Fibrillation of the muscles is an important sign. It is seen only when the disease is progressing, and in the muscles which are obviously wasting. It is never general, as in some cases of progressive muscular atrophy, and since peroneal atrophy is at times advancing and at other times stationary, fibrillation may be in one case conspicuous and in another never seen. It disappears entirely when the progress of the malady becomes finally arrested, and is, therefore, useful as a clinical indication of active advance of the disease. Contractures always occur, and from the nature of the distribution of the atrophy are necessarily confined to the feet and the hands. In the feet, pes cavus with retracted toes is the rule; but sometimes, and in some stages of the disease, the feet and toes may be dropped and the feet inverted. The sphincters are unaffected. The ankle-jerks are diminished or lost in proportion to the wasting of the calf muscles. In the final arrested stage they are usually lost. The knee-jerk is always retained and is usually brisk. The plantar reflexes are usually lost early so far as any response in the foot is concerned, but some response in the upper thigh muscles, upon stimulating the plantar region, often remains. Pain, tenderness and cramp are entirely absent. Conspicuous loss of sensibility is uncommon, but slight loss of deep sensibility, loss of the vibration sense and relative tactile loss may often be detected upon careful examination: but in rarer cases all forms of sensibility may be severely affected, or even entirely lost. Perforating ulcers may be met with upon the soles of the feet, and are explained by the thinness of the feet and their deformity, which, coupled with the clumsiness of the use of the feet, lead to the formation of

severe corns which break down into perforating ulcers. Loss of sensibility also is a factor in their production.

The most striking of all the clinical features of peroneal atrophy is the comparatively slight disability caused by the wasting of the muscles and consequent paralysis, and even the sensory loss, when it is present.

**Course.**—The course is irregularly progressive for a number of years only, and the advance of the disease ceases usually in the third decade of life. Exacerbations of the weakness are likely to be followed in every case by considerable improvement, owing to the secondary fibrosis in the muscles.

**Diagnosis.**—Peroneal atrophy in the early stages is easily confused with progressive muscular atrophy, in that wasting of muscles and fibrillation are the conspicuous features. The onset usually in childhood and the fact that the feet are affected first, the peculiar distal distribution and the presence of any familial incidence, are important. But the only distinction which is absolute is the distribution, for progressive muscular atrophy may begin in childhood and peroneal atrophy may not appear till after middle life, and often familial history is absent in the latter malady. In the course of time the diagnosis always becomes clear, for progressive muscular atrophy never keeps to the classic distribution of peroneal atrophy, nor is it followed by the peculiar fibrosis which characterises the latter.

Dystrophia myotonica when commencing in the peroneal muscles may for a time closely simulate peroneal atrophy. The presence of the least sign of myotonia, the involvement of the face and the atrophy of the sternomastoids, will establish the diagnosis.

The usual forms of myopathy are at once separated from peroneal atrophy by the distribution of the muscular weakness and wasting, which in the former group of maladies is conspicuously upon the face, trunk and proximal muscles of the limbs, and in the latter upon the distal muscles. Peripheral neuritis is more rapid in its onset, and is apt to be associated with marked sensory disturbances, both objective and subjective, and the paralysis is in terms of individual muscles, which is not the case in peroneal atrophy.

**Treatment.**—The general health should be carefully maintained, and the nutrition of the affected muscles aided by the application of massage. Care must be taken, on the one hand, to avoid over-fatigue of the affected muscles, and, on the other, to ensure such regular exercise as is compatible with their capacity. Bicycling, for example, since it employs chiefly the thigh muscles, is a better form of exercise for these patients than is walking. In no circumstances should tenotomies be performed for the deformity of the feet, for such measures tend to destroy the effect of the conservative fibrosis, so essential to the production of a useful limb. The use of heavy mechanical supports is to be avoided above all things. Light, well-fitting boots, so as to interfere as little as possible with the exercise of the damaged muscles, are essential.

## PROGRESSIVE SPINAL MUSCULAR ATROPHY OF CHILDREN

**Synonym.**—The Werdnig-Hoffmann Disease.

**Definition.**—This is a malady of the first year of infancy, often incident upon several children of the same parents, and characterised by the gradual development of progressive muscular weakness and atrophy, which affects the proximal muscles first and most, increases to a complete paralysis of trunk and limbs, and finally affects the bulbar muscles. The disease is invariably fatal in from a few weeks to several months. The most striking pathological changes are a progressive degeneration and disappearance of the ventral horn cells of the spinal cord, and of their analogues in the brain-stem.

**Ætiology.**—In some of the cases the paralysis is noticeable at the time of birth, and the disease is obviously of pre-natal development. In others the children are quite healthy at birth, and the disease develops some time during the first year of life, and most frequently within 8 weeks of birth. Though sporadic cases may be met with, yet in the majority of instances several children of the same mother are affected. Both the pre-natal cases and the post-natal cases may be met with among the children of the same mother. The sexes seem to be equally affected. No maternal ill-health during pregnancy has been noticed, and nothing is known about any other ætiological factor.

**Pathology.**—The most extensive changes are found in the ventral horn cells throughout the spinal cord and brain-stem, and at many levels no normal cells whatever are to be seen. Tigrolysis, swelling and glassiness of the cells, extrusion of the nuclei, disappearance of the dendrites, shrinking of the cells and final disappearance is the sequence of the changes. Degeneration of the anterior roots and of the peripheral motor nerve fibres consequently occurs. These changes are not confined to the lower motor neurones, for in some cases examination by the Marchi method shows extensive degeneration throughout the posterior columns of the cord, indicating that lower sensory neurones were also considerably affected.

The muscles show intense degeneration with hypertrophy of some fibres and atrophy of most of the fibres, waving, moniliform shape, hypernucleation of the spindles, general nuclear increase and fibrosis.

**Symptoms.**—In the cases which are pre-natal, the malady is noticed at the time of birth on account of the tonelessness, flaccidity and the poorness of movement in the trunk and proximal muscles of the limbs. In the post-natal cases there is a gradual onset of similar weakness and flaccidity in the trunk first, and in the limbs afterwards, which usually commences within 6 weeks of birth, but which may not appear until towards the end of the first year of life. The weakness seems always to be least marked in the periphery of the limbs, where curious, slow, involuntary movements of the fingers and toes have been noted in many of the cases. The paralysis is followed by a rapid and extensive wasting of the muscles, accompanied by occasional fibrillary twitchings. Since these children are not only well nourished, but often put on much fat during the illness, wasting of the muscles may not be apparent on inspection or palpation. It can, however, immediately be detected by radiography, which distinguishes sharply between fat and muscle.

As the malady progresses the trunk muscles become completely paralysed, the intercostal muscles being always paralysed before the diaphragm. The limbs become progressively weaker, and, lastly, bulbar paralysis supervenes in those cases where death has not already occurred from respiratory paralysis. The reaction of degeneration is present in the affected muscles. Sensibility may be unimpaired but in several of Collier's cases there was conspicuous loss of pain sensibility over the limbs and trunk. The sphincters are unimpaired until the very last stages of the disease. The superficial and deep reflexes are lost. The ocular muscles are not affected, and intelligence is preserved throughout.

**Diagnosis.**—The peculiar and striking features of the disease make the diagnosis easy, if the symptomatology be known. Amyotonia congenita presents the same helplessness and flaccidity of trunk and limbs as does the Werdnig-Hoffmann disease, and further resembles it in being sometimes congenital, and sometimes having an onset very early in life. In amyotonia congenita, however, the paralysis is not complete, and it tends to improvement and not to progressive increase. Contractures also occur, which are not found in the Werdnig-Hoffmann disease, and, lastly, the definite spinal cord changes of the latter malady are not found in the former. Greenfield, however, considers that amyotonia congenita and Werdnig-Hoffmann paralysis are different aspects of a single disease.

**Course and Prognosis.**—The course is invariably progressive, and is more rapid

the earlier in life the disease commences, and it is most rapid of all in the pre-natal cases, which are usually fatal within a few weeks. With an onset some weeks after birth, life is usually continued for several months, and a few cases have been reported with an onset towards the end of the first year, in which death has been delayed until the third or fourth year.

**Treatment.**—No treatment is known to influence the course of the malady.

## DISORDERS OF THE PERIPHERAL NERVES

### LOCAL LESIONS OF NERVE ROOTS AND NERVE TRUNKS

Individual peripheral nerves may be damaged by a large number of agencies. Trauma may affect them in a variety of ways. Direct penetration by a sharp body such as a knife or glass, or the passage of a fragment of a projectile may sever the nerve completely or partially. Injury by a blow with a blunt agent or severe commotion in surrounding tissues, such as occurs with the passage of a projectile near the nerve, may destroy the axons without interrupting the continuity of the more resistant medullary sheaths and perineurium. Recovery of such a nerve requires the growth of new axons down the surviving medullary sheaths. Similar injuries of less intensity may temporarily abrogate the function of the nerve but be followed by recovery of function in a matter of hours or days. For these three degrees of nerve injury Seddon has suggested the names *neurotmesis*, *axontmesis* and *neurapraxia* respectively. Nerves may also be injured by trauma of a less violent but more sustained character as is seen in the common varieties of pressure palsy such as "Saturday night paralysis", crutch palsy, palsies from pressure of plaster and other splints and chronic overstretching as in the case of the ulnar nerve. Peripheral nerve lesions may follow a variety of general infections such as pneumonia, dysentery and streptococcal illnesses. Nerves may be involved in specific inflammatory processes such as leprosy. Finally they may be involved in new growths. The most important example of this is infiltration with carcinoma from a neighbouring focus, but nerves may be the site of isolated neurofibromata or multiple lesions in cases of Von Recklinghausen's neurofibromatosis.

#### PHRENIC NERVE

This nerve supplies the diaphragm. Paralysis results most often from disease of the spinal cord, but the roots may be implicated in disease of the spine, and the trunk may be injured, in its course through the neck and thorax, by wounds or tumours. Bilateral paralysis occurs in lesions of the cord and spine, and in polyneuritis especially of the diphtheritic and acute infective varieties. Other causes usually affect one side only. When the diaphragm is completely paralysed, the normal inspiratory protrusion of the upper part of the abdomen disappears, or is replaced by retraction of this part with each inspiration. During rest, so long as the lungs are healthy, the respiratory rate does not increase, but if bronchitis or pneumonia arises as a complication, or if the patient exerts himself, the diminished reserve of respiratory power is seriously felt. When one nerve only is affected the diaphragm does not move on that side, but becomes permanently elevated as a result of collapse of the base of the corresponding lung. This is rarely detected by observation of the abdominal movements, but is easily seen on the radiograph screen. It produces no discomfort.

#### THE LONG THORACIC NERVE

This nerve supplies the serratus anterior muscle. When all the fibres of this muscle contract, the scapula moves upwards, forwards and outwards. It contracts

with the pectoralis major in the action of pushing forward the point of the shoulder and in the rapier-thrust movement. It also assists the deltoid in raising the arm. When it is paralysed alone, the position of the scapula at rest is unaltered, but if the trapezius and the rhomboids are paralysed as well the scapula drops, and its lower angle is displaced inwards. Paralysis of the serratus anterior is best demonstrated by causing the patient to hold the arms outstretched before him. The arm is not raised so high on the affected as on the normal side, because the scapula is not fixed and the deltoid works at a disadvantage. Viewed from behind the deformity is characteristic. The vertebral border of the scapula stands out prominently and the hand can be pushed between this bone and the thorax—"winged scapula". On raising the arm from the side, there is difficulty in attaining the horizontal position, but the winging of the scapula is less apparent.

The nerve may be damaged by carrying heavy weights on the shoulder, by falls or blows on the shoulder, and by continued muscular effort with the raised arm. The nerve may be injured alone in gunshot wounds, but as a rule it is associated with lesions of the brachial plexus. In addition, a serratus anterior palsy may develop suddenly in an otherwise healthy person after exposure to cold, or as part of a rare reaction to the administration of serum or antitoxin. In such neuritic cases and in the cases caused by compression, severe neuralgic pains in the neck precede the onset of paralysis. Recovery is always very slow and the defect may be permanent.

#### BRACHIAL PLEXUS

The brachial plexus may be injured by stabs in the neck, by penetrating missiles, by dislocation of the shoulder or fracture of the clavicle, or by pressure of a tumour, aneurysm or cervical rib. Further, the nerves may be torn by forcible dragging on the arm in accidents or during delivery. In most cases the lesion is partial and the symptoms conform in the main to one of the following types:

*Upper plexus paralysis (Erb's palsy).*—This results from an injury to the fifth and sixth cervical roots. The muscles paralysed are: biceps, deltoid, brachialis, brachioradialis (supinator longus), supraspinatus, infraspinatus, rhomboideus, subscapularis, clavicular portion of pectoralis major, serratus anterior, latissimus dorsi, teres major. The arm cannot be flexed at the elbow (flexors of forearm), nor raised and abducted (deltoid). The movements of the wrist and fingers are not impaired. Adduction of the arm is weak (pectoralis major), and rotation is feeble or absent (spinati). On attempting to oppose the shoulders, the scapula on the affected side passes farther from the middle line (rhomboideus). The hand of the affected side cannot be placed on the buttock of the sound side (latissimus dorsi).

The reaction of degeneration is often complete in the deltoid and flexors of the forearm and nearly so in the spinati. It is usually incomplete in the other muscles. Sensation is diminished or lost along the outer border of the whole limb immediately after the injury, but improvement sets in rapidly. For some time the patient experiences pins and needles and burning sensations in the affected area, which last longest in the thumb and index finger. The biceps reflex is lost.

*Lower plexus paralysis (Klumpke's palsy).*—This results from a lesion of the eighth cervical and first dorsal roots, or of the common trunk of the median and ulnar nerves. The intrinsic muscles of the hand and the flexors of the wrist and fingers are paralysed, and the inner border of the forearm and hand is anæsthetic. When the roots are damaged sympathetic fibres may be implicated with the production of myosis, narrowing of the palpebral aperture, enophthalmos and alterations in sweating on the face, neck, arm and upper part of the chest on the affected side.

*Middle plexus paralysis.*—This form of paralysis is a common result of gunshot injuries of the plexus. It affects the muscles supplied by the radial and axillary nerves—posterior cord. As the nerve to the latissimus dorsi arises from the same cord,

this muscle is often paralysed as well. In addition to these simple types, more complicated paralyses occur, in which various parts of the plexus are injured together.

*Paralysis of the medial cord of the plexus.*—Atrophy is confined to the intrinsic hand muscles, and the sensory loss is confined to the hand.

*Incomplete lesions of the brachial plexus* show a remarkable tendency to spontaneous recovery. In many cases recovery is complete in 6 months to 2 years, in others it is partial, and some muscles remain paralysed.

#### THE RADIAL NERVE

Owing to its long course, its position in relation to the humerus, and its peculiar vulnerability to compression, paralysis of the radial nerve is one of the commonest peripheral nerve palsies; although it is a mixed nerve, containing sensory, motor and vasomotor fibres, the symptoms of an injury are almost entirely motor. In the upper arm the nerve supplies the triceps and the anconeus, in the forearm the supinators, the extensors of the wrist and fingers, and the extensors and long abductor of the thumb.

Injury to the nerve is followed by dropping of the wrist and fingers. The wrist and the first phalanges are flexed. The flexion is limp and easily reducible.

When the lesion is in the axilla the whole of the *triceps* is paralysed, and extension at the elbow is lost. Occasionally in wounds of the posterior aspect of the arm the nerves to the triceps are injured, whilst the main trunk escapes. The patient is then able to extend the arm powerfully by means of the anconeus, but if he is made to raise the elbow as high as possible with his fingers on the point of the shoulder, *extension of the bent forearm is impossible.*

In most cases the nerve is injured in the middle third of the arm and the triceps escapes, but the brachio-radialis and *all* the extensor muscles in the forearm are paralysed. *Partial paralyses, such as are seen in lesions of the median and ulnar nerves, are very rare.* The brachio-radialis is not a supinator. Its action is to flex the forearm, whilst the hand is in a position intermediate between pronation and supination. Paralysis of this muscle is detected by the absence of contraction when the pronated forearm is flexed against resistance. Owing to paralysis of the *supinator* supination is abolished. During the movement of flexion of the forearm the biceps acts as a supinator, and during extension the external rotators of the shoulder correspond, though feebly.

Paralysis of the *extensors of the carpus* abolishes both extension and lateral movement at the wrist. The flexors of the carpus play no part in lateral movements. *The extensors of the fingers* extend the first phalanges *only*. Extension at the distal joints is carried out by the lumbricals and interossei. Paralysis of the *extensors and long abductor of the thumb* renders abduction of the thumb and extension of the phalanges impossible. On attempting to abduct the thumb, it passes no farther than the radial border of the hand. In some cases, the second phalanx of the thumb can be feebly extended by the muscles of the thenar eminence.

Many muscles not supplied by the radial nerve work at a disadvantage when the extensors are paralysed. These defects must not be mistaken for signs of injury to other nerves. Owing to the flexed position of the hand the grasp is feeble, but if the wrist is extended passively the grasp is improved. The patient cannot make a fist properly, as the thumb does not oppose the index finger and the fingers cannot be flexed into the palm, until the thumb has been moved aside by the sound hand. The movements of the interossei in abducting and adducting the fingers are also feeble while the wrist is flexed, but are much stronger when the hand is resting flat on a table with the wrist and fingers extended. The complete reaction of degeneration is often found in all the paralysed muscles from the onset. Atrophy becomes obvious in a month or two. Its extent and severity give important evidence for prognosis.

**Sensory disturbances.**—Subjective symptoms are rare. In a few cases, paresthesiæ are felt on the posterior aspect of the forearm and on the dorsal aspect of the thumb. They are of brief duration, and are commoner with partial than with complete lesions. Causalgia is almost never seen in lesions of this nerve. Sensibility to light touch, superficial pain and temperature is impaired over a small area on the radial border of the hand, including the proximal joints of the thumb and the first two fingers. The defect is often very slight, and is only discovered on very careful examination. Deep sensibility is rarely affected. Considering the extensive distribution of the superficial branch of the radial nerve, it is rather surprising that the sensory disturbances are so slight, when the nerve is injured above the origin of this branch.

As a rule, the brachio-radialis recovers first, then the extensors of the wrist, then the extensors of the middle, ring, little and index fingers in this order, and the extensors and abductors of the thumb last of all. On palpation of the muscles during attempted extension, contractions can be felt before any movement is produced. Other signs of impending recovery are the disappearance of automatic pronation and of the flail-like drop of the hand, also diminution of automatic flexion of the fingers after passive extension. Recovery of movement is complete when the patient is able to extend the wrist and all the fingers simultaneously or separately. After this becomes possible, restoration of power is rapid.

#### THE MEDIAN NERVE

Whilst the clinical individuality of the radial nerve is shown in the preponderance of motor symptoms and in the uniform completeness of the paralysis that follows an injury, that of the median is seen in the frequency of partial and especially of painful lesions. Isolated palsy of this nerve is infrequent except as a result of gunshot wounds and other injuries.

**TOTAL PARALYSIS.**—The muscles paralysed are the pronators, the radial flexor of the wrist, the flexors of the fingers except the ulnar half of the deep flexor, most of the muscles of the thenar eminence (opponens, abductor brevis and outer head of the flexor brevis pollicis) and the two radial lumbricals. Stated briefly the symptoms are: inability to flex the phalanges of the index finger and the second phalanx of the thumb; difficulty in flexing the phalanges of the middle finger; defective opposition of the thumb. The appearance of the hand in total lesions is fairly constant. The hand inclines to the ulnar side, the index and middle fingers are more extended than is normal, and the thumb lies on a level with the fingers—the ape-hand.

**Pronation** is incomplete and defective. The patient tries to overcome the defect by rotating the whole limb at the shoulder. Paralysis of the *flexors of the wrist* is seen when an attempt is made to flex against resistance. The tendon of the ulnar flexor alone stands out, and the hand is drawn towards the ulnar side. Even at rest, the flexor tendons are more prominent on the sound than on the affected side.

**Flexion of the fingers** is good in the two ulnar fingers, though weaker than normal. The index cannot be flexed at all, and the third finger only incompletely. Flexion at the proximal joint is usually good in all the fingers including the index, and flexion at this joint with extension at the last two joints is usually well done by the interossei and lumbricals. If the proximal phalanx of the thumb is immobilised, it will be seen that flexion of the terminal phalanx is abolished, owing to paralysis of the *flexor longus pollicis*.

Paralysis of the *thenar muscles* renders opposition and abduction of the thumb defective. By means of the adductor the thumb can be drawn into the palm, but as the radial fingers cannot be flexed nor the thumb opposed, it is impossible to place the tip of the thumb on the tips of the fingers. Atrophy of the muscles becomes obvious in a few weeks. The outer part of the thenar eminence is flattened, and the bulk of the muscles arising from the internal condyle is greatly diminished.

*Sensory disturbances.*—In almost every case there is complete anæsthesia to all forms of sensation in the two terminal phalanges of the index and middle fingers. The skin outside this area may be unaffected even in complete lesions, but in most cases sensibility is diminished in the terminal phalanx of the thumb, and to a less extent over the remainder of the radial half of the palm, including the radial side of the ring finger. The stereognostic sense is lost in the outer fingers. This defect, together with the loss of power, renders the thumb and index finger useless, and makes paralysis of the median the most serious single nerve lesion of the upper limb.

*Vasomotor and trophic changes.*—In many cases the skin in the distribution of the median nerve is red, dry and chapped, and the nails white or purple, and atrophy occurs in the pulp of the affected fingers.

*Recovery* is slow and is rarely complete. Sensation begins to return before power, but the stereognostic sense is often defective, long after movement in the fingers has returned. The pronator and the flexors of the wrist recover first, then the flexors of the thumb and middle finger. Flexion of the index finger and opposition of the thumb, if it is regained at all, remains defective for several years. In searching for signs of recovery, care must be taken lest some "trick-movement", due to contractions of healthy muscles, is misconstrued. For example, when told to flex the terminal phalanx of the thumb, the patient first over-extends and abducts, and then relaxes suddenly. The terminal phalanx then makes a slight passive movement of flexion, which may be mistaken for true active flexion. Recovery is complete when the patient is able to make a good fist with the fingers flexed well into the palm, and the thumb pressed firmly upon the dorsal aspect of the second phalanx of the middle finger.

*PARTIAL LESIONS.*—Partial paralysis of the median nerve is much commoner than the complete form.

*Motor symptoms.*—Flexion of the index finger and opposition of the thumb are most impaired. The flexors of the middle finger and of the terminal phalanx of the thumb may suffer also, but to a less degree, whilst the pronators and the flexors of the wrist often escape entirely.

*Sensory symptoms.*—Apart from the painful lesions to be mentioned later, sensory troubles are usually slight in partial lesions. Anæsthesia is rare, but sensibility to all forms may be diminished in the areas mentioned under complete lesions.

*Vasomotor symptoms.*—The skin is often cyanosed in the distribution of the injured nerve, and it may perspire more freely than in healthy parts. These changes are more distinct when the paralysis is complicated by a vascular lesion.

*Recovery* is naturally more rapid than in complete lesions. The order in which the muscles recover and the tests for complete return of function have been mentioned above.

*PAINFUL LESIONS OF THE MEDIAN NERVE.*—*Causalgia.*—In many cases the most prominent symptom of injury causing an incomplete lesion of the median nerve is pain. It comes on about a month after the injury, at first as tingling or pricking in the finger-tips and palm, later as a constant severe smarting, dragging or burning pain—hence the name causalgia. Added to the constant pain, which never ceases day or night, paroxysms occur, in which the pain increases suddenly in intensity. The application of cold water gives temporary relief, and patients often wear bandages or gloves which they keep constantly moistened. The pain is greatly aggravated by emotional influences.

*Vasomotor changes* are a feature of this type. In many cases perspiration is diminished over the radial half of the palm, and the skin becomes dry and scaly. In others, perspiration is increased over the median area.

*Motor disturbances* are always present, but are usually slight, the weakness affecting mainly the flexors of the index finger and the thenar muscles.

In severe cases the limb is held flexed at the elbow and wrist, with the hand



constantly raised and the fingers extended or hyper-extended. The whole hand atrophies, and irreducible ankylosis occurs with the limb in this position. The skin of the hand is thin and dry. The fingers taper, and the nails are long, brittle, blackened and striated longitudinally. The pain reaches its acme 4 or 5 months after the injury, and then slowly declines, but the limb remains useless. Even in slighter cases, without much deformity, recovery of function is extremely slow, and is rarely complete. The condition is often much improved by early operation and neurolysis of the nerve, or relief may be gained by sympathectomy.

**THE CARPAL TUNNEL SYNDROME.**—The median nerve may be compressed at the wrist as it passes through its tunnel in the transverse carpal ligament. The condition is common in middle life in women engaged in housework, laundrywork and other manual labour, and also at an earlier age in women who have young children. The chief complaint is of pain or numbness in the middle three fingers but frequently discomfort is complained of also in the forearm, and this occurs particularly at night. Pressure at the carpal tunnel is thus one of the causes of acroparæsthesia. In the more severe cases wasting of the upper part of the thenar eminence may be observed and some sensory impairment may be found over the affected fingers. At operation the median nerve is found compressed in its tunnel and swollen for a short distance proximal to its entry into the carpal ligament. Opening up the tunnel relieves the symptoms. In occasional cases some weakness of the fingers results in consequence of the failure of the weakened carpal ligament to retain the flexor tendons in their normal position.

#### THE ULNAR NERVE

This nerve supplies the ulnar flexor of the wrist, the ulnar half of the deep flexor of the fingers, the muscles of the hypothenar eminence, the interossei, the two inner lumbricals and the adductor and inner head of the short flexor of the thumb. Its sensory area is the ulnar border of the hand, the little finger and the inner half of the ring finger.

**TOTAL PARALYSIS.**—Paralysis of the *flexor carpi ulnaris* may be detected by palpating the tendons when the wrists are flexed against resistance. The limpness on the affected side contrasts strongly with the firmness on the sound side. Lateral movements of the hand are unaffected, as these are carried out by the extensors.

Paralysis of the ulnar portion of the *flexor profundus digitorum*. In making a fist, flexion of the index finger is perfect and that of the middle finger good, whilst in the ring and little finger it is absent or very feeble. This weakness is best seen when flexion is attempted with the index and middle fingers extended. Even when the fingers can be flexed by the action of the flexor sublimis, the power of resisting passive extension is completely lost in the terminal phalanx of the two ulnar fingers. Paralysis of the *hypothenar* muscles abolishes lateral movements of the little finger, and diminishes the power of flexion at the proximal joint. Paralysis of the interossei and of the inner two lumbricals leads to the production of the "claw-hand".

The action of these muscles is to flex the fingers at the proximal joints with the distal joints extended. In the "claw-hand" the posture of the fingers is just the opposite of this, namely, extension at the proximal joint with flexion of the distal joints. Although all the interossei are paralysed, the defect is seen only in the ulnar fingers, as the radial lumbricals supplied by the median are still healthy. It is produced by the action of the long extensors, which being now unopposed, over-extend the proximal joints, and by the flexor sublimis which flexes the second joint and draws the distal joint down with it. The clawing of the fingers is greatly accentuated when the nerve is paralysed below the point of origin of the fibres to the long flexors of the fingers. Other features of the "ulnar hand" are atrophy of the interossei and of the hypothenar eminence, and persistent abduction of the little and ring fingers.

The movements of abduction and adduction are lost in the inner two fingers, and often in the middle finger. Further, these fingers cannot be flexed at the distal joint, whilst the proximal joints are extended.

Paralysis of the *adductor pollicis* and of the inner head of the *flexor brevis pollicis* produces peculiar disturbances in prehensile movements. If the patient is asked to grasp a folded paper between his thumb and index finger, and to resist efforts to remove it by pulling, it will be found that this movement, which is normally very powerful, is grossly defective. He cannot grasp the object beneath the thumb with the second phalanx extended; but presses the tip of the flexed thumb against the outer margin of the index finger.

*Sensory disturbances.*—In complete lesions, all forms of sensation are abolished in the little finger, and along the ulnar border of the hand. Beyond this there is usually diminished sensibility on the ulnar side of the ring finger, and over a narrow area towards the centre of the hand on both aspects. Spontaneous pains are rare, and vasomotor changes are usually slight.

*PARTIAL PARALYSIS.*—In partial lesions the same symptoms are found in a less degree. The small muscles of the hand suffer most. Clawing may be slight or absent. Neuralgic pains may be felt in the distribution of the ulnar nerve; but *causalgia* is never seen in lesions of this nerve alone.

*Recovery* of sensation is usually complete before movement is regained. The *flexor carpi ulnaris* recovers first, then the long flexors of the fingers and last the small muscles of the hand. In these recovery is extremely slow. When recovery of movement is complete the patient can abduct and adduct the middle finger with the palm flat on a table, and he can also scratch the table with the nail of the little finger without moving his wrist.

#### THE MUSCULO-CUTANEOUS NERVE

This is rarely affected alone, but is often implicated with the brachial plexus. It supplies the biceps, coraco-brachialis and brachialis. Flexion of the forearm can still be carried out by the *brachio-radialis*; but the power of flexion is greatly diminished. Sensation may be diminished or lost along the radial border of the forearm.

#### THE AXILLARY NERVE

This nerve supplies the deltoid and *teres minor*, and the skin over the deltoid. It may be injured alone in injuries of the shoulder and by pressure of a crutch. The chief symptom is paralysis of the deltoid with almost complete inability to raise the arm.

In war injuries lesions of the nerves of the lower limb are very frequent; but in civil practice, apart from sciatica and foot-drop, local lesions of these nerves are uncommon.

#### THE LUMBO-SACRAL PLEXUS

The *lumbar plexus* may be damaged by abdominal tumours, and its roots by new-growth or other disease of the vertebrae. In a certain number of cases signs of inflammation of the lumbar plexus are found in association with sciatica or neuritis of the *sacral plexus*.

The *sacral plexus* may be damaged by growths or inflammation in the pelvis, by compression during parturition, and by penetrating missiles. It is also often the seat of spontaneous neuritis.

FEMORAL NERVE ( $L_2, L_3, L_4$ )

This is the largest branch of the lumbar plexus. It supplies the iliacus, pectineus, sartorius and quadriceps femoris. It may be injured alone by fractures of the pelvis or of the femur, by dislocations of the hip, or by implication in wounds, psoas abscesses or new-growths.

The most prominent symptoms are loss of power to extend the knee, loss of the knee-jerk, wasting of the quadriceps and sensory disturbances over the anterior surface of the thigh and inner surface of the leg. The psoas always escapes, unless the plexus itself is also damaged; but flexion at the hip may be imperfect through paralysis of the iliacus. Owing to the rapid dispersion of the branches in the thigh, wounds in this part often cause partial lesions. In these the *nerve to the quadriceps* is most often injured. The resulting paralysis causes serious disability in walking as the knee gives way at every step, especially in going down stairs, and lameness lasts for a long time after return of voluntary movement.

OBTURATOR NERVE ( $L_2, L_3, L_4$ )

This nerve is rarely damaged alone. It supplies the three adductor muscles, the obturator externus and the gracilis. The symptoms are weakness of adduction and internal rotation at the hip.

LATERAL FEMORAL CUTANEOUS NERVE ( $L_2, L_3$ )

This nerve supplies an area of skin on the antero-lateral aspect of the thigh. As a result of injury, but more often without obvious cause, the skin in the territory of this nerve may show peculiar sensory disturbances, which have been described under the name of *meralgia paræsthetica*. Most cases occur in men. In women it is usually associated with pregnancy. The nerve is tender on pressure at the point where it passes from under Poupert's ligament, and neuralgic pain or numbness and tingling is felt in the skin, which may be slightly insensitive on objective examination or extremely hyperæsthetic, so that the slightest touch causes pain. The symptoms, which are always unilateral, are made worse by walking, and may cause serious incapacity by their persistence and severity. In severe cases the nerve should be excised.

THE SCIATIC NERVE ( $L_4, L_5, S_1, S_2, S_3$ )

This supplies the flexors of the leg and all the muscles below the knee. It may be involved in pelvic new-growths, or injured by fractures of the pelvis or femur. Next to the radial and ulnar it suffers in gunshot wounds more often than any other nerve.

**TOTAL PARALYSIS.**—The foot drops, and the toes point downwards. Walking is possible, but the patient cannot stand on the heel or toes of the paralysed foot. The knee is raised high, but the stepage is not so marked in total lesions as when the common peroneal alone is paralysed. All movement below the knee is abolished. When the wound is in the buttocks, flexion of the knee is very weak. The foot becomes œdematous if allowed to hang down. Sweating is often absent on the sole and dorsum of the foot, but is normal on the inner side of the foot, which is supplied by the femoral. The skin is dry and thin, and may be scaly. Hyperkeratosis of the sole is common. Subjective sensibility is rarely affected. The skin is completely anæsthetic over the entire foot, except the inner border of the sole and around the internal malleolus. The anæsthesia extends upwards on the postero-external aspect of the calf in its lower two-thirds, embracing the tendo Achillis and external malleolus. Beyond this area of complete anæsthesia there is a wide zone in which sensibility is diminished. The sense of position and passive movement is abolished in the foot and toes. The knee-jerk is present. The ankle-jerk is always lost.

**PARTIAL PARALYSIS.**—In wounds of the sciatic nerve it often happens that the fibres of the common peroneal alone are wounded, since the sciatic trunk often divides into the tibial and common peroneal branches as high as the great sciatic notch. The symptoms are described below under paralysis of these nerves. In other cases, the fibres of the tibial nerve are damaged either alone, or with some of the fibres of the common peroneal. In this case the outstanding clinical features are paralysis of the muscles of the calf and foot, anæsthesia of the sole and, with incomplete lesions, pain similar to that described in partial lesions of the median nerve.

#### COMMON PERONEAL NERVE

This nerve may be injured as it winds round the fibula by wounds or fractures or by compression of a tight bandage. The paralysis is usually severe, all the muscles being equally affected. The foot is dropped and inverted, and the toes are slightly flexed. Dorsiflexion of the foot, extension of the proximal phalanges of the toes and abduction of the foot are impossible. The patient can walk, and he can stand on tiptoe, but he cannot run, and walking is made difficult by the foot-drop. Subjective sensory disturbances are usually absent. The skin is anæsthetic over a narrow band which extends from the outer surface of the leg in its middle third, downwards beside the outer border of the tibia, and along the middle of the dorsal aspect of the foot as far as the base of the toes. For an inch or so, on both sides of this band, the sensibility of the skin is diminished. The knee-jerk and ankle-jerk are present. The plantar response is always flexor. Vasomotor changes are slight, and trophic changes are absent.

#### TIBIAL NERVE

This nerve is rarely injured alone. It supplies the popliteus, the calf muscles, the flexors of the toes and the intrinsic muscles of the foot. When it is paralysed, the patient is unable to stand on tiptoe, or to extend or invert the ankle, or to flex his toes. Paralysis of the interossei leads to a claw-like deformity of the foot, associated with lowering of the heel and raising of the metatarsus—talipes calcaneo-valgus. The calf muscles are flabby and the ankle-jerk is abolished. Sensation is lost on the sole, except along its inner border, on the outer border of the foot and on the plantar surface of the toes. Causalgia, similar to that in paralysis of the median, is very often present.

The distal portion of the tibial nerve may be injured by a penetrating missile or a deep wound in the calf. Movements of the ankle are unaffected and anæsthesia is confined to the sole of the foot and heel, or merely to its inner half. The paralysis of the intrinsic muscles of the foot may escape detection, and the lesion may easily be overlooked, especially when the nerve is injured below the origin of branches supplying the flexor longus hallucis and the flexor longus digitorum. The symptoms then are pain in the sole of the foot, anæsthesia on the sole and paralysis of the plantar muscles.

**Treatment of Local Nerve Lesions.**—Treatment must depend on the nature and degree of the lesion. During the long period which elapses between the onset of paralysis and the first signs of recovery, even in cases of simple physiological interruption of the nerves, every effort must be made to prevent degeneration of the muscles, to keep the circulation of the limb active, and to prevent the occurrence of contractures and deformities. Massage, movements, electrotherapy and suitable appliances all have their uses. With regard to operative treatment, it must be remembered that more than half the cases of nerve injuries undergo spontaneous cure. It is advisable, therefore, to wait 3 or 4 months before an operation is undertaken. If, at the end of this time, the wound is soundly healed and all signs of sepsis have

disappeared, and if, as a result of repeated examinations, no sign of recovery has been detected, no harm can be done by exposing the nerve. If it is found to be divided completely, the ends should be "freshened" and sutured end to end. If the nerve is notched laterally, the edges of the notch should be pared and sutured, care being taken to preserve the bridge of uninjured tissue. Sometimes the nerve at the site of the lesion appears as a fibrous, flattened band between two swellings on the nerve. In most of such cases the nerve is completely divided, and the condition calls for resection of this fibrous tissue and end-to-end suture. Another common finding, when the nerve is exposed, is a nodule or cicatricial swelling in the course of a nerve which has maintained its continuity. In these cases the continuity of the nerve should not be interrupted. It should be freed from adhesions, and incised in the long axis of the swelling. Operations which involve grafting of nerves have met with little success. For an account of the advances in the technique of the surgical treatment of nerve injuries which have been made as a result of experience gained in the Wars of 1914-1918 and 1939-1945, special treatises must be consulted.

The treatment of painful forms of nerve lesions is extremely difficult. In severe cases external applications and internal medication entirely fail. Simple freeing of the nerve sometimes gives relief. Where this fails, it may be advisable to practise complete division followed by immediate suture. In other instances sympathectomy, by excision of the stellate ganglion in the case of the upper limb and of two or more of the lumbar sympathetic ganglia in the case of the lower limb, may give lasting relief.

## INTERSTITIAL NEURITIS

**Synonym.**—Neuro-fibrositis.

**Definition.**—A painful malady which commonly attacks the large nerve plexuses or nerve trunks but which may affect any peripheral nerve, and is believed to be due to inflammation of the interstitial connective tissues which surround and bind together the nerve fibres into the nerve trunks.

**Ætiology.**—It is in general a malady of middle life, being unknown in childhood and uncommon in old age. It is often associated with other forms of fibrositis and especially with arthritis, *e.g.* the brachial nerves being affected in some cases of arthritis of the shoulder and the sciatic nerve in certain cases of arthritis of the hip. Injury involving stretching, bruising or wounding of a nerve trunk may produce it, but it is necessary to bear in mind that pain following an injury, even after a long interval, may be the result of the rupture of an intervertebral disk which has been injured at the same time. Gout, diabetes and chronic nephritis are well known clinical associations of interstitial neuritis.

**Symptoms.**—These are those of irritation of the nerve fibres. Pain is usually the outstanding feature. It radiates in the area of distribution of the affected nerve, *is of a dull, aching character, with acute exacerbations and is often very long-lasting* and wearing to the patient. The affected nerve is tender to pressure and stretching. Subjective peripheral sensations, such as tingling, burning or numbness, are usual and are often the first symptoms. There is marked hypotonus of the muscles of the affected limb, followed by a degree of general wasting, not confined to the muscles supplied by the affected nerve, but resembling arthritic muscular atrophy. Fibrillation sometimes occurs and cramps are common. The deep reflexes of the limb are increased. Trophic and vasomotor changes are not infrequent.

**Diagnosis.**—There is often considerable difficulty in the diagnosis of interstitial neuritis on account of the almost identical clinical picture which may occur in the early stages of pressure upon nerve roots or nerves by tumours, or as a consequence of the irritation of one or more nerve roots by the extruded nucleus of a ruptured

intervertebral disk. The special problems of the sciatic nerve are discussed under the heading of sciatica, but the following points are of value in distinguishing in general between interstitial neuritis and the effects of pressure on nerves. With pressure lesions the pain is rarely so severe as that of interstitial neuritis, tenderness on pressure of the nerve trunks is absent and signs of loss of function—paralysis and sensory loss—come on early. The most careful search should be made in every case for any possible cause of local pressure, such as primary and secondary neoplasms, vertebral and spinal tumours and spinal caries. To make a diagnosis of interstitial neuritis in the presence of a mammary or other carcinoma, or after its removal, is to advocate the highly improbable, whatever the symptoms may be.

**Treatment.**—The details of treatment vary according to the site of the nerve or nerves affected, but the general principles are to secure rest and to avoid all those things which excite or increase the pain. In most cases warmth in all forms has a beneficial and comforting effect; the part should be kept warmly clad, but if special applications, such as radiant heat or infra-red rays, excite pain they should not be persisted with. Salicylates and all the analgesics of the coal-tar series are valuable aids. In the acute stage, morphine preparations may be required to obtain sleep for the patient, but later, combinations of aspirin with barbiturate hypnotics suffice.

#### CERVICO-OCCIPITAL NEURITIS

This condition, which is by no means rare, is characterised by pain in the upper part of one side of the neck, radiating over the branches of the upper cervical plexus, the great auricular being the most common, and the supra-sternal, supra-clavicular and supra-acromial branches less common seats for the pain. The fibrositis not infrequently co-involves the fibrous structures in the region of the articular and transverse processes, giving rise to pain and stiffness of the neck on movement. When the pain is confined to the great occipital distribution alcohol injection is sometimes most efficacious.

#### BRACHIAL NEURITIS

Two varieties of neuritis affect the brachial plexus and its branches, namely, a paralytic variety and a non-paralytic, the latter being one of the forms of interstitial neuritis.

##### PARALYTIC BRACHIAL NEURITIS

This variety, rare before 1939, has been common in England during recent years, and occurred not infrequently in the armies abroad. The cause of the condition is unknown, but the course of the malady resembles that of an infective disease, and in many cases the onset of the neuritis has occurred while the patients were in hospital suffering from an infectious illness of the respiratory or alimentary system.

**Symptoms.**—Severe pain in the shoulder or side of the neck, radiating down the arm is usually the first symptom, but in a few cases no significant pain occurs. In the more severe cases general malaise accompanies the onset. After a few days paralysis is noticed, affecting, as a rule, some of the more proximal muscles innervated from the brachial plexus. Paralysis of the serratus anterior, with consequent winging of the scapula, is especially frequent, and if the patient is in bed because of other symptoms, this disability may escape notice until he is up and about again, and begins to use the arm of the affected side. If the paralysis affects the muscles of the upper arm, wasting is soon evident. All the tendon-jerks of the affected arm or of both

arms may be abolished. Tenderness is present over the brachial plexus and may persist for several weeks. Sensory loss is, as a rule, slight or absent. The cerebrospinal fluid is usually normal.

**Differential Diagnosis.**—This malady, as a rule, only requires to be known about to be recognised, but in subjects of military age or younger the diagnosis has to be made from poliomyelitis. In the latter, the onset is more abrupt and in adults is accompanied by a greater degree of malaise and fever, stiffness of the neck is usual and Kernig's sign may be present; the cerebrospinal fluid contains a considerable excess of lymphocytes, followed by a gradual rise of protein during the weeks succeeding the onset of the paralysis. The paralysis tends to have a segmental distribution, whereas in the case of brachial neuritis it has much more tendency to be limited to the muscles supplied by one or two individual nerves.

**Course and Prognosis.**—In this variety of brachial neuritis the pain usually passes off within a few days and sensory loss, if any, is soon recovered from, but the outlook as regards recovery of the muscular paralysis is always doubtful, and if such occurs, it takes many months.

**Treatment.**—The cause of the disease being unknown, treatment can only be on general principles. Analgesics are given for the relief of pain, and the affected limb is supported in such a position as to relax the paralysed muscles. Preparations of vitamin B are often exhibited, but it is doubtful whether they are of any value in aiding the recovery of the affected nerves in this disease.

#### INTERSTITIAL BRACHIAL NEURITIS

**Ætiology.**—This variety of brachial neuritis is somewhat uncommon, and is met with chiefly in patients over the age of 40. It often arises spontaneously, but is frequently associated with arthritis in the shoulder or neck, and it may follow injury to the brachial plexus from any violence causing undue separation of the head and the shoulder.

**Symptoms.**—Brachial neuritis of this variety has the general characters of interstitial neuritis. The pain, which is often of abrupt onset, may be of great severity and may be at first referred to the region of the plexus itself, the back of the scapula, the axilla, the forearm or the hand. Whatever its site, the pain is at first intermittent, but it soon becomes continuous and spreads over the whole upper limb. Tingling and numbness in the hand, and trophic changes in the skin and finger-nails are the rule. With minimal degrees of this form of brachial neuritis, tingling in the hand in the morning is a common symptom.

**Diagnosis.**—It may be impossible to make the diagnosis from brachial pain due to protrusion of one of the intervertebral disks in the lower cervical region (*vide infra*). Other conditions likely to cause confusion are arthritis of the shoulder and cervical rib, but in neither of these conditions is there tenderness of the nerve trunks or of the plexus.

**Treatment.**—One of the great difficulties in this malady is that in the upright position the weight of the arm and shoulder carries the latter downwards, and so stretches the inflamed plexus, adding greatly to the pain. The patient, therefore, should be kept in bed and in general on his back. Further, every movement of the hand or arm tends to increase the pain, and splints which keep the arm in the abducted position and the shoulder raised so as to prevent tension upon the plexus are invaluable.

#### BRACHIAL PAIN DUE TO A PROTRUDING INTERVERTEBRAL DISK

In a considerable number of cases brachial pain which would in the past have been diagnosed with confidence as due to brachial neuritis is, in fact, the result of irritation of one or more cervical nerve roots by a displaced intervertebral disk.

In such cases the onset of pain is usually sudden, and often follows forceful movement of the neck or prolonged strain on the cervical muscles with the head partially rotated, as may occur in supporting a heavy weight.

The pain is usually described as being intense in severity, and is felt across the base of the neck and between the shoulder blades, and is usually worse on one side. It is aggravated by movement or jarring of the neck or by straining.

After a few days the cervical pain usually abates somewhat in severity but pain extends down the arm to the digits on one or other side of the hand.

When examined, the patient is found to have considerable limitation of movement of the neck, and may show severe signs of a radicular lesion in the arm in the form of muscular wasting or weakness, sensory impairment and diminished reflexes. The root most commonly affected is the sixth cervical and the patient's chief complaint is of pain in the arm and pain, tingling and numbness in the index finger and to a less degree in the thumb; on examination some sensory impairment is found over the index finger and the triceps jerk is diminished or lost, and, after a time, some diminution of the muscles of the forearm is apparent on comparison with the normal limb.

Such cases usually recover gradually with symptomatic treatment but some stiffness of the neck may remain. Recovery can often be greatly accelerated by manipulation of the neck combined with axial traction, which should only be carried out by an expert in manipulative methods.

## CERVICAL RIBS

**Ætiology.**—The development of the ribs at the thoracic inlet depends on the mode of formation of the brachial plexus, for the nerves are large structures in the embryo at a time when the ribs are soft and pliable. When the plexus is "normal", a well-formed first rib springs from the first dorsal vertebra. If, however, the plexus is "post-fixed", that is, when the contribution to the plexus from the fourth and fifth cervical segments is small and the fibres from the first and second dorsal segments form a powerful cord, this cord in rising over the first dorsal rib may compress and deform it to such an extent that it presents the characters of a rudimentary rib. On the other hand, and this is more frequent, when the plexus is pre-fixed, that is, when the contribution from the upper cervical segments is relatively large and that from the dorsal segments is small, a supernumerary rib is allowed to develop from the seventh cervical vertebra. When this pre-fixation is pronounced, the seventh cervical rib is often very large and is easily felt in the neck, and in these cases symptoms are usually absent. In a certain number of cases in which the abnormality is intermediate in degree, symptoms are caused by compression of the lower cord of the plexus as it passes over the supernumerary rib, or over the deformed first rib. This compression may be exercised by the bony portion of the extra rib, but more often the nerves are damaged by a fibrous prolongation of the rudimentary rib which connects it with the first rib.

But these abnormalities in the ribs only cause symptoms in some 10 per cent. of the cases in which they are present. Further, the symptoms are often unilateral with bilateral supernumerary ribs, and the symptoms are often most prominent on the side of the smaller extra rib. Again, the onset of symptoms is usually delayed until adult life is reached. It is clear, therefore, that some contributory cause must come into play. This is found in the dropping of the shoulder girdle, which is normal in adolescents, and is often excessive in persons whose muscular tone is low. In a child the clavicle rises boldly as it passes outwards. In a normal adult male the clavicle is almost horizontal, in women it droops slightly, and in those who develop symptoms of pressure on the nerves, the outer is usually distinctly lower than the inner end.



In the latter, the lowest cord of the plexus is submitted to constant rubbing against the extra rib which rises and falls during respiration, and it is compressed by any movement of the arm which depresses the shoulder girdle. Relief is obtained by raising the shoulders, and patients soon learn to support the limb and to assume attitudes in which pressure on the nerves is relieved.

Women suffer most often, the right arm being affected more often than the left. The onset is usually gradual, but occasionally it comes on suddenly after childbirth, or on lifting a heavy weight.

**Symptoms.**—These may be sensory, motor or vasomotor, either singly or in combination. Subjective sensory disturbances are most frequent. They take the form of numbness and tingling or neuralgic pains. *Paræsthesiæ* are most often unilateral, and are frequently confined to the ulnar or to the radial side of the hand and fingers. It is rare for all the fingers to be affected. Pain, when present, is usually felt below the elbow. It is often neuralgic, darting down the arm and again confining itself to one border of the limb. It hardly ever radiates from the neck.

Objective sensory disturbances are usually slight or absent. They may be found over the ulnar or radial border of the distal portion of the limb in an indefinite area, which does not conform to the distribution either of the ulnar or radial nerve.

Muscular atrophy is not so frequent as subjective sensory disturbance. In the "median type", wasting is confined at first to the abductor and opponens pollicis muscles, and the outer part of the thenar eminence shows a remarkable reduction in size, which contrasts strongly with the inner part, which retains its normal bulk. In the "ulnar type", wasting appears first in the small muscles of the hand supplied by the ulnar nerve. In some cases all the muscles of the hand and, to a less degree, the flexors in the forearm show considerable wasting. The atrophy is frequently bilateral and symmetrical.

Vasomotor disturbances are very common. The hands feel hot or cold, they may be œdematous or discoloured and the changes may suggest Raynaud's disease. Pressure on the subclavian artery sometimes causes inequality of the pulse, and the pulse on the affected side may be obliterated by depression of the shoulder. The inequality disappears when the arm is raised.

**Diagnosis.**—The presence of pain, *paræsthesiæ* or vasomotor disturbances in the upper limbs, or wasting in the muscles of the hands, should always arouse the suspicion of supernumerary or rudimentary ribs. When pain is the only symptom, its distribution along one border of the arm or hand, and the patient's account of the manner in which it may be increased or diminished by raising the shoulder girdle or performing movements which depress it, usually direct attention to the cause. Symmetrical atrophy in the hands may suggest progressive muscular atrophy of spinal origin, but this diagnosis is usually rendered untenable by the association of sensory troubles or vasomotor phenomena, or by the findings on radiographic examination of the neck. For the differential diagnosis from syringomyelia, see p. 1547. Symptoms indistinguishable from those which commonly result from the presence of a cervical rib occur in a small number of patients in whom no cervical rib is present. In most cases of this kind, the patients have very sloping shoulders, and the symptoms are believed to be due to compression of the roots of the brachial plexus between the fibre-bundles of the scalenus anterior muscle. In other cases, either because of the lowness of the clavicle or because the first rib is unduly high, the subclavian artery is compressed between these two bones, when the corresponding arm hangs down or when it is raised and abducted. Obliteration of the circulation causes a numbness in the hand and forearm, which comes and goes according to the posture of the arm. The numbness may become persistent because of thrombosis at the site of compression, and the patient may first come for advice when this has occurred. Aneurysm is another occasional consequence of the damage to the artery.

**Treatment.**—Pain may be relieved by rest with the arms suitably supported.

Atrophy calls for operation to remove the offending rib. Pain is always relieved by operation, either immediately or after an interval of some months. The progress of atrophy is always retarded, and complete recovery may occur if an operation is undertaken early.

### ACROPARÆSTHESIA

**Definition.**—Acroparæsthesia is the name given to a syndrome of uncomfortable tingling in the extremities without demonstrable sensory loss or other abnormal physical signs.

**Ætiology.**—It is unusual for all four limbs to be affected; acroparæsthesia in the arms is much commoner than that in the legs. In the arms it is almost limited to women, whereas in the legs it is much commoner in men. There seems to be an hereditary element in its causation. As first described it was associated with arthritis and it seems to be commoner in arthritic subjects, but both maladies occur in the same age group. In both sexes the condition usually comes on in middle life, but it also occurs in younger women during pregnancy.

**Symptoms.**—The tingling may be present at all times, but it occurs above all during the night and wakens the sufferer from sleep; some patients complain of the inability to sleep as much as of the discomfort. The tingling is in some way due to the use of the limbs during the day in vigorous work, or in continuous standing or car-driving, and if the patient rests throughout the day he or she is, as a rule, soon relieved of his nocturnal symptoms. Many of the patients are middle-aged women who have been compelled to do vigorous housework to which they have not been accustomed from youth. In general, warmth aggravates the tingling and the sufferer who is awakened in the night puts the affected limbs outside the bedclothes. In the less severe cases the symptoms are worst during the early part of the night and after a number of hours of broken sleep the patient is able to sleep without interruption for the rest of the night. In other cases the symptoms continue throughout the night and are still present in the morning; then the hands may appear, or may feel, swollen, and the patients complain of awkwardness of the fingers, but impairment of postural or other sensation can rarely be demonstrated.

The symptoms are subject to long remissions, but the liability to them is not often completely lost.

**Diagnosis.**—There are no objective signs of nervous or vascular disease. The most careful examination must be made to exclude such causes of paræsthesiæ as sub-acute combined degeneration and early polyneuritis (e.g. diabetic or lead). If the tingling is limited to a part of the hand it may be due to compression of the median nerve in the carpal tunnel, or to disturbance of the ulnar nerve, or to compression of a nerve root by an intervertebral disk. Slight wasting of muscles may give a clue to the presence of some organic disease. The state of the pulses in the affected limbs may suggest the presence of a vascular disturbance to which the symptoms are attributable.

**Treatment.**—As has been stated, the tingling, as a rule, ceases if the patient does no work, but social circumstances rarely make continued leisure possible; the patient may, however, be able to find more suitable employment or to make changes in his or her habits of work, or a holiday, particularly with sea-bathing, may initiate a remission. Sponging the affected limbs with cool water once or twice in the day and possibly at night gives considerable relief in most cases. The combination of aspirin gr. 10 with phenobarbitone or other hypnotic, taken at bedtime, enables the patient to sleep.

### SCIATICA

The term "sciatica" is applied in a somewhat imprecise manner to conditions in which pain is experienced along the course and in the distribution of the sciatic

nerve—that is to say, in the buttock, back of the thigh, outer side and back of the leg and the outer border of the foot. It is important at the outset to notice the limitations of this distribution and, in particular, to notice that the sciatic nerve does not supply any structures on the front of the thigh, and so pain in that region or in the groin is not included in sciatica.

Cases of sciatica as thus defined are common, and many of them have a prolonged course and other well-described features. Until recent years they were all confidently attributed to interstitial neuritis (sciatic neuritis) but it is now recognised that, while a number are probably due to this cause, many are the result of irritation of one of the roots of the great sciatic nerve by the extruded nucleus of a ruptured intervertebral disk, and others are cases of referred pain in the sciatic distribution. The differential diagnosis between these different varieties of sciatica is frequently a matter of great difficulty, and in fact in many cases it cannot as yet be made with confidence.

#### SCIATICA DUE TO PROTRUDING INTERVERTEBRAL DISK

Sciatica is the syndrome to which herniation of the nucleus pulposus of a lumbar intervertebral disk most commonly gives rise.

**Ætiology.**—The majority of cases give a history of injury at, or shortly before, the onset of symptoms. The injury is commonly of the variety known as a strain of the back, due to sudden bending, the lifting of heavy weights or sudden movements of the back, as when striving to avoid a fall. Males are more commonly affected. In females, childbirth, especially with instrumental delivery, is an additional cause.

**Pathology.**—Formerly the condition under discussion was one recognised on laminectomy, and spoken of as endochondroma of the disk. Actually in the circumstances enumerated above, the disk ruptures and its nucleus (nucleus pulposus) subsequently herniates into the vertebral canal. The commonest site of such a lesion is in the lumbar spine, below the termination of the spinal cord, and the extruded mass causes irritation and compression of one or more of the roots of the cauda equina. The disk most frequently ruptured is that between the fifth lumbar vertebra and the sacrum (fifth lumbar disk), and the spinal root affected is the first sacral. The fourth lumbar disk is also commonly ruptured and the third lumbar occasionally so. The rupture of higher lumbar intervertebral disks is infrequent. In each case the spinal root most affected is that emerging just below the site of the lesion, *e.g.* the fifth lumbar root when the fourth lumbar disk is ruptured and so on. Multiple ruptures are not very uncommon.

**Symptoms.**—The outstanding feature is pain. It begins in the small of the back either at the time of the injury or after an interval of some hours, days or weeks. It may remain limited to the back, but in most cases it extends, after a variable interval, down the back of one thigh, and then down into the leg and possibly into the foot, so that the clinical condition becomes one of “sciatica”. The exact distribution of the pain in the leg depends on which spinal root is affected (*vide infra*). The pain is severe and lancinating, aggravated by stooping, by coughing and sneezing, and by turning in bed, and relieved by lying still. Flexion of the extended leg at the hip is always painful (Lesègue’s sign), and the patient adopts an attitude of partial flexion of the affected limb at the knee and hip, which avoids tension on the sciatic nerve and its roots.

The objective physical signs fall into two groups, namely, (1) those referable to the spine, and (2) those due to impairment of function in the affected nerve-root or roots. The lumbar spine is flattened and is tilted at the site of the lesion; the tilt is usually away from the side of the sciatic pain but may be towards it and in some cases the tilt alternates. Radiographic examination reveals the flattening of the lumbar curve and the tilting more clearly, and it may show a suggestive reduction of one intervertebral space but this is not usual. The nervous signs are in general those

of impairment of function of a single spinal root. Most commonly the first sacral root is the one involved, and the signs which develop are as follows: The ankle-jerk is abolished. The muscles of the calf and the peronei become slightly wasted, and the change in outline is apparent when the two legs are compared with the patient standing up or lying prone. The power of flexion of the small toes is diminished. The glutei on the affected side are flattened. Sensation is impaired along the outer border of the foot and on the outer half of the sole, and the patient has a sensation of numbness or tingling in this area. The impairment of sensation may be a loss or weakening of pain appreciation, and loss of tickle on the affected area of the sole, or a loss of light touch appreciation, or a loss of sense of position of the small toe, or all of these combined. When the fourth lumbar disk is ruptured and the fifth lumbar root is consequently most affected, the site of the worst pain is on the outer side of the leg and perhaps on the dorsum of the foot, wasting of the calf is less pronounced, and the ankle-jerk is more often diminished than abolished; an area of sensory loss for light touch or impairment of pin-prick appreciation may be found on the outer side of the calf. In severe cases some disturbances may be found in the functions of the first sacral root as well as in those of the fifth lumbar. With lesions of the higher lumbar disks the pain is maximal in the fourth or higher root distributions, and the knee-jerk may be diminished or lost.

It should be borne in mind that in a proportion of cases the nervous symptoms are entirely irritative, and consequently objective signs due to impaired root function are lacking. Spinal signs are usually present, and ultimately some wasting appears, but in a number of such cases it is as yet impossible to make the differential diagnosis from sciatic pain due to other causes.

**Diagnosis.**—When the diagnosis is in doubt special radiographic examination after injection of Myodil into the theca shows a filling defect in the Myodil shadow, corresponding to the knuckle of cartilage indenting the theca. This method of investigation is not infallible, but in the present state of our knowledge its results should be taken as a practical guide.

In almost every case the problem is to distinguish the symptoms of a ruptured intervertebral disk from "sciatica" due to other causes. Most cases of sciatica in people under 40 years of age are due to ruptured discs. As age increases, other causes assert themselves more strongly, but in people who are of athletic type, given to such forms of physical activity as gardening, horse-riding and golf, and who are free from arthritis, ruptured disk is always a likely cause. If there is some history of injury or strain, if both the spinal and nervous groups of signs are present, and if the latter are limited to the distribution of a single root, there is little doubt about the diagnosis. In cases of sciatic neuritis, tenderness along the line of the sciatic trunk is pronounced, and pain and tenderness are seldom limited to the distribution of a single spinal root. In cases of referred sciatic pain, reflex changes, muscular wasting and objective sensory loss are absent. Very prolonged and, especially, recurrent sciaticas are mostly due to ruptured intervertebral disks.

**Course and Prognosis.**—In the absence of operative treatment, the symptoms usually subside gradually in the course of from 6 weeks to 6 months. In a very few cases they clear up more quickly, and in quite a number they persist in some degree for years, sometimes better and sometimes worse. The muscular wasting, though obvious, never becomes severe and there is never total paralysis of the affected nerve-root.

**Treatment.**—It is not known how the structures within the vertebral canal adapt themselves but in most instances the pain subsides without operative removal of the protruding mass. It is to be presumed that the affected nerve root suffers the minimum of physical irritation when the patient takes up the posture which is for him least painful. In general, the patient should remain at rest in his most comfortable position and be given such pain-relievers of the nature of aspirin, veganin and

the like, as may be necessary, together with sedatives if called for. In the most acute cases an injection of morphine, gr.  $\frac{1}{4}$ , or pethidine, 100 mg., may be necessary at night, but both these drugs should be used with great care because of the danger of addiction. Physiotherapy may be comforting after the acute phase has passed, but it is doubtful whether it has any curative effect. When the patient has been free from pain for a week, while still in bed, he may be allowed to sit up and very gradually begin to move about, but he should avoid doing anything which causes pain and he should rest when pain begins. If pain is recurrent when the patient has begun to move about, support of the lumbar spine by a plaster jacket may give relief.

Operation for the removal of the protruding portion of disc is advisable (1) if after 6 weeks or so the pain is not definitely diminished, (2) if the sciatica is recurrent, (3) if the patient's employment involves heavy work and much movement of the back. The operation is not a severe ordeal and most patients are walking again within 3 weeks. In general the results are excellent, but in some cases some pain persists or returns.

#### REFERRED SCIATIC PAIN

In some cases of sciatic pain there are no manifestations of disease of the sciatic nerve itself, either in the way of impaired function or of tenderness, and the pain is believed to be a referred pain excited by disease of other structures within the nerve distribution of the spinal segments from which the sciatic nerve arises. Such pain is abolished by the cure of the primary disease or anæsthetisation of the structure which it affects. Conditions which may give rise to referred sciatic pain are arthritis in the hip joint, arthritis in the sacro-iliac joint, disease of the lower lumbar vertebrae or of the sacrum, trauma of the gluteal muscles and lesions of the vertebral ligaments. It should be noted that malignant disease of the lower vertebral bones may cause severe referred sciatica at a time when no bony change is revealed by radiography, and the occurrence of sciatic pain in a patient who has suffered from carcinoma is to be interpreted in the light of this knowledge. Elliott and Weddell have shown that the presence of so-called rheumatic nodules in the gluteal muscles is not to be regarded as evidence of fibrositis there which might excite sciatic pain, because the nodules are due to local muscular spasm consequent upon irritation of nerve fibres, and are not primarily a rheumatic manifestation.

Referred sciatic pain is usually moderate in intensity. Its distribution is usually in the calf or on the outer side of the leg, or on the outer side of the ankle. The calf muscles are slightly tender and are the seat of discomfort, which causes the patient to make movement of them at frequent intervals. The absence of all signs of impaired nervous function has already been mentioned, and is the most important diagnostic feature.

In all cases of referred sciatic pain the treatment is that of the exciting condition. Injection of a local anæsthetic into the disordered structure abolishes the pain temporarily, and occasionally the relief is permanent, especially if the anæsthetic is used in oily solution, the effect of which is more lasting than that of an aqueous solution.

#### OBSTETRICAL PARALYSIS

It is important and useful to group together under this heading all those conditions of paralysis occurring, either in mother or child, which are the result of the processes of labour in the passage of the fetal head through the pelvis. Autopsies upon the still-born, and upon children who have survived birth for a few days only, have shown that hæmorrhage into the meninges is of common occurrence, and it has been argued that such meningeal hæmorrhages are the cause of many of the conditions of cerebral paralysis which are present immediately after birth, or which appear during the first

year of life, and especially the cause of cerebral diplegia. The pathological conditions found in the brain in cases of cerebral diplegia, however, are such as make it impossible that they could be caused by meningeal hæmorrhage, for no sign of old hæmorrhage is ever found, nor could hæmorrhage cause a general cell atrophy of the brain without signs of any local lesion. It seems clear, then, that though meningeal hæmorrhage may be of common occurrence during birth, and may be the cause of still-birth, yet there is no clinical or pathological evidence to show that it gives rise to any lasting cerebral defect.

The following conditions may occur: (1) In the child: facial paralysis; hemiplegia from laceration of the brain substance; fracture-dislocation of the spine with transverse lesion of the spinal cord; injury to the brachial plexus from the separation of head and shoulder in traction; and injury to peripheral nerve trunks at the elbow, axilla or groin, in using traction with the finger.

(2) In the mother: paralysis of the supply of the lumbo-sacral cord and obturator nerve from prolonged pressure of the head against the sacrum and pelvis.

*Facial paralysis.*—This is usually caused by the pressure of the forceps upon the facial nerve as it crosses the ramus of the jaw, but it has been known to occur where instruments have not been used. When unilateral, as is the common event, it gives rise to little or no difficulty with sucking, and is evidenced by the unsightly deformity of the face, which is drawn over to the sound side. When bilateral, it is one of the causes of complete inability to suck, and on account of the flaccid symmetry of the face may easily be overlooked. It necessitates spoon feeding for a considerable time. Obstetrical facial paralysis invariably recovers within a few weeks and does not give rise to after-contraction. Gentle stretching and massage of the face with the finger is the only treatment required.

*Hemiplegia* from laceration of the brain may occur during delivery in contracted pelvis from the pressure upon the sacral promontory, and has been caused by the use of forceps. It is exceedingly rare, and is generally rapidly fatal from the associated hæmorrhage. It may occasionally be survived, with an irreparable hemiplegic condition.

Fracture-dislocation of the spine is produced by traction upon the aftercoming head by pulling upon the trunk, and it may be associated with injury to the brachial plexus. It occurs most often in the lower cervical region, and the transverse lesion of the spinal cord is usually complete.

Injury to the brachial plexus may occur in traction either upon the head, or upon the trunk, if the head is aftercoming, and is caused by an undue separation of head and shoulder on one side rupturing or straining the brachial plexus. The paralysis is usually of the upper arm or Erb type, the fifth and sixth roots being most affected, and the deltoid, biceps and supinator longus muscles being paralysed, but the whole plexus may be involved and even torn completely across. Traction upon a prolapsed arm has caused lower arm or Klumpke type of paralysis, in which the first dorsal and eighth cervical roots are most affected, and the intrinsic hand muscles and the flexors of the forearm are paralysed. The obstetrical lesions of the brachial plexus are for the most part serious lesions, many of the cases making no motor recovery at all, though sensibility is usually regained. The prognosis depends upon the severity of the damage to the plexus, as to whether the roots are actually torn or only bruised. The slight cases recover well enough.

Injury to the peripheral nerves from pressure or traction upon the flexures is seldom severe enough to prevent a rapid and complete recovery.

Paralysis of the lumbo-sacral cord and of the obturator nerves in the mother, immediately after parturition, is an exceedingly interesting clinical condition. In the first place, the lumbo-sacral cord is in a much more exposed position as regards the foetal head engaging the pelvis than are the other nerves of the sacral plexus, and may be subjected to such severe pressure as causes paralysis, and in the second place,

the obturator nerve actually crosses the brim of the pelvis and must of necessity be pressed upon by any large fetal head which passes the pelvic brim. The lumbosacral cord paralysis is evidenced by dropped foot and paralysis of the anterior tibial and peroneal muscles and if it is severe, by loss of sensibility over the distribution of the fourth and fifth lumbar roots. Sometimes the third lumbar root area is affected. The obturator nerve involvement is shown by weakness or paralysis of the muscles supplied by the obturator nerve, namely, all the adductor muscles of the thigh. The paralysis may be noticed directly after parturition, or when the patient begins to get about upon her legs. The lumbosacral paralysis is usually unilateral, and is nearly always upon the right side. The obturator paralysis is not uncommonly bilateral, and both forms of the paralysis may coexist. There may be numbness, but no pain. This condition nearly always occurs with a first delivery, and often the child's head has been unduly large. It may recur with subsequent deliveries, but this is not a common event.

The prognosis is absolutely favourable, every case making a complete recovery in from a few weeks to a few months. The treatment is rest in the first place, with gentle massage and passive movements, and when power begins to return the patient may commence to get about.

## POLYNEURITIS

**Synonym.**—Multiple Peripheral Neuritis.

**Introduction.**—The clinico-pathological condition known as polyneuritis, and seen in its most typical form in diphtheritic paralysis, or in alcoholic neuritis, represents a very striking and uniform reaction of the nervous system. Invariably associated with it is a reaction of the myocardium, so that there is in cases of polyneuritis a recognised liability to sudden fatal heart failure. It is in diphtheritic paralysis and beriberi, another form of polyneuritis, that this mode of fatal termination is most often seen. Indeed, beriberi may appear as a rapidly fatal cardiac illness before any signs of involvement of the nervous system have had time to develop.

**Ætiology.**—At first sight the factors that give rise to polyneuritis fall into three groups: (i) certain chemical poisons, (ii) the toxins of certain bacteria and (iii) certain disorders of metabolism. Widely differing as these three causative factors may seem to be, there is reason to believe that a common underlying factor which is immediately responsible for polyneuritis may underlie them all. It is probable that in the case of groups (i) and (ii) the pathogenic substance gives rise to a disorder of metabolism in the course of which a toxic metabolite is produced in the body, this acting as the direct poison for nervous system and heart muscle. In the metabolic group (iii) the same process is in action. Thus, in beriberi, for example, the illness ensues upon the ingestion of a diet deficient in vitamin B<sub>1</sub>. In the absence of this substance carbohydrate metabolism is disordered and a toxic metabolite is produced. Thus, beriberi is not, as the biochemists formerly insisted, a starvation-degeneration of the nervous system, but an intoxication strictly comparable with that obtaining in other varieties, ætiologically considered, of polyneuritis. The final and complete proof of this unity of causation of polyneuritis, in whatever circumstances it is seen, is not yet available, but there is an increasing body of evidence in favour of it.

Returning to the ordinary ætiological classifications of polyneuritis, we see that in alcoholic or arsenical polyneuritis the poison is taken by the mouth, and presumably the final common toxic substance reaches the nervous system by the bloodstream. In diphtheritic paralysis, on the other hand, the exotoxins are produced focally at the site of the diphtheritic ulceration, whether on the fauces, or, as in extra-laricial diphtheria, at some other local site on the body surface. This unique channel of entry gives rise in diphtheritic paralysis to a group of symptoms not found in other

ætiological varieties of polyneuritis. This group includes palatal and accommodation paralyses, which precede the appearance of polyneuritis. It is noteworthy that in the case of extrafaucial diphtheria this initial paralysis is not palatal, but is anatomically related to the site of the diphtheritic lesion (skin ulceration or wound). Yet the paralysis of accommodation may occur whatever be the site of the diphtheritic lesion. It is believed, therefore, that the exotoxins gain access to the nervous system by conduction from the seat of the lesion via the axones of the nerves which innervate this region. They pass upwards in the axis cylinders to the central nervous system and produce their toxic action directly there, this action being reflected peripherally again as a motor and sensory paralysis of the muscles and skin (or mucosa) in the region of the lesion. Thus a diphtheritic ulcer on a finger may be followed by a local paralysis of that part before polyneuritis develops. The subsequently developing polyneuritis is then probably produced in the manner described above, while the accommodation paralysis may indicate a specific action of the toxin upon the nervous mechanism concerned. We thus have a local, a specific and a general group of symptoms. The analogy of the local, specific and general phases of tetanus will occur to the reader.

A peculiar effect of abnormal metabolism is the occurrence of polyneuritis in association with bronchial carcinoma.

Acute febrile polyneuritis and Landry's paralysis have no known causal factors. They make their appearance in apparently healthy persons, adequately nourished and free from all discoverable signs of infection, and it is extremely difficult in the present state of knowledge to account for them on any hypothesis of avitaminosis, or to suggest any possible mode of intoxication.

Many of the intoxications of the nervous system commonly included under the heading of polyneuritis are associated with lesions and clinical manifestations which are not those of polyneuritis. Such substances, to name but a few, are lead, mercury, copper, carbon disulphide and carbon monoxide, and it would be erroneous to regard these as causes of polyneuritis.

**Pathology.**—The changes in the nerves are those of parenchymatous neuritis, and longitudinal sections stained by the Marchi or Weigert-Pal methods show severe degeneration of the fibres. The alterations are most intense in the small branches supplying the skin and muscles, and they diminish in severity as the larger branches are approached. They are best seen in the terminal branches of the musculo-spiral and anterior tibial nerves. The wasted muscles often show a reduction in the size of their fibres, and an increase of connective tissue—fibrous myositis. The spinal cord may be healthy, but in almost all cases examination by modern methods shows changes in the nerve cells and degeneration in the tract fibres derived from the posterior roots.

**Symptoms.**—As might be expected from the composition of the peripheral nerves, the symptoms of polyneuritis may consist of disorders of movement, sensation and autonomic function, and these disorders are symmetrical and typically begin in the peripheral portions of the limbs and spread proximally. The relative severity of these disturbances varies from one variety of polyneuritis to another, and the detailed symptomatology of each variety is more fully considered below. The motor disorder is in all instances a lower motor neurone paralysis, with the characteristic weakness, reflex loss and tendency to wasting of the muscles: a marked propensity to contracture is universal. Bilateral drop foot is in a large number of cases the first objective motor manifestation. The sensory disorders are similarly peripheral and symmetrical and may involve both superficial and deep sensibility and may be both positive (pains and paræsthesiæ) and negative (anæsthesiæ). The first complaint is usually of numbness in the feet and in the hands, and this extends proximally, and is soon accompanied by objective sensory loss, which by reason of its mode of development soon has characteristically a "glove and stocking" distribution. In some varieties the autonomic



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defects are seen in alterations in sweat secretion and trophic changes in the skin, nails and other tissues.

The tendency to myocardial weakness which has already been mentioned, though characteristic only of certain varieties, should be borne in mind in all cases.

The cerebrospinal fluid in the infective types of polyneuritis contains an excess—usually a great excess—of protein, the globulin fraction also showing an increase; the other elements of the fluid are normal, except that in rare cases of acute infective polyneuritis cellular increase may be found.

**Diagnosis.**—The diagnosis of polyneuritis from other diseases rarely presents serious difficulty. It is made from the combination of symmetrical flaccid paralysis with sensory loss of the "glove and stocking" distribution, and tenderness of the muscles and nerves, confined to, or most intense in, the distal part of the limbs. A variable degree of polyneuritis is an associated feature of subacute combined degeneration of the spinal cord, and this disease may easily be confused with polyneuritis. The differential clinical features are given on p. 1553 and, as pointed out there, the distinction at an early stage, may in some cases be made with confidence only by examination of the blood for the characters of pernicious anemia. The development of extensor plantar reflexes is an absolute point against polyneuritis, while a great excess of protein in the cerebrospinal fluid is equally against subacute combined degeneration. When sensory disturbances and diminished tendon reflexes are prominent symptoms and muscular weakness is slight, *tabes* may be suggested, and the resemblance is still greater when ataxia is present. Difficulty usually arises when the distinction has to be made between *tabes* and alcoholic neuritis, in a patient who has courted both diseases. In most instances the diagnosis can be made from the nature and distribution of the sensory changes. The lightning pains of *tabes* cannot be mistaken by anyone who is familiar with their peculiar characters. Anæsthesia of the extremities is common to both diseases, but diminished sensibility around the nose and across the chest is peculiar to *tabes* and is present in almost every case. In neuritis the calf muscles and nerve trunks are tender, whereas in *tabes* the sensibility of these structures is usually greatly diminished. Hyperæsthesia to touch and temperature, and great exaggeration of the abdominal reflexes, also suggest *tabes*. Examination of the cerebrospinal fluid usually puts the diagnosis beyond doubt.

Rarely does polyneuritis come on with such rapidity as to simulate poliomyelitis. When it does so the occurrence of any peripheral sensory loss may reveal its nature, and the absence of cells in the cerebrospinal fluid shows that the illness is not poliomyelitis.

**Course and Prognosis.**—In a few instances myocardial failure or respiratory paralysis brings about a fatal issue at the height of the illness. Otherwise the normal course of the disease is a stage of invasion followed by a stage of recession, leading to complete recovery. The duration of these varies greatly according to the ætiology of the malady. In rare cases recovery fails to occur and in the chronic hypertrophic types of the disease this is the rule.

Disability after recovery from the neuritis may result from muscular contractures, wasting or neuritic pains.

**Treatment.**—The first essential is to remove the patient from the influence of the exciting cause. In alcoholic cases, rigid precautions are necessary to prevent secret access to alcohol. To attain this, treatment in an institution is almost a necessity. In most instances when the cause, whatever it may be, is removed, gradual improvement sets in and complete recovery ensues, in a time that varies with the severity of the symptoms. During this time the physician's most important duty is to prevent the occurrence of deformities and contractures. From the beginning each joint in the affected limbs should be moved passively to its full range several times each day, and care should be taken to ensure that the attitude of the limbs during rest is a suitable one, especially that the feet are maintained at right angles to the legs by the use

of appropriate apparatus. Drawing up of the heel must be prevented at all costs.

Gentle massage is soothing in the acute stage, provided muscular tenderness does not preclude it. Later, more vigorous rubbing may be given, and the patient should be encouraged to move the limbs voluntarily. Electricity is seldom called for. Analgesic drugs and soothing applications may be needed at the onset. Thereafter local treatment to the limbs is combined with measures to improve the patient's general condition.

The administration of vitamin B<sub>1</sub> preparations has now a great vogue in the treatment of both multiple (parenchymatous) and interstitial neuritis. In the latter its use has no theoretical justification or practical value, and even in the former, though its use is rational it yet remains to be proved that the course of the malady is materially influenced. This may be due to inadequacy of dosage in the past, and the parenteral injection for from 2 to 4 weeks of 1000 to 2000 units daily is the minimum dosage likely to be efficacious. Even with this dosage it is not yet clear that the course of any ætiological variety of polyneuritis is materially influenced, and extravagant claims should be treated with great reserve.

#### ALCOHOLIC NEURITIS

In former years alcoholism was perhaps the commonest cause of severe peripheral neuritis, but at present alcoholic polyneuritis is a rare disease in the British Isles. It occurs most often in women, especially in those who take small amounts of alcohol frequently, and it has often been the first indication of secret drinking. There is much evidence that the disorder results as much from the deficient diet and the chronic gastritis commonly found in alcoholic subjects as from the direct toxic effect of the alcohol taken.

The onset is insidious, and in most cases premonitory symptoms, such as numbness and tingling in the extremities or cramps in the muscles of the lower limbs, are present for several months before actual weakness occurs. Subjective sensory troubles are a marked feature, even in the early stages. Besides numbness and tingling the patients complain of feelings of excessive heat or of coldness in the limbs, or of severe aching or cutting pains in the legs. Painful cramp in the calf muscles is a common symptom. It is often worst at night, and may interfere seriously with sleep. Objective examination usually reveals sensory loss, in which the various elements of sensation are affected in a manner which is almost pathognomonic.

Stated briefly, there is anæsthesia of the skin with hyperæsthesia of the deeper structures. Light touches are not appreciated at all or many are missed, the temperature sense is defective, and the prick of a pin causes no pain, whereas even moderate compression of the muscles may cause the patient to cry out. The sensory loss is greatest in the feet and hands and diminishes towards the knees and elbows. Muscular tenderness is usually greatest in the calves. The soles of the feet are also unduly tender. Hyperalgesia is often well marked before anæsthesia of the skin appears. To the disability caused by pains and spasms, weakness of the muscles is added in all but the slightest cases. The arms may suffer first, but in most cases the extensors of the toes, the dorsiflexors of the ankle, and the extensors of the fingers and wrists are attacked in progression, and double foot-drop and wrist-drop result. To overcome the foot-drop, the knees are raised high in walking. This gives to the gait the "steppage" character which is common to all forms of peripheral neuritis. In most cases the distal flexor muscles are also affected, but to a slighter degree. In severe cases, weakness extends to the proximal muscles and even to the muscles of the trunk. The affected muscles become soft and diminish rapidly in bulk. Unless precautions are taken, contractures occur in the flexor muscles and produce deformities of the limbs, which add greatly to the difficulties of treatment.

At the onset the knee-jerks are exaggerated, but in most cases by the time the patient comes under observation all the tendon reflexes are absent. The cutaneous reflexes may be unaltered, diminished or absent. Sphincter control is retained. Slight bilateral weakness of the face is often present but severe paralysis is rare. Ptosis, nystagmus and weakness of the external ocular muscles have been observed.

Trophic and vasomotor disturbances in the extremities are common. The hands and feet often perspire freely at first and then become unnaturally dry, and they may be white and cold or red and hot. In some cases œdema of the hands or lower extremities is present. In chronic cases the skin of the hands and fingers is thin, smooth and shiny, and the nails are ridged and brittle.

In almost every case of alcoholic neuritis there is some *psychical defect*. One form—Korsakoff's psychosis—is characteristic of and almost peculiar to this disease. The most prominent feature is failure of memory for recent events and loss of appreciation of time and place. A patient who has been bedridden in a hospital for nervous diseases for several weeks, when visited by the resident physician who has attended her daily, will "recognise" him at once as Dr. X, whom she has not seen since he brought her first child into the world some years ago. She is now, she says, in a lying-in hospital which she entered yesterday, and has just been confined with her second baby, who is in bed beside her. She also "recognises" strangers at her bedside, and connects them with events of long ago. Everything is related in the most circumstantial manner, and if the facts were not known her tale might well be accepted as truth. In most cases the mental defects are not so gross. There is merely a failure of memory, to which is added moroseness and irritability, caused by withdrawal of alcohol.

#### ARSENICAL NEURITIS

Peripheral neuritis may be caused by a single large dose of arsenic, or it may result from prolonged use of the drug in the treatment of such diseases as Hodgkin's disease, chorea and severe anæmia. It is a rare malady, and the likelihood of its appearing under the last-named conditions is negligible. The toxic action of arsenic with alcohol seemed to be greater than that of either alone.

The description given of alcoholic neuritis applies to this form as well. Hyperæsthesia of the skin and tenderness of the muscles are more constant and more severe in the arsenical form, and paralysis and atrophy of the muscles are often more widespread and more rapid in their progress. Hyperkeratosis of the soles and pigmentation of the skin are characteristic of arsenical poisoning. In a suspected case, the diagnosis can be confirmed by the discovery of abnormal quantities of arsenic in the urine or in the hair and skin.

The mental changes described in connection with alcoholic neuritis under the heading of Korsakoff's psychosis may be present, especially when repeated poisonous doses of arsenic have been taken.

#### DIPHTHERITIC PARALYSIS

The exotoxin of diphtheria is highly selective for nervous tissues, and some form of paralysis occurs in a very high proportion of the cases. The intensity of the paralysis bears no constant relation to the severity of the local infection, for cases in which the original disease has passed unnoticed may be followed by serious damage to the nervous system. Walshe has classified the nervous manifestations of diphtheria into three distinct groups, namely, the local, the specific and the generalised paralyses.

*Local* paralysis occurs in parts related anatomically by nervous connections to the site of the diphtheritic lesion. In faucial diphtheria, the local palsy appears in the palate. In extra-faucial diphtheria, *e.g.* infected sores on the limbs, the local palsy appears in the muscles supplied by the segments of the cord to which afferent nerves

from the infected focus pass. The reason for this is, that toxins elaborated by the diphtheria bacillus ascend from the primary focus to the cord or the medulla. Having reached the central structures, they diffuse to neighbouring motor cells and, by injuring them, cause paralysis of the muscles they supply. Paralysis of the palate therefore does not occur except in faucial diphtheria.

The *specific* manifestation of diphtheria is paralysis of accommodation. Like trismus in tetanus, it is not due to a local lesion, but occurs in many cases, whatever the site of origin of the toxins. It is present in cases of both faucial and extra-faucial diphtheria, and is the local effect of exotoxin accepted from the general blood-stream.

The third or *generalised* form of diphtheritic paralysis is multiple neuritis. It follows extra-faucial as well as faucial diphtheria, and is also a result of the action of exotoxin circulating in the blood.

As faucial diphtheria is the commonest form, the most frequent nervous symptom is *paralysis of the soft palate*. It is shown by the nasal quality of the voice and by the regurgitation of fluids through the nose. As a rule, the weakness is bilateral and equal, but in some cases it is greater on the side on which the local lesion is more severe. It makes its appearance in most instances about the end of the second week, but may come on as early as the fourth day, and as late as the sixth week. The soft palate is relaxed, and its movement on phonation is diminished. The palate may be insensitive, and its reflex is often diminished or lost. Recovery usually occurs in a few weeks. In rare instances the muscles of the pharynx and the vocal cords are paralysed. Together with palatal palsy, it is common to find marked weakness and tenderness of the sternomastoid muscles and masseters. These are also local effects.

*Paralysis of accommodation* appears about the same time as the palatal palsy, perhaps a few days sooner. The reaction of the pupils to accommodation as well as to light, can almost always be obtained. The trouble is subjective, and is shown by defects of near vision—for example, by inability to read small print. Hypermetropes suffer great inconvenience. In myopes it may pass unnoticed. Paralysis of any of the extrinsic ocular muscles with strabismus and diplopia may occur, and this may be either nuclear or peripheral in type.

*Multiple neuritis* usually comes on 3 to 6 weeks after recovery from the throat infection. Its presence is often detected when patients begin to exert themselves during convalescence. Weakness and aching pains in the legs, unsteadiness in walking, clumsiness in performing fine movements with the hands, feelings of pins and needles in the extremities—all these are common early symptoms. Weakness affects in varying degree the muscles of the neck, trunk and limbs. It is generally slight in degree, greater in the lower than in the upper extremities and greater in the extensor muscles than in the flexors. Marked local atrophy is uncommon. In severe cases, life may be endangered by paralysis of the intercostals and of the diaphragm, but fortunately one set of muscles has usually begun to recover before the other is seriously affected. The small muscles of the hands and feet and the muscles of the calves and forearms are almost always tender on pressure. They are soft and flabby, and often show a partial reaction of degeneration.

Sensory ataxy is almost always present, and is often severe when the paralysis is trivial. It causes the patient great inconvenience, as it interferes seriously with walking and with the finer movements of the hands. Objective examination reveals sensory impairment of the "glove-and-stocking" type. On the hands and feet, the loss to light tactile stimuli is often complete, pain and temperature being less affected. As the limb is ascended, sensation gradually becomes normal. Even when the sensibility of the skin is but little diminished, the sensations of position and of passive movement in the extremities are often seriously impaired, and the sense of vibration is often lost.

In the early stages and for a few days the tendon-jerks are exaggerated, but are lost later in every case. Their return is often long delayed, and it is common to see

patients months after recovery of normal power, in whom the knee-jerks are still absent. It is common also to find them absent many months after an attack of diphtheria in patients who give no history of nervous symptoms during the attack. The skin reflexes are usually retained, and stimulation of the sole gives a normal response.

Cardiac failure is a grave but uncommon complication. It is of myocardial origin. Vasomotor paralyses and disturbances in the nutrition of the skin, which occur so often in other forms of peripheral neuritis, are never seen in diphtheria. In those that survive the attack, complete recovery from the nervous troubles always occurs.

#### ACUTE FEBRILE POLYNEURITIS

**Synonym.**—Acute Infective Polyneuritis.

At various times small epidemics of a form of polyneuritis characterised by a febrile onset and by the involvement of the facial nerves have been described (Osler, Gordon Holmes, Rose Bradford and others).

Nothing is known of its aetiology and it is probably not essentially different from Landry's paralysis in nature, though less fulminating in onset and not so liable to grave involvement of the trunk muscles.

The onset is with slight fever, headache and malaise, pains in back and limbs, and such general symptoms as a coryza or gastro-intestinal irritation. The fever persists for 2 or 3 days only. A few days then elapse before the signs and symptoms of polyneuritis develop. It is said that the proximal limb muscles are more severely involved than the distal muscles, a point of distinction from other forms of polyneuritis, but this relative incidence of weakness is not invariable and has probably been over-stressed. The trunk muscles do not escape, and the face is often bilaterally paralysed. As in other forms the paralysis is of the lower motor neurone type, flaccid, atrophic and with loss of tendon-jerks. Sensory loss is very slight, and there is relatively slight muscular tenderness. The cerebrospinal fluid may show a high rise in the protein content, but is otherwise normal.

The clinical course is variable, and sometimes fluctuating in the individual case. Death may ensue from paralysis of the respiratory muscles, but recovery in the majority of cases is fairly rapid. There is the usual tachycardia of polyneuritis. If the patient survives the acute phase, complete recovery ensues.

#### DIABETIC NEURITIS

In many patients with glycosuria, symptoms are present which point to changes in the peripheral nerves. In some cases the only symptom is neuralgic pain in the distribution of one or more nerves. This is commonest in the lower limbs, where it simulates sciatica, and sugar is found in the urine in the absence of any other sign of diabetes. In other cases, a single large nerve trunk suddenly becomes paralysed.

*In severe diabetes the knee-jerks and ankle-jerks are diminished or lost in more than half the cases.* This may accompany subjective sensory troubles in the lower limbs, or it may appear as an isolated symptom. The muscles are very often tender and the vibration sense of the feet is frequently absent. To objective examination, the sensibility of the skin is usually intact. Perforating ulcers of the feet have been observed. Only in very rare instances does the neuritis proceed to the stage of generalised peripheral paralysis of motor and sensory structures.

#### PROGRESSIVE HYPERTROPHIC POLYNEURITIS

Dejerine and Sottas described an extremely rare progressive form of polyneuritis, sometimes developing in infancy, showing an heredo-familial incidence, and characterised by thickening of the nerve trunks due to hypertrophy of the sheaths of

Schwann. In recent years other cases of hypertrophic polyneuritis have been described which have no hereditary or familial character. There is evidence that some, at least, of the cases described under this heading were examples of primary amyloidosis of the peripheral nervous system.

**Pathology.**—The thickening of the nerves may be palpable during life, but is not invariably so. Microscopically this thickening is found to be due to masses of non-nucleated tissue arising from the sheath of Schwann.

**Symptoms.**—The malady develops and progresses very slowly with peripheral weakness, muscular wasting, sensory loss, loss of tendon-jerks. There may be noted, in addition, kyphoscoliosis, nystagmus and ataxy of movement. It was formerly thought that the Argyll Robertson pupil was an integral part of the symptom-complex, but this is not the case.

**Prognosis.**—Death ultimately ensues from intercurrent disease.

**Treatment.**—There is no known treatment which is effective.

## LEAD PALSY

The nervous effects of lead poisoning are confined almost entirely to motor neurones. Subjective sensory disturbances are often slight or absent, and in most instances there is no objective sensory loss.

**Pathology.**—Aub in 1923 showed that the first event was the local concentration of lead in those muscles which were about to be paralysed and that the paralysis was a muscular event primarily, and that, secondarily, the lead ascends along the motor axons and may finally cause the death of the ventral horn cell. The degenerative changes in the nerves are confined almost entirely to the motor fibres, and are most intense in the intramuscular twigs supplying muscles of the extensor groups. Normal and degenerated fibres are found side by side, the former becoming more numerous as the nerve is traced upwards. Degenerative changes due to the action of lead are also found in the affected muscles.

**Symptoms.**—In most cases of the common *antebrachial* or *wrist-drop* type, paralysis is limited to the extensor muscles of the fingers and wrists—that is, to the muscles supplied by the musculo-spiral nerve. But the brachio-radialis and the abductor longus pollicis, also supplied by this nerve, usually escape. Inability to extend the first phalanges of the two middle fingers, owing to weakness of the common extensor, is usually the first difficulty. The special extensors of the index and little fingers, the long extensors of the thumb and the extensors of the wrist are next attacked, and the characteristic wrist-drop appears. As a rule the paralysis becomes severe about a week after it is first noticed. By this time it is usually bilateral and symmetrical, but for several days, or even for several weeks, it may be confined to one side. The affected muscles waste rapidly and the back of the forearm becomes flattened, thus rendering the intact brachio-radialis more prominent. In this form, loss of power always precedes atrophy, and some muscles may show weakness without any wasting. Recovery is almost always complete. Simple weakness without atrophy usually passes off in a few weeks. If the wasting is moderate and the muscles still react to faradism, recovery may be expected in a few months. When the atrophy is severe, a year or more may elapse before recovery is complete.

Occasionally the deltoid, biceps, brachialis and brachio-radialis muscles are affected, either alone or in company with the forearm muscles—*upper arm* or *brachial* type. Less often paralysis occurs in the legs, the muscles supplied by the peroneal nerve, namely, the long extensors of the toes and the peronei, being chiefly involved—*peroneal* type. Like the brachio-radialis in the arm, the tibialis anterior, although supplied by the peroneal nerve, usually escapes. This type is usually associated with paralysis of the forearm muscles, and runs the same course.



In the form of paralysis described above the features are similar to those of a traumatic lesion to a nerve. Loss of power precedes, and may be more extensive than wasting, faradic irritability of the muscles is lost or diminished while the reaction to galvanism is retained, and recovery is usually complete. It is therefore called the degenerative form. In the second form, the paralysis has the characters of progressive muscular atrophy. Weakness and wasting come on together, faradic and galvanic irritability of the muscles are both diminished in proportion to the wasting, and the paralysis is often permanent. This is known as the primary atrophic form. It occurs especially in the small muscles of the hand—*Aran-Duchenne type*—but is sometimes irregular in its distribution and affects many muscles in all four limbs. It is often associated with the first form, but may occur alone. Wasting comes on slowly, and accompanies the loss of power, instead of succeeding it. It is much more intractable than the degenerative form, and often persists after muscles showing the first form of paralysis have recovered. (See also Lead Encephalopathy, p. 368.)

### LANDRY'S PARALYSIS

In the year 1859 Landry applied the name "acute ascending paralysis" to a case in which acute flaccid paralysis with loss of reflexes and without sensory disturbances commenced in the periphery of the lower limbs, and rapidly spread upwards. The arms were next involved, first in the periphery, and later the trunk, respiratory muscles, neck and lastly the cranial muscles were involved, and death occurred from respiratory failure. He made a careful microscopic examination of the spinal cord with the methods then at his disposal, and failed to detect in it any morbid changes. He subsequently described this symptom complex, which has since borne his name, from an analysis of ten cases.

Since this time a large number of cases have been recorded which, from the acute nature of the onset, and from the spreading nature of the paralysis, have been described as cases of Landry's paralysis. This name should be restricted to those cases of acute spreading paralysis, in which disorders of sensibility and sphincter trouble are absent or little marked, and in which recovery is complete if the patient survives, and in which no gross lesion is found within the nervous system after death.

Acute poliomyelitis may also, in rare cases, give rise to a spreading paralysis, and cause much difficulty in diagnosis; but it is invariable that some permanent paralysis remains upon recovery, and, further, the lesions of poliomyelitis are both gross and characteristic.

**Ætiology.**—What is known of the causation of the disease in general resembles very closely that of acute polyneuritis. It affects males much more frequently than females, and occurs chiefly in adult life between the ages of 16 and 54 years.

**Pathology.**—Slight hyperæmia of the spinal cord, and especially of the grey matter, with a few punctiform hæmorrhages, is the only change noticeable upon naked-eye examination. Very definite histological changes are found upon microscopic examination in the anterior horn cells and in the cells of Clarke's column, where any degree of change may be found, from an early pericentral chromatolysis to a complete loss of the chromatin granules and concentration of nuclei.

The cerebrospinal fluid is clear. It may present no abnormality either as regards cell or albumin content. In other cases there is an excess of albumin, and in this respect it resembles the cerebrospinal fluid of polyneuritis, which is usually albuminous, and sometimes so highly so as to clot spontaneously. In a few instances the fluid contains numerous lymphocytes.

**Symptoms.**—The onset is in some cases abrupt, with the appearance of the characteristic spreading paralysis. Much more frequently the paralysis is preceded by certain premonitory symptoms, which may last from a few hours to days or weeks.

These symptoms may consist in malaise, headache, lassitude, insomnia, anorexia, constipation, gastralgia, vomiting and diarrhoea, and there is not infrequently slight elevation of temperature. More characteristic still among the prodromal signs are subjective disturbances of sensibility. Pains in the back and limbs are common, and may be of a dull aching nature, or they may be sharp and shooting in character. Numbness, tingling, "pins and needles" and other paræsthesias may occur over any part of the body, and are most commonly complained of in the periphery of the limbs. The muscles may be locally tender during this prodromal stage.

It is not uncommon for the paralysis to commence in the periphery of the lower extremities, to ascend rapidly and to involve the muscles in the order of their innervation from the spinal cord, the trunk becoming affected before the upper extremities, and the intercostal muscles before the diaphragm. The muscular weakness may commence in any group of muscles, as, for example, in the face, neck, upper extremities or trunk, and when so commencing the spread of the paralysis is downwards, constituting a descending type of paralysis.

In Landry's paralysis, as in acute polyn neuritis, the innervation of the respiratory muscles seems to be peculiarly resistant to the toxin.

In those cases which recover the advance of the paralysis ceases, and those muscles which have been most recently affected begin to show some recovery quickly.

When the disease does not prove fatal either from respiratory failure, pulmonary complications or sudden syncope, the paralysis ceases to spread, and the patient enters upon the stage of recovery.

The paræsthesiæ, which have been described with the onset, often persist, and there may be cramp-like pains. Not uncommonly the muscles are tender upon deep pressure; but there is never that severe degree of tenderness met with in some forms of peripheral neuritis as, for example, in alcoholic neuritis. There is exceptionally blunting of sensibility, most marked in the periphery; but this is never deep, and is rapidly transient.

Though from the general weakness of the trunk muscles there may be some difficulty in emptying the bladder and rectum during the first few days, and even retention with overflow incontinence that may require catheterisation from the same cause, yet these last but a few days. The deep and superficial reflexes disappear early with the onset of the first signs of the paralysis in the affected regions. The psychic functions remain unimpaired throughout.

**Diagnosis.**—The rapidly spreading character of the paralysis in Landry's disease is so striking as to necessitate distinction only from those few maladies in which a similar rapidly spreading paralysis may occur, and these are acute spreading myelitis, intrathecal hæmorrhage, acute poliomyelitis (spreading type) and acute polyn neuritis. Acute spreading myelitis is at once distinguished from Landry's paralysis by the severe sensory loss and sphincter paralysis, which in the former condition develop *pari-passu* with the motor paralysis and, further, if the myelitis does not involve the lumbo-sacral enlargement of the spinal cord, an extensor plantar reflex will be observed.

The rare, spreading form of poliomyelitis presents difficulty in diagnosis, especially in the acute stage. The general symptoms and the pyrexia are apt to be more severe in poliomyelitis. An onset in childhood is more suggestive of poliomyelitis than of Landry's paralysis. A fairly high polymorphonuclear leucocytosis in the blood, and a lymphocytosis in the cerebrospinal fluid, are in favour of poliomyelitis. The persistence of local atrophic palsy on convalescence is absolute evidence of poliomyelitis. The distinction of Landry's paralysis from acute febrile polyn neuritis depends on the mode of spread of the paralysis, and on the possible presence of numerous cells in the cerebrospinal fluid.

**Prognosis.**—In about one-half of the cases the paralysis advances until the respiratory and bulbar muscles are involved, and death occurs from respiratory failure, usually on the third or fourth day, but sometimes not until 10 days or more have

elapsed. So long as the paralysis is extending, and especially when the respiratory and bulbar muscles are failing, the prognosis is very grave. The extension of the paralysis may, however, cease at any stage, and when this occurs the prognosis at once becomes favourable, even though there be considerable involvement of the respiratory and bulbar muscles.

**Treatment.**—The patient must be placed at complete rest, and the discomfort and panic which are likely to arise from the utter inability to move must be assiduously relieved by frequent changes of posture. The greatest care must be taken that the patient is adequately fed with nutritious and light food. Stimulants are usually indicated. A mercurial aperient should be administered early and the bowels regularly relieved, for in some cases obstinate constipation occurs. The bladder should be catheterised, if there is difficulty in micturition. Both pain and pyrexia may be relieved by the administration of salicylates or aspirin.

Atropine tends to check accumulation of secretion within the bronchi. Oxygen may be administered where cyanosis occurs, and it may be necessary to place the patient in a Drinker respirator. When once there are signs that the malady has passed its height, and that recovery is commencing, little treatment is required except careful nursing and feeding. Gentle massage may then be employed.

## MUSCULAR DISEASES

### PRIMARY MUSCULAR DYSTROPHIES

**Synonym.**—The Myopathies.

Under this heading, a disease is described in which the voluntary muscles undergo primary degeneration, independent of detectable disease in other parts. To facilitate description, a number of clinical types have been distinguished according to the age at which the disease appears, to the group of muscles first attacked, to the presence or absence of pseudo-hypertrophy, and to the prominence of the hereditary factor. The chief of these are—(1) the pseudo-hypertrophic type; (2) the juvenile type of Erb; (3) the facio-scapulo-humeral type of Landouzy and Dejerine; (4) the distal type.

The first type is fairly constant, but there is in reality no sharp division between the different forms. That the others do not represent separate diseases is proved by the appearance of more than one of them in members of the same family. The disease is familial, and it is also hereditary in the sense that it may appear in some or all the members of a family through several generations.

The changes in the muscles in the myopathies are essentially the same as those which occur when muscles degenerate from any other cause, namely, a slow and progressive atrophy of the contractile elements, with a concurrent increase of fat and fibrous tissue. However in most cases of myopathy swelling or hypertrophy of some of the muscle fibres is a feature of the microscopic picture, and this hypertrophy is believed to represent an early stage of the degenerative process. In the pseudo-hypertrophic form the connective-tissue hyperplasia is excessive in some of the affected muscles and their bulk is increased. In the other forms of the disease, and in those muscles in the pseudo-hypertrophic form which become weak without any increase in size, the overgrowth of connective tissue may balance the loss of bulk due to atrophy of the contractile tissues, and the diseased muscles retain their normal size; or atrophy may proceed faster than hyperplasia, and the muscles waste from the beginning.

#### 1. PSEUDO-HYPERTROPHIC MUSCULAR DYSTROPHY

**Ætiology.**—The cause of the disease is unknown. In many instances no antecedent cases can be traced in the family. In others, a family history is obtained,

always on the mother's side. Isolated cases occur, but more often several children are attacked in each generation. Boys suffer more frequently than girls in a proportion of about 5 to 1. Sometimes one sex alone suffers, sometimes both. It is rare for all the children to be attacked. The males who escape beget healthy children, whilst the females, who appear to have escaped, may transmit the disease to some of their offspring.

**Symptoms.**—The symptoms appear in early childhood. The onset is often delayed to the fourth or fifth year, rarely until towards puberty, and very rarely until as late as the twentieth year. In cases of late onset, enlargement of the calves has usually been present for many years. Weakness appears first in the muscles of the pelvic girdle. The child, who usually looks fat and strong, begins to walk late, he falls easily and rises again with difficulty. He does not romp as other children do. He cannot skip or jump, and he has great difficulty in mounting stairs. At first the muscles may be normal in size, but, as a rule, some show obvious enlargement before the fifth year is reached. The enlargement is most conspicuous in the calves, the buttocks and the infraspinati. The erector spinæ, the quadriceps in whole or part, the deltoid, the supraspinatus and the triceps often show considerable hypertrophy. Occasionally the masseters are enlarged. At the same time other groups of muscles atrophy. This is most severe and most frequent in the latissimus dorsi and in the lower part of the pectoralis major. Later it extends to other muscles, and ultimately to those which were at first hypertrophied. The neck and face are spared. There is no exact correlation between the size of the diseased muscles and their power, but weakness is usually greatest in those which show most atrophy. The defects are greater in the proximal muscles, and diminish distally. The hands often retain good power to the end. This distribution of paralysis gives rise to certain characteristic defects of attitude and movement.

In standing the legs are placed far apart, and the upper part of the trunk is thrown back, so that a plumb-line from the most prominent vertebra falls behind the sacrum. This attitude compensates for the forward tilting of the pelvis, resulting from weakness of the glutei, which normally raise the anterior border of the pelvis by lowering its posterior border. In the sitting posture the lordosis disappears, for now the attachments of the flexors of the hip are approximated, and these muscles no longer lower the anterior border of the pelvis. On lying down the lordosis appears again, but can be abolished by relaxing the flexors of the hip-joint, that is, by flexing the hips passively. In walking, the feet are widely separated, and to clear the ground with the advancing foot the body is inclined first to one side and then to the other. This "waddling" produces a gait like that seen in congenital dislocation of the hip. The early preponderance of weakness in the extensors of the hip and knee is betrayed by the great difficulty experienced in mounting stairs.

The manner in which the child rises from the supine to the erect position is almost pathognomonic of the disease. He first tries to sit up, but fails. He then rolls over on his belly, and raises himself first on his knees and elbows, and then on his hands and feet. Next he places his hands on his knees, and as it is impossible for him to raise the trunk actively owing to weakness of the extensors of the hip, he literally climbs up his thighs. Pushing the extensors may be enough to enable him to complete the movement; if not, he jerks the shoulders back suddenly and gains the erect posture by a writhing movement, whose details are difficult to follow. To climb the thighs successfully a certain amount of power is necessary to hold the knees slightly flexed. When this power is lost he is no longer able to rise. The arms are also used to assist the weak legs in sitting down and in getting up from a chair.

As time goes on the weakness increases, and invades all the muscles of the trunk and limbs. Some of the muscles become shortened, and distortions are produced by permanent alterations in the position of the joints. The knees and elbows become

flexed, the feet take up the attitude of talipes equinus, the spine becomes curved and the whole body is grossly deformed.

The deep reflexes and the electrical excitability of the muscles diminish gradually as the wasting increases. Sensation is unaffected. The sphincters are not involved. The mental condition shows no abnormality.

**Diagnosis.**—The diagnosis is usually simple if a few of the outstanding features of the disease are known. The defects of attitude and movement, especially the mode of rising from the supine position, together with the characteristic association of enlargement of the infraspinati and calves with atrophy of the latissimus dorsi, form an unmistakable combination.

**Prognosis.**—This is most grave. Few patients reach adult life, and most die within 10 years of the onset of the disease.

**Treatment.**—Drugs have no beneficial influence. Glycine in large doses has been advocated but there is no reliable evidence that it affects the course of the disease. Massage and passive movement are useful in the prevention of contractures, and the efficiency of the muscles may be prolonged by suitable exercises. Walking should be practised daily, until it becomes impossible. Very often this is lost owing to contractions of the calf muscles, and is regained after tenotomy.

## 2. OTHER TYPES OF MUSCULAR DYSTROPHY

**Ætiology.**—The separation of the remaining types of myopathy from the pseudo-hypertrophic form is not an absolute one, as isolated cases are occasionally met with which seem to form a connecting link between the several varieties. The varieties, however, are habitually separate in occurrence, and in families in which numerous cases conforming to the types to be described hereunder have occurred throughout several generations, no cases presented the peculiar features of the pseudo-hypertrophic form. Moreover, the sex incidence as well as the period of onset is different in the two varieties, and it is possible that there is some essential pathological difference between them, and that they are separate diseases. With regard to the types of myopathy unassociated with pseudo-hypertrophy, no doubt exists as to their fundamental unity. They are merely varieties of one disease.

The influence of heredity is much more prominent than in the pseudo-hypertrophic form. Isolated cases occur, but they are rare. In most instances several members of a family are affected in the same and in succeeding generations.

The sexes suffer equally. The time of onset varies within wide limits—from infancy to old age. When the wasting begins in the face (*facio-scapulo-humeral type*) the disease frequently begins in childhood; but sometimes it begins there late in life. In the cases where it is first noticed in the muscles of the shoulder and pelvic girdle the onset is most frequent between the ages of 15 and 35 (*Erb's juvenile type*); but here, again, it may begin in childhood or early old age, and the term juvenile is hardly applicable to it. The same variations in the age of onset are noticeable in cases where the atrophy begins in the forearms and legs (*distal type*).

The various types may be exemplified in members of the same family, and in the same family the age of onset may show extreme variation.

The cause of the disease is quite unknown.

**Symptoms.**—In the so-called juvenile form weakness and wasting come on simultaneously. In most cases they are first noticed in the arms; but in some families the legs suffer first. Of the arm muscles the biceps, triceps and brachio-radialis are most often first affected. The lower part of the pectoralis major, the latissimus dorsi, trapezius and rhomboids are attacked in most cases. Atrophy of the serratus magnus is common; but it may escape even in severe cases. The deltoid, supraspinatus, infraspinatus and subscapularis usually escape. Atrophy of the forearm and hand muscles is rare.

In the legs, the flexors of the hip, the extensors of the knee and the glutei are most frequently affected. The muscles below the knee often escape entirely.

In the face the zygomatic muscles and the orbicularis are attacked. The face is dull and expressionless, the naso-labial fold is obliterated, the lips are habitually separated and the lower lip projects—myopathic facies. The face does not light up in conversation, in blinking the eyes are incompletely closed, and the articulation of labial consonants is defective. In smiling the mouth forms a straight line, instead of its angles being drawn upwards and outwards by the zygomatici. The power of whistling is lost. When the patient closes his eyes, or compresses his lips as forcibly as he can, they can be forced open with great ease. The buccinators are often affected, the tongue and the masticatory muscles never. The spinal muscles often atrophy, and in a few cases the abdominal muscles have been involved. The excitability of the muscles to faradic and galvanic stimulation usually diminishes in proportion to the wasting. The muscles never show fibrillary tremors. Sensibility is unaffected, and all the other functions of the nervous system are normal. Deformities are neither so common nor so severe as in the pseudo-hypertrophic form.

**Diagnosis.**—In isolated cases the diagnosis of myopathy from spinal progressive muscular atrophy is based upon the distribution of the wasting, upon the disproportionate weakness and the absence of fibrillation in the affected muscles and the age of the patient. When a family history of atrophy is obtained, dystrophia myotonica and peroneal muscular atrophy must be excluded. Dystrophia myotonica is distinguished by the peculiar prolonged response of some of the muscles to voluntary, electrical and mechanical stimulation, and by the distribution of the wasting. Atrophy of the sterno-mastoids, which is constant and severe in dystrophia myotonica, is never seen in the forms of myopathy now under consideration. In peroneal muscular atrophy the combination of atrophy in the lower limbs and small muscles of the hands, together with sensory disturbances in the lower limbs, is distinctive. In an early case, when the hand muscles are still normal and sensory changes are absent, the differentiation from myopathy may be impossible for a time.

**Prognosis.**—The disease shows wide variations in its course and duration. The atrophy may remain confined to the group of muscles in which it begins, or extension may take place after an interval of several years. It rarely extends beyond the muscles mentioned above. In most cases, even in those that begin in childhood, progress is extremely slow, and as no symptom of the disease is necessarily fatal, death usually results from other maladies unconnected with the disease.

**Treatment.**—Owing to the variable course of the disease, it is impossible to estimate the value of any treatment that may be employed. Massage, and especially voluntary exercises designed to bring the weakened muscles into play, seem sometimes to retard the progress of the disease.

## AMYOTONIA CONGENITA

**Synonyms.**—Oppenheim's Disease; Myotonia Congenita.

**Definition.**—A malady of early childhood, usually congenital and sometimes familial, characterised by extreme flaccidity, smallness and weakness of the muscles, which are not actually paralysed, by lowering of the faradic excitability of the muscles, by loss of the tendon-jerks and by contractures in the region affected.

**Ætiology.**—In most cases the disease is present at the time of birth; in a few cases it has appeared during the first year of life in an apparently healthy child, and sometimes following an acute illness, such as bronchitis or diarrhœa. Usually sporadic, it has occurred in several children of the same parents. Some authorities consider that it is a variant of the Werdnig-Hoffmann disease (*q.v.*) (p. 1565).

**Pathology.**—The chief morbid changes are found in the muscles. In these very

conspicuous pathological conditions are present, closely resembling those found in the myopathies. The three most striking conditions are—(1) the minute size of the majority of the muscle fibres, from  $7\mu$  to  $12\mu$ ; (2) the presence of a few very large or "giant" fibres reaching  $140\mu$  in diameter, and larger than any fibre occurring in normal muscle; (3) marked regressive changes in the giant fibres. There is increase of the connective tissue between the muscle bundles. Reduction in numbers of the ventral horn cells of the spinal cord occurs, and the ventral roots are small and poorly myelinated.

**Symptoms.**—The extreme flaccidity of the affected muscles is noticed from the time of birth. They are small and weak, and though there is no muscular wasting and no absolute paralysis, yet in many cases the limbs cannot be raised against the action of gravity, nor can the head be held up. The great relaxation of the muscles and ligaments allows of the most fantastic attitudes being assumed without pain. When the child gets older, he is unable to sit up, but when placed in the sitting position the spine bunches up from absence of any muscular support, and he is unable to support his weight upon the weak legs. The amyotonia is symmetrical, and affects the legs always, the trunk often, the arms not infrequently, but never the face. Notwithstanding the flaccidity, some degree of flexor contracture is usually present. The faradic excitability of the muscles is much lowered, but not lost. Sensibility and the sphincters are not affected. The superficial reflexes are normal, but the deep reflexes are invariably absent in the affected regions. The children are usually intelligent, with good bodily development and growth proceeds normally.

**Diagnosis.**—This presents no difficulty on account of the presence of the flaccidity at birth, the absence of the deep reflexes and the tendency slowly to improve. It has to be separated from those maladies to which it bears a superficial resemblance, namely, the myopathies, rickety weakness, obstetrical, infantile and diphtherial palsies.

**Course and Prognosis.**—Some of the children succumb during the early and severe stages of the disease, but the tendency of the disease is to improve slowly in the course of years, and in some cases almost complete recovery with return of the knee-jerks occurs.

**Treatment.**—This consists in aiding the natural tendency to improve with massage, passive movements and exercises, in treating contractures with tenotomy and in attending to the general health and nutrition.

## DYSTROPHIA MYOTONICA

**Synonym.**—Myotonia Atrophica.

**Definition.**—A disease of familial incidence, which begins usually in the third and fourth decades of life, and which is characterised by muscular atrophy of peculiar distribution and unlike that of any other disease. This atrophy occurs first and most in the sterno-mastoids and facial muscles, next in the muscles of the forearms, and may also be found in the muscles of mastication, in the vasti, and in the dorsiflexors of the feet and peronei. Associated with this wasting, but not commensurate with it, nor necessarily occurring in the same muscles, is a peculiar difficulty in relaxing the muscles after effort, called "myotonia", which gives to this malady an especial feature which at once separates it from all other forms of muscular atrophy. Signs of bodily dyscrasia are often present, the most important of which are cataract, premature baldness, atrophy of testicles, loss of sexual power and general bodily wasting. This disease was first placed upon a firm clinical basis by Batten and Gibb, and Steinert in 1909. Curschmann in 1912 adopted the term *Dystrophia Myotonica* as being more correctly descriptive.

**Ætiology.**—This condition is probably always familial, and the heredity is homologous—that is, it is transmitted from the same child-rank, in a number of

apparently unconnected families at a common distance from one and the same ancestor, and often it seems to be entirely confined to one child-rank. The descent of the latent tendency is equally through the males and females, but the males more frequently transmit. The presence of the heredo-familial disease in earlier generations is often betrayed by other signs, such as cataract, frequent celibacy, childless marriages, high infant mortality and a dying out of certain branches of the family. The malady has been observed at the age of 10 years, but usually the onset occurs between the ages of 20 and 35 years. A large number of the patients have been unusually gifted and proficient in athletics prior to the onset. Both sexes may be affected. No exciting causal factors are known.

**Pathology.**—No definite changes have been found in the nervous system. The muscles presenting the myotonia have repeatedly been examined and found normal. In the atrophic muscles the morbid process singles out certain fibres especially, so that thick and thin fibres are found lying together. There is increase of the muscle nuclei round thick and thin fibres alike, though some atrophic fibres may be found with no increase of nuclei. Recent biochemical and electrographic studies by Brown and Harvey of a form of congenital myotonia in goats suggest that there is no functional disorder of neuromuscular transmission of the motor impulse, but that the disorder is in the muscles themselves.

**Symptoms.**—The onset is gradual and the course extremely slow. The first symptom to call attention may be, either the difficulty in relaxing after muscular effort—the clinging of the hand to the tool which has been grasped, the smile that is so slow to disappear—or the weakness and wasting of the muscles. The two chief signs of the disease—the myotonia and the wasting—seem to have no connection the one with the other, either as regards coincidence in time or place. The myotonia may appear years before there is any obvious wasting. Moreover, the muscles which show the most conspicuous myotonia are often those which are not wasted, and finally those muscles which waste greatly tend to lose any sign of myotonia which they may have had. The extent and the intensity of the muscular atrophy and of the myotonia show great variations. The atrophy may be widely spread, and many muscles may be myotonic, or the former may be severe and the myotonia slight, or both may be present in minor degree only. Lastly, there are cases in which only the atrophy or only the myotonia is present. The myotonia consists in an inability to relax a muscle immediately after it has been put into voluntary contraction, and the greater the effort used in contracting the muscle, the greater the difficulty with relaxation. The patient grasps one by the hand, and is unable to disengage the hand, but pulls it away still grasping, and it may take seconds to relax. He smiles quickly to a suitable stimulus, and the face remains fixed at the height of the smile for long after the emotion has vanished. In eating, his jaw becomes fixed, he is unable to perform alternating movements in the muscles which are affected except at a very slow rate. When the myotonia is severe and general, he is liable to fall like a log when walking, from inability to relax muscles which have been put into contraction. The myotonia is seen most often and to a greater extent in the flexor muscles of the forearm and in those of the face, but it may be quite general. In the same patient it may be very marked at one time and absent at another. The muscular weakness and wasting usually have a most typical distribution, involving the sternomastoids and other muscles of the neck, the facial and masticatory muscles—giving rise to the sad “myopathic” face, the vasti of the thighs, the dorsiflexors of the feet and the flexor muscles of the forearms, and this is the usual order in which the muscles are affected. It is always in one or other of these groups that the wasting commences, but sometimes the sequence of muscles attacked is quite different. Fibrillation does not accompany the atrophy. The electrical reactions show a reduction both to faradic and to galvanic stimuli, with a tendency to a polar change. The “myotonic reaction” consists in a very long-lasting contraction when the muscles are stimulated with every



form of stimulus, and if the latter be strong it may last as long as 30 seconds. This is usually present in the muscles which are myotonic and not wasted and some modification of it is often superadded to the other electrical changes in those muscles which are wasted.

The affection of the muscles of the face and jaw entails some alteration of articulation and phonation. The voice is low, it lacks intonation and has a definite nasal quality. Sensibility is not affected.

The rule is for the tendon jerks to be diminished or lost, and it is very rare for all the jerks to be present in any case.

Apart from symptoms and signs connected with the muscles, the most important sign of the dystrophy is cataract, which occurs in more than half of the cases. This cataract is often met with in otherwise healthy brothers and sisters of those who have the muscular changes, and in otherwise healthy members of earlier generations in the afflicted families. In succeeding generations after its first appearance, the age of occurrence of this cataract shows remarkable "anticipation"—that is, commencing at first as senile cataract, it appears at an earlier and earlier age with each successive generation, until with fully developed myotonia atrophica it appears in youth. The presenile cataract of the dystrophic generation begins as small peripheral opacities, first in the posterior and later in the anterior cortical lamellæ, sometimes with fine point-like opacities scattered through the lens. It ripens quickly to a total soft cataract, with a small central nucleus.

The genital organs remain infantile in some cases; celibacy and childless marriages are common. More often sexuality is normal until the onset of definite symptoms, after which desire and power disappear, and ultimate atrophy of the testicles is usual. Early frontal baldness is the rule. A general wasting of all the tissues of the body is seen in many cases.

**Diagnosis.**—There is no difficulty in the diagnosis when the distribution of the muscular atrophy is typical and when myotonia is obvious; it simply involves a recognition of the unique characteristics of the disease. When the myotonia precedes the wasting, the age of onset will distinguish this malady from Thomsen's disease, myotonia congenita, and the oncoming of any sign of facial weakness or muscular wasting will make the diagnosis certain. When the myotonia does not appear until long after the wasting is apparent, the diagnosis is much more difficult, but the wasting of the sternomastoids is characteristic.

**Course and Prognosis.**—This malady usually progresses very slowly, but occasionally very extensive and incapacitating wasting of muscles and weakness may develop within a year of the first symptom. Some cases seem to remain stationary for very long periods. The tenure of life is certainly short in all cases, and does not appear to be prolonged beyond the middle of the fifth decade. The oldest patient reported in the records as still living was aged 50 years.

**Treatment.**—It has been found that the administration of quinine, gr. 10 to 15 daily, lessens the myotonia considerably. Neither electrical treatment nor massage has the slightest effect in altering the course of the disease.

## MYOTONIA CONGENITA

**Synonym.**—Thomsen's Disease.

**Definition.**—A very rare malady, commencing in early childhood, which is hereditary and familial, and characterised by a striking slowness in the relaxation of the muscle after voluntary effort. On voluntary contraction the muscles pass into a spasm which relaxes very slowly, resembling the contraction of the veratrinised frog's muscle, and its subsequent slow relaxation. Peculiar changes in the electrical excitability of the muscle and hypertrophy of the muscle fibres are constant.

**Ætiology.**—Beyond the facts that the malady is usually hereditary and familial, only a few sporadic cases occurring, and its incidence in early childhood, nothing is known of the causes. Cold, heat, fatigue and hunger conspicuously increase the symptoms.

**Pathology.**—The affected muscles are actually hypertrophied, and are always firmer to the feel than normal muscles, while sometimes they show a board-like hardness. The individual fibres show considerable hypertrophy.

**Symptoms.**—The presence of the disease first becomes evident from slowness, clumsiness and awkwardness of movement, with a great tendency to fall if the balance is upset. This is often most noticeable after rest, when, on attempting to move, the limbs seem glued down and move very slowly. Often the patient is able with exercise to work the stiffness off, and the myotonia lessens in the muscles which are being used; but if he is suddenly called upon to put another set of muscles into action, as, for example, by losing his balance, he is at once caught up by the myotonia and so is apt to fall. In other cases the myotonia increases or is uninfluenced by exertion. The muscles of the legs are, as a rule, most affected, but sometimes all the muscles of the body may be involved.

Passive movement does not reveal the presence of any rigidity. The abnormality affects only the relaxation of the muscles after voluntary contraction, the peculiar feature being the slowness of relaxation due to the continuance of the contraction of the muscle fibres for a variable number of seconds after voluntary impulses have ceased. The peculiarities of electrical excitability bear the name of the "myotonic reaction" of Erb. The contraction, either on faradic or galvanic stimulation, lasts much longer than the normal and relaxes very slowly, and this is more marked the stronger the current used; with the application of galvanism, slow wave-like contractions of the muscle are seen to proceed slowly from the cathode to the anode. There is no pain, no sensory disturbances or loss and the sphincters and reflexes are unaffected.

**Diagnosis.**—The only malady which can be confused with Thomsen's disease is dystrophia myotonica, in which the myotonic symptoms and signs are identical. In the latter malady, the onset is at a much later age, the incidence of the spasm is upon local groups of muscles, and the characteristic weakness of the facial muscles and atrophy of the sternomastoids, etc., at once distinguish it.

**Course and Prognosis.**—Thomsen's disease has no tendency to shorten and destroy life. It tends to become more marked from infancy to puberty, and then less marked again as age increases. It has never been known to recover spontaneously.

**Treatment.**—No cure for the disease is at present known. The administration of quinine hydrochloride, in doses of gr. 10 to gr. 15 by mouth t.d.s., may give considerable symptomatic relief. Conditions which increase the myotonia, such as cold, fatigue and hunger, should be avoided. Most patients are the better for regular exercise, as was observed by Thomsen, who was himself afflicted with the disease.

## MYASTHENIA GRAVIS

**Definition.**—A chronic malady of adult life characterised by an excessive fatigability of the voluntary muscles, especially those innervated by the cranial nerves. This leads to a variable paralysis of the muscles concerned, which is brought on or rapidly increased by exertion, and tends to improve with rest, but which may ultimately become permanent.

**Ætiology.**—The malady seems to have become more prevalent in this country during the past 30 years. It affects predominantly young adults between the ages of 20 and 30. It very rarely occurs before puberty, but cases beginning in middle or late life are by no means as uncommon as was formerly supposed. The sexes

are equally affected. Nothing is known of any causal factor, either immediate or remote, though the first onset of symptoms has not infrequently been noted after an acute infection, particularly of the naso-pharynx. The one clinical association which cannot be ignored is with exophthalmic goitre, for not only may myasthenia follow that disorder but the ocular palsies and muscular weakness which may occur in Graves' disease bear no small resemblance to those of myasthenia.

**Pathology.**—The only change found within the nervous system, either central or peripheral, is slight atrophy of those nerve cells which supply long paralysed muscles, and these changes are certainly not primary. Nor is there any essential histological change in the affected muscles except where long-standing complete paralysis is associated with the degeneration of long disuse. Small aggregations of lymphocytes, known as lymphorrhages, have been described in the muscles in some cases.

In a large proportion of the cases subjected to autopsy some degree of persistent thymus has been found. This may vary between a well-formed organ weighing several grammes and small remnants or thymic rests. These thymic elements may show evidence of proliferation or degeneration.

Chemical examination reveals no significant disturbance in the metabolism of glucose, calcium, phosphorus or creatinine, although, in common with most muscular disorders, creatinuria may be present in myasthenia. There is evidence that the muscle potassium is increased, and that it reverts to normal when the myasthenic symptoms are abolished by an injection of neostigmine.

The view expressed in earlier editions of this book that the seat of the disorder of function responsible for myasthenia gravis is at the myo-neural junction has of recent years received confirmation from observations made with physostigmine and the synthetic substance neostigmine (Prostigmin). It is believed that the normal transmission of impulses from the motor nerve fibres to the voluntary muscles through the motor nerve endings depends upon the liberation at the end-plate of acetyl-choline. In myasthenia the failure of effective innervation may be due to the inadequate liberation of acetyl-choline, or to its premature or excessive destruction by choline esterase, or to the presence of a curare-like substance antagonistic in its action to acetyl-choline. The administration of physostigmine temporarily delays the destruction of acetyl-choline by the choline esterase normally present in the blood, and during the period of its activity renders muscular contraction normal. The exact nature of the defect still awaits elucidation.

**Symptoms.**—The onset of the disorder is usually insidious but in rare cases may be acute. The symptoms can all be related to excessive fatiguability of muscles, and thus make their appearance after use and improve with rest, and are most severe in the evening and least marked on first waking in the morning. The muscles first affected are usually those innervated by the cranial nerves, particularly the external ocular muscles, but as the disease progresses the extent of the disorder spreads to involve the muscles of the neck, limbs and trunk. Sometimes, however, the characteristic weakness is universal from its commencement.

Ocular symptoms are of the greatest importance. The clerk finds that towards the end of the day he is seeing double, or that one or both upper eyelids droop. In the morning on waking the ptosis and diplopia have both disappeared, only to return after another day's work. The school teacher notices that as he lectures his voice gradually grows weaker and more husky, and acquires a nasal quality. This too clears up with a rest, and is invariably worse towards the end of the day. Difficulty in swallowing is a common symptom. At the commencement of a meal all may be well, but as it goes on the food is forced down with increasing difficulty until finally swallowing is no longer possible. Many patients find that they can eat their solid meals only in the early part of the day, and by evening can at best sip fluids. Nasal regurgitation of fluids towards the end of the day is common. The act of chewing

may give rise to so much fatigue of the masticatory muscles that only soft foods can be taken, and towards the end of a meal the lower jaw may be too heavy for the exhausted muscles to sustain, and the patient may be seen supporting it with the hand and attempting in this way to supplement the process of mastication. The muscles of the face commonly share the weakness. Friends observe that towards the end of the day the patient's face is expressionless, or comment on the peculiar "snarling" quality of the smile. The patient may complain that he cannot smoke a cigarette or whistle, as the lips cannot maintain a sustained pressure. In severe cases the eyelids can only be closed with difficulty, and it may be noticed that the patient sleeps with the eyes open. Fatigue of the neck muscles may be an early symptom. The head feels more and more heavy and finally can only be supported with the aid of the hand. The weakness may affect any or all of the muscles of the limbs and trunk, though the arms are more frequently involved than the legs. The soldier may find that after a few minutes rifle drill becomes impossible, or the schoolmaster that after writing on the blackboard for a short time he is no longer able to support the weight of his arm. Women may complain that they cannot keep their arms up long enough to do their hair. Whatever the initial presenting symptom may be, the extent of the disorder gradually spreads until a wide range of voluntary movements is affected.

Few diseases present a more characteristic picture than does myasthenia gravis in its established stage. The variable and usually asymmetric ptosis is seldom absent. It can readily be brought on or increased by asking the patient to look upwards for a few seconds, and when severe one or both eyes may be fully closed. Unlike the ptosis of tabes, there is little compensatory wrinkling of the forehead, because the frontales share the weakness of the levatores palpebrarum. The ocular palsies are characteristic; any or all of the external ocular muscles may be involved, and strabismus is common. The paralyses rapidly increase in severity and extent with ocular movement, and a few attempts to glance from side to side may bring all oculomotor activity to an end. The pupils are always normal in their reactions. The ocular more than any other muscles show a tendency to develop complete and unvarying paralysis in long-standing cases, and, with the exception of the extremely rare disorder described as progressive nuclear ophthalmoplegia, there is no disease other than myasthenia which gives rise to a complete external ophthalmoplegia with normal pupils in the absence of other signs of nervous disease. Fortunately when the stage of permanent ophthalmoplegia is reached the optic axes are usually parallel and diplopia disappears.

The facies of myasthenia, with its lack of expression, the inability to close or pucker the eyes or to wrinkle the forehead and the peculiar, weak, nasal smile, is unmistakable. Weakness of the muscles of palate, pharynx and larynx may be general or localised, and at first is present only after use. Permanent paralysis of the soft palate is commonly seen in chronic cases, that of the vocal cords or pharynx being much more rare. Severe weakness of the tongue may be associated with some reduction in the size of the organ but with this rare exception wasting is not seen in myasthenic muscles, nor are the tendon reflexes disturbed. Sensibility and sphincter functions are unimpaired. The excessive tendency to fatigue which is responsible for the symptoms of myasthenia is also seen in the muscles in their response to electrical stimulation. With an interrupted faradic current the contraction of the muscles is at first normal, but instead of remaining at a similar strength for an indefinite period it rapidly decreases until it disappears altogether. If the stimulation is discontinued for a few minutes and then recommenced, there is a further response, which tires more readily than the first. After exhaustion by faradism, some volitional response remains.

**Diagnosis.**—This is seldom a matter of difficulty if the variable paralysis, increasing with fatigue and improving with rest, is conspicuous, for this phenomenon

occurs in no other disease. Even so, in its early stages, the malady is often mistaken for a hysterical disturbance. More legitimate difficulty may arise when only isolated and permanent paralysis is present, especially as such cases are liable to present themselves in ophthalmic or laryngological departments. It should be remembered that any unilateral or bilateral palsy of muscles supplied by the cranial nerves may be myasthenic. Here the history of slow onset, with variable paralysis and fatigue phenomena, can nearly always be obtained, and the absence of the usual signs of gross lesions of the brain-stem nuclei, or of progressive diseases affecting the latter, should avoid confusion. When, as sometimes happens, myasthenia begins with a unilateral ophthalmoplegia or laryngoplegia, the diagnosis may be really difficult. The possibility of such should be borne in mind, and a careful watch kept for the appearance of conclusive evidence. An intramuscular injection of 1 ml. of the standard solution of neostigmine may be used as a diagnostic test, its effect being to bring about within half an hour the temporary abolition or very great amelioration of any variable symptoms that are due to myasthenia gravis.

**Course and Prognosis.**—Although myasthenia gravis is invariably a dangerous disease, as its name implies, its course is extremely variable. In some cases the degree of the muscular involvement steadily increases in extent and severity until a fatal outcome is reached in a few months or years. In such cases death usually results from progressive respiratory failure or from aspiration broncho-pneumonia consequent upon pharyngeal and laryngeal palsy supervening upon a state of inanition. Not infrequently death is sudden and unexpected and appears to be due to syncope. In other cases, the disorder may remain confined for a long period to small groups of muscles, particularly those of the eyes, and may result in a condition of multiple cranial nerve palsies of an unvarying character with a survival period of 20 to 30 years. In such cases more generalised and active symptoms may reassert themselves at any time, and death may occur after many years of stability. In yet a third group, long periods of complete remission may occur, ultimately followed by a recurrence of characteristic symptoms, which on this occasion may prove to be progressive.

**Treatment.**—The treatment of this disorder was revolutionised by the discovery of the specific effect of physostigmine and its synthetic relative neostigmine. Few things in medicine are more dramatic than the sudden amelioration of symptoms, the relief of ptosis, the recovery of ocular movement and the return of facial expression, that follows the administration of one of these drugs. The effect is, however, transitory, lasting only from 4 to 6 hours, and is in no sense curative. It is usual to administer 2 to 4 ml. of neostigmine (1 to 2 mg.) subcutaneously two or three times daily half an hour before meals. If the drug causes abdominal discomfort or palpitation it may be combined with atropine sulphate gr.  $\frac{1}{10}$ . Alternatively, the drug may be given by mouth in doses of 10 to 25 mg. three or four times daily. In severe cases the period during which the effect of the drug is wearing off may be attended by severe and alarming weakness, and over a prolonged period the beneficial action of the drug tends to lessen and an increased dose is required to be effective. The administration of ephedrine gr.  $\frac{1}{2}$  to 1 b.d., has been found beneficial: it may be sufficient of itself to keep a mild case in reasonable comfort or it may be used as an adjunct to neostigmine.

The frequent association of a persistent thymus with myasthenia has long received attention and has led to attempts to treat the disorder by influencing this organ. Numerous isolated examples of improvement in symptoms following radiotherapy to the thymus are recorded in the literature, but the results were not constant. Of recent years a number of cases have been treated by surgical removal of the thymic remnants, with encouraging results. This operation is one which carries a considerable mortality, and should only be attempted by an expert in thoracic surgery. Of the patients who have been so treated some have shown a degree of improvement amounting to a cure and quite different from anything seen with neostigmine therapy.

Others, after a period of improvement, have relapsed. Others, again, have shown no material alteration in their condition. The procedure should at present be regarded as an encouraging but not yet fully established advance in treatment.

## FAMILIAL PERIODIC PARALYSIS

**Definition.**—A flaccid paralysis affecting the muscles of the trunk and of the extremities, associated with loss of the deep reflexes and diminution or loss of faradic excitability in the muscles. The paralysis is temporary in character, though it may be fatal during the attack, and it recurs at intervals. It is a rare malady, some 200 cases having been reported in the literature.

**Ætiology.**—It has been noted as early as the fifth year, and as late as the thirtieth year; but usually it appears about the age of puberty. Most of the cases occur in the male sex. Heredity is very marked, and the malady has been traced through five generations. Transmission may occur either through the male or through the female, and not infrequently a generation is skipped. Several members of the same family are usually affected.

**Pathology.**—Several cases have come to necropsy, but no lesion which could be associated with the symptoms was found. Biopsy of the muscles has given entirely negative results. During an attack, significant fall in the serum potassium has been demonstrated. An attack may be brought on by a large intake of glucose, especially if an injection of insulin is given at the same time.

**Symptoms.**—The clinical picture is so striking as to be almost dramatic. The patient retires to bed feeling perfectly well, and awakens in the morning without pain or malaise, but with a flaccid motor paralysis, which always involves all four extremities, and which may reach all the muscles of the body, except those of the organs of speech, deglutition and respiration, and even these are often partially involved. Severe involvement of these vital muscles during an attack has caused death. The bladder and rectal functions are retained, and it is unusual for the patient either to void urine or fæces during the attack. The paralysis is usually at its height on waking; but it may subsequently increase. After fasting for a variable time, from a few hours to a few days, it passes off, sometimes gradually, sometimes rapidly. In one family it was astonishing how the patients on waking in an attack could judge invariably how long the particular attack would last. They could judge with unfailing certainty when ability would return, and were in the habit of arranging their business accordingly. Most of the patients in addition to the severe attacks of paralysis suffer from what they call "morning weakness", temporary inability to grip with the hands, and slight disability with the feet on waking. The paralysis in periodic paralysis is flaccid, and there is loss or marked diminution of response to faradism during the paralysis. The deep and superficial reflexes are lost in the paralysed region. Objective sensation is not affected; but there may be subjective sensations of tingling and numbness, and the muscles may be a little sore and stiff after the attack. Flushing of the face and profuse sweating may occur during an attack. There is an invariable tendency for the attacks to diminish in frequency and severity after middle life is reached.

**Diagnosis.**—This must be evident to any one acquainted with the symptoms of the disease.

**Treatment.**—Potassium chloride in large doses (up to gr. 30 or 40) will avert or cut short an attack. No other remedial measure is known.

J. PURDON MARTIN.  
J. ST. C. ELKINGTON.

## SECTION XIX

# PSYCHOLOGICAL MEDICINE

### INTRODUCTION

PSYCHIATRY is concerned with forms of illness as widespread and diverse as those of somatic medicine. There are almost as many beds in mental hospitals, colonies for defectives and allied institutions as in all other hospitals put together; and there is an undoubtedly large, if unnumbered, part of the population who have mild mental disorder not needing mental hospital care: hysteria, obsessional neurosis, hypochondria, chronic depression, paranoid states and so forth. The diversity of this widespread group of illnesses depends on their being disorders of mind—disorders, that is, of the human function which comprehends and sums up all other functions of the organism, serves to relate a human being to his complex environment, and is the chief token that he is an individual, and not a sample. Mental disorders are therefore varied, as are the people who suffer from them. It is only by ignoring most of what is individual in these illnesses that a few common types or categories can be recognised, comparable to the "diseases" of somatic medicine. Such a procedure is necessary for practical ends; material must be classified. Moreover, a biological foundation may be assumed for the syndromes with which psychiatry works. They stand for the main ways in which a human being can become mentally unhealthy. There are only a few such ways, and they are determined by the structural and functional patterns inherent in the organism. Diversity arises through their becoming manifest under the influence of each individual's special environment and in combination with his other inherited tendencies. Diversity, therefore, can be due to a combination of single hereditary causes and to the effect of each individual's environment throughout his life upon his development and behaviour. There is always interplay between inheritance and environment. Part of the psychiatrist's business is to discover how this interplay has led to the present illness. The interplay, moreover, is sufficiently varied in the course of each patient's life to make prognosis and the effect of treatment a matter of individual study, rather than of summary inference from the diagnosis, once made.

Treatment is only another special instance of the environment acting on the patient; its power and limitations for him cannot be judged without considering what effects this or that experience has had on his previous life. Consequently the psychiatrist, even more than the general physician, must study illness in two ways: first, as showing some typical pattern of morbid behaviour with characteristic pathological changes, and tending to run along well-known lines; and secondly, as a patch of personal biography, something to be understood, rather than classified in terms of psychology and physiology. The two methods are complementary, though, in a brief textbook presentation, the former must be the more prominent.

There is no dividing line between somatic medicine and psychiatry. Psychiatry, although it has to work in part with social and psychological conceptions of which general medicine has hitherto felt less need, suffers greatly when it limits itself to this way of regarding mental phenomena. It cannot safely ignore the relationship between bodily happenings and the patient's state of mind. Crude instances of this relationship are the delirium that accompanies an acute fever and the irritable fatigue (neurasthenia) that may follow it; the insanity that is due to cerebral tumour or general paralysis of the insane; the obsessional neurosis that follows encephalitis lethargica; and the hysterical symptoms of disseminated sclerosis. There is no

mental disorder, mild or severe, in the causation of which bodily disease may not play an important part. Moreover, it is not only in crude instances of structural or chemical disease that the relationship between bodily and mental illness may be recognised. A human being does not exist as a rarefied mind united with a solid body; he is an organism all of whose subsidiary functions contribute to this highest function—his mind—which brings him not only consciousness, but also an integrated behaviour in relation to his surroundings. Disturbances, transient or permanent, of these part-functions (for example, in the sensory apparatus or the circulatory system) will have some effect on his state of mind. Changes in the central nervous system are the most obvious instance of this, but the endocrine glands, the autonomic nervous system and the metabolic processes are often of notable significance in the various maladjustments summed up as mental disorder. A human being is constantly responding to, and influencing, his surroundings; but his doing so is conditioned by the various parts of his body and the way they are working. It is likewise, and equally, necessary to weigh psychological influences and effects when deciding the pathogenesis or the treatment of predominantly physical illness. The part that emotion may play in the chain of events that cause or aggravate peptic ulcer has been lately demonstrated in a manner to convince the sceptic, and there is less dramatic but equally weighty evidence attesting the interplay between psychological and physical happenings which may influence the outcome of many a surgical or other illness. Much of the recent enthusiasm for "psychosomatic" medicine turns on a belated recognition of this. It is plain that psychiatric issues must be the concern of all doctors, not merely the psychiatrist's preserve; and that psychological happenings differ from physiological in their deceptive accessibility to familiar methods of observation, in their almost Gordian complexity, and in the concepts found most useful for describing and explaining them, rather than in any essential quality which would keep them permanently distinct.

Before the categories and clinical features of mental illness are described, the principles of psychopathology, prognosis and treatment call for some very brief consideration, since without them psychological medicine written down is a repellent catalogue of details. Though the principles set forth may seem trite or too obvious to be worth stating, it is unfortunately the case that they are often not applied as fully as they might be to the clinical study and treatment of mental disorders.

**Psychopathology.—INTRINSIC CAUSES.**—The intrinsic causes of mental disorder are those which depend on heredity and on phases of development, *e.g.* the climacteric. Extrinsic causes, which come from the environment, are either mental experiences or physical damage. The distinction between intrinsic and environmental, like that between physical and mental, is convenient but artificial; a long sequence of related happenings both within and without the patient's body goes to the causation of any mental illness. It is, of course, possible in many instances to discover some indispensable link in this chain of causes—an intoxication with alcohol, for example, a syphilitic infection of the brain, an inherited predisposition to periodic insanity, a bereavement—which may legitimately be singled out as the chief cause and classified as intrinsic or extrinsic, but this is more valuable for formal and didactic purposes than clinically. Actual cases usually show a complicated aetiology. Thus, a man whose parents had both been subject to melancholia became himself profoundly depressed after the death of his wife, and attempted suicide by drowning. He survived, but during the resulting pneumonia he was delirious and threw himself from an upper window, crying out that he must go to his wife. The causes of the mental disturbance in this case were many and obvious; numerous they always are, but not always obvious. One cause may, of course, be prepotent.

The more detailed the analysis of a patient's endowment and experiences, the more entangled physical and psychological, internal and external factors seem to be.

**Heredity and constitution.**—The hereditary factor is not a general neuropathic



taint; there are specific predispositions to one or other anomaly. These predispositions are transmitted in accordance with familiar genetic principles, summed up in the modern gene-theory of inheritance. Studies of families and of twins have proved the importance of the hereditary factor in the major non-organic psychoses, though they have not yet sufficed to reveal with certainty the number and location of genes concerned in the transmission of the hereditary types of morbid reaction.

Among the main reasons for this incompleteness in our knowledge is the impossibility of concluding that an inherited trait is not present, merely because it is not manifest in some recognisable form. Other inherited factors and, most of all, the environment, will in many cases determine whether an individual predisposition is to become evident or not. Thus a man may have an inherited tendency to melancholia which remains latent until a financial reverse or disease of the cerebral arteries provides the conditions necessary for its manifestation. It is true that some inherited predispositions, *e.g.* to Huntington's chorea, are almost independent of the environment in this respect, but such are exceptional.

More than one type of proneness to mental disorder can be inherited by the same person. He may, for example, be prone not only to periodic insanity, but also to schizophrenia. Muddled proclivities of this kind account for anomalous clinical pictures, frequently met with and difficult to classify as either one syndrome or another. The "either-or" kind of diagnosis is often out of place or misleading in psychiatry because of the commonness with which more than one constitutionally rooted type of illness may be found in the same patient. Syndromes are frequently combined; to grasp their clinical meaning one may have to investigate the patient's family not only as to mental disorder, but as to normal characteristics of temperament also.

The signs of a transmissible tendency to some mental disorder may not be actual illness, but only a special kind of personality. There are certain varieties of personality which show some of the essential features that characterise certain types of mental illness; the differences between personality and illness seem then to be of degree rather than of kind. Moreover, those who manifest one or other type of illness are often found to have had the type of personality that is functionally similar to it. So close may the similarity be that it is difficult to decide when the illness has begun, because there was no sharp dividing line, in time or in form, between the more or less normal previous personality and the actual disorder. This frequency of association and similarity of form between the normal state and the illness points to the constitutional background of mental illness, and shows how hereditary tendencies can express themselves in more or less normal ways in personality before the catastrophe of an obvious illness has directed attention to them. Nor is it only in the personality that inherent proclivities may be revealed; certain types of bodily structure, too, occur much more frequently in those with a particular mental constitution or mental illness than in the rest of the population. The most striking instance of this is the frequency with which a "pyknic" bodily habit and a "syntonic" personality are found among those who have periodic attacks of mania or melancholia (see p. 1646). It is not common to find pure examples of mental or physical types in the population, and recent work, *e.g.* that of Sheldon, has aimed at making it possible to designate the mixture of components in any individual by a taxonomic formula rather than by ascribing them all to one or other type; but whatever method of description be employed, the association of osseous and muscular structure with a particular personality structure and perhaps with a predominant form of autonomic response seems frequent enough in healthy as well as mentally ill persons to warrant classing physique, physiological behaviour and personality together, however tentatively. Such constitutional features, whether mental or physical, indicate that inherited tendencies can body themselves forth in normal physical and psychological structure before morbid exaggerations of them make an appearance. The varieties are some-

times called by appropriate names, *e.g.* schizoid, cyclothymic, syntonio, obsessional, hysterical, paranoid. The relationship is not a simple one. There are very many people with these types of personality who never fall mentally ill.

A pronounced personality, belonging to one or other of these types, does not indicate that the person who exhibits it is likely to have a mental illness, but only that if he should have a mental illness, it will probably be of the corresponding type. As with all inherited anomalies of which the crude manifestation is delayed until adult life, there may be for many years none or only mitigated signs of the proclivity; these may be indistinguishable from what occurs in normal people. The more pronounced the anomaly of personality, the more likely that it portends a mental illness, or, at any rate, a proclivity to the mental illness in specially adverse circumstances.

In studying personality, the psychiatrist can have recourse to several techniques, besides direct observation and the descriptive method based on the reports of those familiar with the individual studied. The most ambitious are projective methods, of which the Rorschach ink-blot and the thematic apperception test are examples. The patient's fantasy is evoked by more or less standardised stimuli, and inferences drawn from what he says and does in these circumstances. Expert and cautious interpretation is indispensable. This applies to the whole of the growing array of psychological methods of assessing personality.

In the foregoing, personality and constitution have been spoken of as though they were static, innate attributes of the human organism. Neither of these epithets, however, is appropriate, not even in respect of bodily constitution. Responsiveness and plasticity are essential to human development of every kind; there is a constant interplay of personality with the outer world, modification of it and by it. The main pattern of development is doubtless determined by innate, inherited factors—bodily structures grow, instincts come into play and the general direction of functional activity is predetermined. But general directions and main patterns mean little unless they are given body and content by individual experience. Nutrition, for example, can deflect the body from its ordained pattern or enable its fulfilment; all sorts of physical interference can maim it or improve it: the same is profoundly, if obviously, true of the mental side of human growth and maturity. Consequently, each patient's personality is not to be assessed as conforming to a frozen artificial type, but as a complex of dynamic functions, changing in outward form, sometimes in unstable equilibrium, and none the less powerful for being subterranean. Here, as was said earlier of psychiatry in general, there must be two ways of viewing the data: in classes, and as individual living biographies to be understood rather than schematised. Both methods are necessary to any complete psychopathology.

*Phases of development.*—A concrete instance of the foregoing is the change that occurs at certain turning-points, such as puberty, pregnancy or the climacteric. Endocrine and other physical changes at these epochs may be accompanied by psychological disturbances, the severity and form of which bring them under the notice of the psychiatrist. They are dramatic episodes in a lifelong process of growth, maturity and involution or decay, which is marked by plasticity and development of varied functions in the first stage, stability and differentiated adaptation in the second, emotional lability and suspicion, intellectual narrowing, rigidity, failing grasp and memory, in the last. The mental disturbances which may occur at different ages are much influenced by these intrinsic factors and tendencies.

*EXTRINSIC CAUSES.*—The outer world impinges on human beings from the day of their birth, or even their conception, in more and more complicated ways, as they themselves become more complicated. In other words, the environment is, for the individual, as complicated as he can make it; and that will depend on how far he has himself developed hitherto. Human beings deal selectively, not merely passively, with experience. At each stage of their growth, previous experience helps to determine what they will select from their environment, and how they will use this and

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*EXTRINSIC CAUSES.*—The outer world impinges on human beings from the day of their birth, or even their conception, in more and more complicated ways, as they themselves become more complicated. In other words, the environment is, for the individual, as complicated as he can make it; and that will depend on how far he has himself developed hitherto. Human beings deal selectively, not merely passively, with experience. At each stage of their growth, previous experience helps to determine what they will select from their environment, and how they will use this and

integrate it, to serve in its turn as the partial determinant of further growth and integration (the other determinants being innate ones). "Experience" is here being used in the widest sense to denote the response of a human being to the impact of the outer world upon him, whether it be consciously recognised as such or not at the time.

It is, therefore, impossible to give adequate consideration to any aspect, including the psychological, of a human being's way of dealing with the outer world unless one pays regard to his previous experience, mental and physical, and to the present state of his whole organism, mental and physical. The cultural milieu in which he has grown up must be taken into account. Too partial a regard for subsidiary functions, whether physiological or psychological, may lead one away from the living human being, who is an integrated organism, not a collection of disparate mental and physical systems; similarly, too concentrated a gaze on this latter aspect, i.e. on the socially organised person, to the neglect of part-functions, may make one see only a disembodied spirit, as remote from medicine as from daily life.

*Physical experiences.*—Some external happenings influence the mental state chiefly by way of the body: infection, physical trauma, intoxication and metabolic and endocrine disturbances due, wholly or in part, to environmental influences may result in mental disorder. In many of these instances, the mental change is mediated by way of some cerebral damage, and the clinical picture is of the organic neurogenic kind, e.g. dementia. It would be wrong to attribute the whole of the mental disorder to the cerebral damage; but to it is referable the core of the psychosis. Some diseases have an incidence on special functions and parts of the central nervous system, which determines characteristic features in the mental picture, e.g. the anxious fidgetiness of the patient who has had chorea, the stiff mind and obsessional thoughts and movements of the post-encephalitic, the hysterical phenomena of the elderly arterio-sclerotic patient or the man poisoned with carbon monoxide, the aphasia and apraxia of the post-apoplectic, the silly "moria" of the cerebral tumour. In the main, however, it is not possible to correlate mental symptoms with special areas or kinds of cerebral damage—partly because the brain is not the only structure concerned, partly because it acts as a whole, and also because the presumptive changes in it are too evanescent and delicate to be accessible to our crude methods of examination. Even the electro-encephalogram, which seemed to promise so much, has contributed little to the understanding of cerebral happenings in mental disorder other than epilepsy, though it is valuable in suggesting the presence or indicating the site of a lesion, e.g. in the temporal region.

To limit oneself to the brain in studying the somatic correlates or basis of mental phenomena would be an error. In the physical accompaniments of emotion, the whole body participates through the mediation of the vegetative nervous system and the endocrine glands. This is significant, because emotional upset is one of the most important phenomena of mental disorder. The sequence of psycho-physical happenings of which an emotional upset is the climax and the outward sign, may be started not only by some mental happening, but also by physical experiences—intoxication with a drug, or a circulatory disturbance, or a metabolic upheaval such as acute hypoglycæmia. Whether, for example, this hypoglycæmia comes from outside, as an injection of insulin, or arises (as it rarely may) from within the body, as a "spontaneous" deficiency, is of little consequence in its bearing on the mental disturbance engendered. The chief emphasis lies on the physical apparatus through which so widespread an affection of the whole organism can be evoked, just as in other circumstances the emphasis would lie on the psychological apparatus which serves the same end. This applies more widely than to emotional disturbances alone. Where a symptom is, on the face of it, definitely physical or definitely mental, its causation may not be inferred to be exclusively of the same order; the chief cause of, say, an anorexia may be a series of mental experiences or an attack of migraine or

a uræmia or a pituitary disease. Study of the anorexia alone cannot serve to discriminate them; not even study of the psychological state alone, or of the physical state alone may suffice. Very often the physical and psychological factors in causation are mingled inextricably—they represent, of course, different facets of the same series of phenomena.

*Mental experiences.*—Mental growth is dependent on daily experience for its material. Experience can be subdivided into perceptual, emotional and other kinds, but such a division is fictitious. The means by which daily experience is incorporated with our mental equipment and acquires an influence over our subsequent behaviour in all respects can only be understood if we avoid thinking of emotions, instincts, perceptions and other abstractions as real entities, as distinct and separately operative forces. Memory, for example, is not merely an intellectual function by which we recall a happening into consciousness in more or less verbal terms, but a device, or function, by which past happenings are able to influence subsequent behaviour; the ways in which they do so, and the form in which the earlier experience is reproduced into consciousness, will be greatly influenced by its original emotional, as well as more purely perceptual, aspects, and by other physical and mental experiences—a distressing repetition of the experience, for example, or a physical happening like concussion or cortical atrophy.

There are general needs in mental life—instinctual needs—which bring us into relation with our immediate surroundings, lead us to feed ourselves, maintain our lives, reproduce, and aim at other ends which have been variously formulated by philosophers, saints and psychologists. These biological forces, however denominated or classified, are not peculiar to human beings, but in respect of human beings are so much more accessible to minute enquiry along verbal lines, that complex conceptual systems have been built up to describe them. Comparative and experimental psychology have partly corrected unreal refinements and highly metaphorical interpretations; physiology can also help here. Unduly speculative subtleties, e.g. some psycho-analytical ones, are ill-suited to medical needs. The influence of previous experience on all subsequent behaviour is as evident in physiological happenings as in the mental field; the special language and formulations and hypotheses of psychology are not to be taken as permanently distinct from those suitable to less highly integrated functions, though much must be conceded to the special complexity and character of psychological phenomena. Such terms as projection, sublimation, conversion, symbolism, identification, repression, amnesia, perseveration, displacement of affect, cover special instances of the general relationship between inherent tendencies of the organism and their material substrate, and the influence of past on present experience and behaviour.

In dealing with the multifarious world about him, a human being is constantly obliged to select what he will perceive, and in what form he will perceive it; pure "objective" perception never occurs. To perceive things at all, he must give them meaning by relating them to himself and to his previous experience. Unless he can do this, not necessarily consciously, he is at the mercy of his environment, as a newborn baby is. Perception is therefore an active process; it has instinctual and emotional, as well as cognitive aspects. It depends partly upon memory for being able to give meaning to what it perceives; such memory need not be conscious. Consciousness, it is well to bear in mind, is only an attribute of psychological happenings, not their essence or their criterion; mental life goes on with varying degrees of consciousness attaching to it. There is no sharp division between conscious and unconscious mental life: no region called "the Unconscious" with its own rules and contents. Many of the psychological happenings most significant for psychiatry go on without clear consciousness of them, but in appropriate conditions they may be accompanied by much more, or by full, consciousness. Biologically and psychologically regarded, consciousness is an attribute, like movement or the ability to learn,

immensely important for us human beings, but not a "present-or-absent" factor decisive for our mode of mental conduct.

Perception being thus an active process, which makes use of past experience, it not only selects its material and invests it with meaning, but in doing so may distort it, and give it a special "false" meaning. Unwelcome emotions may be thus projected on to external objects or happenings, which are then regarded as hostile or contemptuous, or in some other way significantly related to one's self. This is not remote from the process in visual perception, whereby one projects the image on one's retina into the external world, and is convinced of its reality there; the further process of clothing it with emotional significance depends on one's inherent tendencies and one's previous experiences. Paranoid symptoms, ideas of reference, grandiose and self-reproachful delusions exemplify this. Hallucinations and kindred phenomena are a special instance of the interplay between material substrate (*e.g.* in cocaine poisoning), inherent tendencies (*e.g.* visual fantasies of children) and past experience (*e.g.* hallucinations of homosexual abuse or divine commands). Similarly, by fantasy and imagination the outer world can be manipulated or denied according to the heart's desire, just as by body-images of proposed movement the way is prepared for purposive muscular action. In giving meaning to present things, personal connections between them and earlier experiences are established; whether normal or morbid, this ascription of "symbolic" meaning to everyday objects is indispensable to thought, and is most striking in our use of spoken or written language, where sounds and shapes are conventional symbols for the most diverse experiences. Some of our words are personal to ourselves, and are used in an individual way; in morbidly heightened form, this process may issue in schizophrenic neologisms, or oddities of expression. Similarly an obsessional patient may feel towards some word or object a superficially incomprehensible mixture of attraction and repulsion, which is due to this word or object being the symbol of some earlier experiences that have been of great moment in his life. To see how it has come to be such a symbol calls for minute study of his earlier experiences. Physical happenings in one's own body may symbolise present emotions or earlier experience of a momentous and emotionally painful kind. A gesture of disgust may normally be evoked unconsciously by a banal happening, which has somehow become emotionally coloured by past experience. A headache or nausea may embody our dissatisfaction with a present situation. So hysterical "conversion" symptoms may reflect and symbolise an inner emotional struggle, as may also some obsessional movement, schizophrenic stereotypy or hypochondriacal fear. The body, with all its functions, is the background of psychic life, and resonates to it.

What experiences will be important in determining the form of mental symptoms, depends much on the emotional disturbance they originally provoke, and this, in turn, on the instinctual drives which they touch on and disturb. Instinctual needs may conflict, and the emotion accompanying the conflict prove so disturbing that it cannot be borne in its naked form; "repression" serves the end of making this more or less tolerable, through disguising or distributing it. So emotion may be shifted from one object to another, and paradoxical or unexpected emotions be thus aroused by objects on to which the affect has been displaced. Or energy mainly directed to plain ends, *e.g.* sexual love, may be diverted into less obvious channels, and when thus "sublimated" and mingled with features derived from other instinctual sources, its origins may be hard to recognise. Sexual needs so often conflict with others that many of the most powerful motives for the production of mental symptoms come from the struggle.

To describe the whole of instinctual life, however, in terms of sex and aggression, as has sometimes been done, is only possible if one strains the meaning of these words out of all knowledge. It is as unwise to make the sexual paramount in psychogenesis as to burke it.

The patient's present symptoms, it is clear, must be examined in the light of his earlier experience. Thus one elucidates in detail the content of his illness and some of the causes of its occurrence. In doing so it is not necessary to push back all one's enquiries to a supposedly crucial stage of early childhood. The experiences of the first 2 or 3 years of life are, like all subsequent experience, contributory to mental development, and they show certain sequences of phenomena characteristic of such development. Moreover, their relative simplicity makes it possible to recognise in these early reactions the instinctual drives, or (more correctly) the "inherited functions" which become manifest when the environment supplies the necessary material, though, of course, it cannot supply the necessary energy and direction; these last must come from within. On the other hand, the functions recognisable in the relatively simple reactions of early childhood are not the same as those which may be seen in later years when the organism is more fully grown, any more than an infant's physical structure and functions are identical with those of the more differentiated adult. The obvious continuity of the actual happenings in a human being's lifetime does not justify one in trying to analyse and reduce all adult mental phenomena into terms of child psychology, nor does clinical practice usually require it.

The effect of war and famine upon the incidence of mental illness has obvious importance. The psychiatric disorders which occur in war do not differ in kind from those of more normal times, but certain forms of disorder, especially panic, exhaustion, psychogenic semi-stupor and gross hysteria in men, become commoner and sometimes more severe. People are exposed to unaccustomed dangers; their privations are both material and emotional; they have to surrender some of their independence and individuality; and they are thrown together in groups and therefore prone to share in group-feelings and group-behaviour. It is not known whether the losses, fears, misery and other psychological burdens and cruelties of modern war and its aftermath directly lead to an increase in certifiable mental illness, though such exogenous factors as malnutrition and infectious disease which war favours may have this effect. It is, however, neurotic disorders that chiefly excite attention during war, as they are then more certain to be ascertained; they interfere with military efficiency, they can impair morale, and a far higher proportion of affected people come under medical scrutiny than is customary during peace.

**Course and Prognosis.**—The making of a correct diagnosis may in psychiatry indicate the general drift of an illness—towards recovery, chronicity, progression or relapse—but is of even less use than in the rest of medicine for showing how far this will apply to a particular patient. For this, careful study of the individual history and illness are indispensable. The prognosis can be inferred from the causes, the mode of development and the form of the disorder.

Where a known external cause has been at work, its point of attack, its severity and persistence will affect the issue. This applies equally to such "organic causes" as poisons and cerebral diseases and to "mental causes", like economic misery or frustrated love. The physician must consider how long the environmental cause has been acting, what changes it is known to produce—cell-degeneration or gloom, fibrosis or fantasy—and whether it is likely to persist. He must also ask if the patient's previous history has shown that he is specially sensitive to such a trauma. This brings in the intrinsic causes. How has the patient previously reacted to this sort of interference or to any disturbing circumstances? Has he fallen more and more into unsatisfactory habits in meeting his daily life and its difficulties? How has his whole character developed? Is there good evidence of his being able to cope with partial deviations from mental health? Has he inherited tendencies to benign or to progressive illness? Which seem to be the most useful reparative or stabilising features in his personality? How far are his struggles with the world an outcome of his intrinsic endowment, evident in various guises since his childhood, how far have they been forced upon him by an adverse milieu? How old is he? There is



that syphilis is less often contracted and earlier treated. The psychological reactions to a physical disease or blemish may be favourably modified or averted, when foreseen. It is for obvious reasons impossible to counteract mental disorder by regularly protecting the patient from physical or psychic trauma; in any case, a life guarded against risks and painful experiences would be almost certain to issue in mental ill-health, out of its very emptiness. By altering a patient's environment and way of living one may, however, be able to avert an impending illness: only study of the individual patient can show how this end may be achieved. Making the patient's environment easier for him may be difficult in some instances because doing so would conflict with his obligations toward other people; and even if, on balance, a change of this sort seems essential, the patient may thereafter be troubled by guilt and shame. This is particularly evident in unsettled times.

The work people do and the conditions under which they do it influence their mental health. By ensuring that good vocational advice is available to those about to enter the field of employment and to those whose maladjustment is connected with their occupation, useful preventive work can be done.

How far the treatment of behaviour disorders and neurotic traits in childhood can be trusted to avert outbreaks of definite mental illness in later life is a disputable matter, but it is fairly certain that by taking advantage of his plasticity and responsiveness, a bent can often be given to the energies of the maladjusted child, which will result in his being socially better adapted and better able to deal with his problems. The more persistent the beneficial influences one can bring to bear on development at this impressionable age, the more valuable the prophylactic effort.

Many of the most effective and urgent measures of mental hygiene that may be recommended to the community as a whole are still largely of a negative kind: what to avoid rather than what to do. This applies particularly in the field of sexual practice and belief where needless fears and harmful education are rife, as with regard to the masturbation of adolescence—a normal and comparatively harmless phase of sexual development.

**TREATMENT OF THE ACTUAL ILLNESS.**—This is almost as varied as aetiology. There are no specific methods of treatment of sure efficacy; nor can treatment safely be limited to one approach, whether physical, psychological or social. There is no valid distinction between palliative and curative therapy: the distinction should be between more efficacious and less efficacious. The nearest approach to a successful causal therapy is attained with those mental disorders which are closely related in time and form of occurrence to some indispensable cause, e.g. a toxic delirium, a reactive depression or anxiety, an interstitial syphilis of the brain. But these are rare conditions if one considers the whole of mental illness. The treatment of general paralysis by artificial fever was not causal, its theory was dubious, its basis quite empirical; yet it was the most important therapeutic advance in psychiatry for a hundred years. One cannot despise any measure that promotes the recovery or well-being of the patient: the giving of drugs, the prevention of suicide, occupational therapy, analysis of motives, induced convulsions, removal into favourable surroundings, hypnosis, insulin, re-education and other means of helping the patient are not to be graded in an arbitrary hierarchy, nor should recovery be called spontaneous—as it often is—if it has occurred after treatment which did not include psycho-analysis or vigorous physical procedures.

Sometimes a patient's condition demands energetic intervention; sometimes it demands restrained symptomatic treatment; sometimes social adjustment is called for; sometimes drugs. Whether the accent in treatment shall fall on the physical or the psychological or the social side will often be less important than care that all the available resources are used. It should not be taken for granted that a diagnosis connotes a method of treatment: e.g. that psycho-analysis is the only thorough treatment for obsessions, while for depression convulsant therapy is the "proper" method.

Nor, to mention another common error, should it be lightly assumed that a heavily tainted family history or other evidence of a strong constitutional factor indicates that treatment is out of the question, a superfluous struggle against fate.

Treatment may be considered as social, psychological and physical. For some types of illness obviously much more stress will fall on one than on another of these, e.g. in hysteria, general paralysis of the insane, epilepsy.

*Social and occupational treatment.*—The first task in social treatment is to decide where the patient is to be looked after. Is he fit to be at home, should he be in a hospital, or in some other environment? The decision as to the need of a psychiatric hospital rests in the first instance on the danger the patient presents to others, or the chance of his committing suicide. These two problems of behaviour were at one time almost the only grounds of admission to a mental hospital, but such questions of "certifiability" need no longer preoccupy the psychiatrist, since voluntary treatment has broadened the scope of the mental hospital and modern conditions made it suitable for many patients who would ordinarily be regarded as "neurotic", rather than "mental", "psychotic" or "insane" (e.g. early cases of general paralysis masquerading as neurasthenia, or obsessionals who fear their own impulses and want to be protected against themselves).

The social decisions in treatment cover much more than merely the mental hospital issue. If the patient's immediate environment contains many disturbing influences, it will be desirable for him to be away from them temporarily at least, so long as this does not entail worse troubles; summary decisions are here impossible. It may be useless to get a woman who is paranoid about her neighbours to move to another district to escape them, unless it is the actual conduct of the neighbours and not the patient's morbid attitude that is provoking her suspicion of them. It requires a close knowledge of the facts as well as wisdom and psychiatric experience to give advice on matters that may wholly alter the course of a patient's life—advice, say, about separating from his wife, giving up his job or emigrating to the Dominions. Many instances of this might be offered. Neurotic patients are often advised to get married, especially if loneliness and sexual needs trouble them, as though marriage were a panacea; such advice by rule of thumb too often makes their condition worse, ruins the life of the person they marry and results in offspring that have to be treated at a child guidance clinic. Weary, depressed patients are often harmfully urged to go to dances and lively seaside resorts where they must try to look happy. Hysterical patients do not benefit by being put among people who are hostile and contemptuous, any more than in an atmosphere of mawkish sympathy and compliance.

In the social treatment of patients indispensable help can be given by trained psychiatric social workers. Their assistance is not restricted to the patient's economic problems. No psychiatric hospital or clinic, whether for outpatients or inpatients, children or adults, can do its work effectively unless a psychiatric social worker is a member of its staff, to provide expert information and advice on all the social aspects of the patient's illness, and to carry out social measures of treatment. Similarly, a non-medical psychologist must be available for help in dealing with educational and vocational problems and the administration of specialised tests.

Occupational treatment is important for all kinds of mental disorder. Where there is acute overt emotional disturbance, rest is at first desirable, as also for confusional and delirious states. In these conditions opportunity for occupation must be gradually offered to the patient as his disorder subsides; steady, simple work is preferable to the restless unsatisfying fickle activity in which he would often engage, if left to himself. The less acute any mental disturbance, the more necessary is it that occupation should be urged upon the patient, and that it should be disciplined and congenial. This applies equally to gross psychoses and minor affections of the neurotic sort. Allowance must be made for the patient's bent, his symptoms and personality, and especially his more or less conscious reasons for working and not

working; hence there will be much diversity in the conditions of his occupation, whether it be therapeutically contrived in a hospital, offered at a Rehabilitation Unit or sought out as remunerative work in the open market. Mental health cannot be permanently retained unless one does some satisfying work; often it cannot be recovered unless one does. Work is not satisfying, in the long run, if it is done mainly as a diversion to fill in time.

*Psychological treatment.*—There is no form of treatment which has not a psychological aspect and result. The term psychological treatment or its synonym "psychotherapy" is, however, conventionally limited to those forms which depend upon direct and personal relationship between the patient and the physician. They have been given separate names, and divided into schools and techniques. Stress may be laid upon the prestige of the physician (as in hypnosis), the patient's attachment to him, in all its complicated phases ("transference"), the trained understanding and thoroughness with which he clears up the patient's problems (persuasion, re-education, distributive analysis), or on his qualities of personality—enthusiasm, energy, warmth, candour, wisdom. In so far as psychological treatment is necessarily based on a personal relationship it cannot be made a routine except in its non-essentials: whatever rules the psychiatrist follows or whatever the training he has undergone, he himself is more important than his method in benefiting the patient. To that great extent psychotherapy is not a scientific procedure. That is not to say that method and training are of no consequence—far from it—but only that they are devices whereby the influence of one human being upon another's mind and conduct can be turned to the best medical ends and the dangers inherent in such a relationship minimised.

The more specialised, intricate or esoteric the method, the less suitable is it to be used by any but the expert. It is not proposed here to detail the many kinds of technique that have been employed. The general rules that must be followed in any psychotherapy are:

1. To regard the removal of symptoms as a good thing, but the maintenance of normal social adaptation as far better. It is bad to get rid of one symptom only to see it replaced by another, but much worse to get rid of all symptoms only to see the patient at the end of treatment a dependent and introspective hypochondriac of the mind, a social invalid.

2. To seek for the psychological causes of the patient's illness only to the extent that the patient's well-being demands, which is often far short of what one's own interest and psychological curiosity would demand.

3. To consider carefully whether any shock to the patient, any aggravation one produces in his illness even temporarily, may be a sign of bad treatment.

4. To be satisfied with the patient's recovery, and not to aim at his promotion to a state of ideal mental health and self-understanding. It is better that treatment should be quick and effective than drawn out to meet theoretical standards.

5. To understand the development of the patient's illness, and to interpret it both to him and to oneself, in terms of real experience rather than of hypothetical forces.

6. To treat the patient without allowing one's own emotions to be more concerned in the course and outcome of the treatment than is usual in the treatment of a physical illness.

7. To aim at harmonising the patient's mental life by giving his ill-managed energies fitter material to work at, and release from the burdens laid on them by past experience.

It is impossible to describe in general terms what the psychotherapist does, otherwise than by metaphor or analogy: he promotes the ventilation and desensitisation of emotional disturbances; he elucidates latent or obvious muddles, disentangles conflicting tendencies, giving them new incentives and a different direction; and so

guides the patient through the maze of his life's experience, as recalled in memory, that he is then better fitted for dealing with current experience, knows himself better and has somewhat purged himself of past harms. All "analytic" methods review the patient's life as he recalls it under special conditions, *e.g.* of free association, hypnosis, biographical scheme, etc. They stop at different points, some aiming at emotional clearance by abreaction, some at a redirection and liberation of the instinctual bases of character, while others remain content with an educational achievement.

Whether psychotherapy, in the above sense, is to be applied will depend on the following factors: the patient should be willing to co-operate in the treatment; free from such hindering disabilities as, say, deafness; able to give the necessary time; of at any rate average intelligence; still capable of modification (as he would not be in old age, or with very long-standing and indurated habits of faulty reaction, or with organic cerebral disease); and, finally, endowed with a considerable residue of normal mental functions with which one may work. The more profound his aberrations, as in schizophrenia, or the more extreme his emotional disturbance, as in agitated melancholia, the less is he fit for psychological treatment of this individual and specialised kind. Psychological treatment, however, in the literal and larger sense of the words, is essential for every variety or stage of mental illness, and every degree of co-operativeness or intelligence. It is a wide notion, including all that may ease or reassure the patient, bring him to a better relationship to those around him and with himself, and protect him from being distressed by the ignorance, lack of tact, or thoughtlessness of others. It is as much negative as positive. One must avoid arguing with the patient, telling him lies "for his own good" or to avoid unpleasant scenes, cajoling him, making promises that will not be kept, threatening or punishing him, jesting at his expense, losing one's patience with him, assuming he is indifferent to what goes on because he looks indifferent, provoking him by petty supervision or frequent rebukes; one should not assume that he is quite irresponsible or quite responsible, nor talk theory to him, nor get on a false footing through ready assent to his delusions and his point of view. The physician and the rest of those who are in contact with the patient must do certain positive things: make due allowance for his disorder influencing his conduct, use their understanding of the psychological happenings without saying so, take advantage of every opportunity created by other methods of treatment. When occupation, narcosis, hydrotherapy, a course of insulin, massage, a physical illness or other happenings bring him more closely into contact with nurses and physicians there are chances of unobtrusive psychological treatment in the wide sense.

Of late much effort has been put into treating patients, not as individuals, but as members of a group. Though less economical of time and labour than had been hoped, this has the advantage of utilising for therapeutic purposes the influence that patients have on one another. Many devices have been employed, from social club meetings to "psycho-drama"—plays that originate with the patients and touch on their conflicts, and are followed by a group discussion. The procedures are still experimental, and have not made individual treatment superfluous.

*Physical treatment.*—"Mechanical restraint" and violence are now foreign to the treatment of insanity; the patient may be unrestrained and violent, but his treatment may not. It is still necessary, however, to restrain a patient who is bent on harming himself or others, and physical force may be the only way of doing so, or of giving a patient by tube enough food to keep him alive when he abjures the natural way of eating. But force must always be a last resort; and chemical substitutes for it seem only a little less of an evil. Drugs have their place in the treatment of all kinds of mental disorder, but their use easily turns to abuse. Whether one is giving morphine and hyoscine in an emergency to an acutely excited catatonic, or prescribing aspirin for a mild hysteric, the chief danger which must be borne in mind is not over-

dosage, habituation or suicidal misuse, but the habit of stupefying or satisfying a patient with drugs when other means might be taken, better suited to his condition. Sedative drugs should not be a short cut; neither should they be eschewed. They should be given when other measures will not serve, as for some obstinate form of insomnia, anxiety, agitation and restlessness, or when their use obviates greater troubles, e.g. the pulling of bandages from an operation wound. The symptoms of intoxication must be watched for with more than usual vigilance when bromide is being given, because if unrecognised as such they may lead to certification—for an avoidable drug-made psychosis. Continuous narcosis for several days with the patient sleeping through 18 or more of the 24 hours, is sometimes efficacious in abbreviating an acute attack of mental illness or giving complete rest to an exhausted, very anxious person; it is not without risk, except in skilled hands.

There are other drugs to which the above cautions scarcely apply, e.g. endocrine preparations, remedies specific and otherwise for the physical basis of "organic psychoses" (e.g. arsenical treatment for syphilis of the central nervous system), and aperients. Insulin for promoting hunger, calcium for those with hysterical hyper-ventilation fits, amphetamine (Benzedrine) and acetylcholine for anxiety, and a number of substances—from nitrous oxide to amylobarbitone (Amytal)—that relieve catatonic stupor, or facilitate psychological enquiry and treatment, have all been found useful on occasion. Recently hypothermia induced by chlorpromazine (Largactil) has been employed, but its value is highly doubtful. The same may be said of malononitrile.

Three methods of physical treatment have been introduced and widely employed since 1935, namely: (1) insulin in large doses to produce hypoglycæmic coma repeatedly; (2) convulsant drugs and, latterly, electrical stimulation of the brain, to bring about fits and (3) surgical incision of both frontal lobes—leucotomy—to sever the connection of the anterior portions with the thalamus. Although the former procedures, and their many modifications, are often referred to by the single ill-chosen term "shock therapy", they have little more in common than that they are crude empirical methods of altering mental disorder for the better, their *modus operandi* being still a matter of conjecture. Since the insulin method demands skill and experience, if considerable risk to life is to be avoided, it has not been so much used as convulsant treatment. Its field of application is schizophrenia, especially the early acute forms with good prognosis. Convulsant treatment is now given almost always by the electrical method. Though first devised for schizophrenia, it has limited success there except in the acute stuporose forms and those associated with an affective syndrome. Its efficacy in involutional and some other affective disorders is, however, striking. It terminates obstinate melancholias and abbreviates attacks of depression which would otherwise take many months to clear up.

Frontal leucotomy has a more insecure place as yet than the other two methods. It has been, or should be, restricted to patients who seem proof against other forms of treatment, e.g. those with chronic agitated depression, long-standing schizophrenia accompanied by violent outbursts, or intractable obsessional disorder. The proportion of deaths in a fairly large collection of cases has been between 3 and 4 per cent.; of recoveries (obviously dependent on the patients selected for operation), about 25 per cent.; another 40 per cent. are said to be clinically much improved; about 65 per cent. of those operated on do not improve sufficiently to leave a psychiatric hospital. The procedure does not reduce formal intelligence, but blunts spontaneity and control, and may impair judgement and foresight; it may lead to epilepsy (in from 4 to 8 per cent. of cases), or urinary incontinence. Some of the successes attained by the operation in apparently hopeless cases indicate that its uncertainty and crudity do not put it out of court; modifications in the site and extent of the cut are still being made, with promising results.

The three forms of intervention described stand or fall, not by appeals to general principles or evidence that they are rational and safe, but by proof of their value in

alleviating specific types of mental illness. They evoked a somewhat uncritical enthusiasm and hopefulness in some who had previously been given to ill-informed nihilism about the prospects of any treatment; consequently the mistaken notion has gained ground that before the advent of these methods patients who got well must have done so "spontaneously", and that unless a mentally ill person has had "shock therapy" or "psychotherapy" he cannot be said to have had any treatment at all.

Exercise or massage and hydrotherapy are beneficial as much for their psychological as for their physiological results; the latter, however, are not negligible, as may be seen in the effect on an excited or an anxious patient of a continuous bath at body temperature. The chief importance of diet lies in the frequent refusal of food by patients depressive, hysterical, stuporose, paranoid, hypochondriacal or overactive. Feeding by the nasal or œsophageal tube is a necessity in many such instances, after every other method has failed. Rarely a special diet is called for, as in the symptomatic psychoses of diabetes, pernicious anemia or pellagra, and also for some temporary disabilities of the alimentary tract. As a rule, however, such dietetic régime, and indeed all physical treatment of localised psychogenic disturbances of function in a bodily system, is an expedient rather than a settled and adequate mode of treatment. Many patients with a visceral neurosis (*e.g.* "effort syndrome"), a hypochondriacal preoccupation, a hysterical anomaly, or a somatic delusion are greatly harmed by the prolonged physical investigation and treatment they receive: it confirms the symptom, localises it all the more and brings fresh ones in its train. Sometimes one has no choice; a progressive hysterical contracture, a dermatitis artefacta, a sore infected by constant picking, a tooth loosened by obsessional knocking at it demand treatment.

The caveat against lightly resorting to physical treatment of psychogenic anomalies is especially applicable to operative surgery, *e.g.* "cleaning up the septic foci".

## CLASSIFICATION

The ideal classification would be on a uniform basis, according to the nature of disordered physical and psychological function, or according to innate and external causes. Since we do not know enough to do this, a mixed ætiological, functional and clinical grouping is used. It is obviously provisional. The chief division is between those mental changes accompanying distinctive somatic disorder and those for which no such physical relationship has been demonstrated. The former are called symptomatic, or organic; the latter constitutional or functional. It is needless to illustrate the point that everything found in the latter may be seen also in the former. The reverse of this is not true, because there are some symptoms—due to the loss or damage of essential tissues, especially in the central nervous system—which can only occur when the material substrate is grossly damaged.

Although the "functional" group is made up of those conditions for which no distinctive somatic disorder can be found responsible, it by no means follows that their causes or basis are therefore purely psychological. Theoretically, such a belief is untenable, since physiological and psychological are only different facets of the same phenomena; and as a matter of observation certain physical disturbances so regularly accompany these disorders, and a physical configuration may be so linked with them, that there is small doubt that eventually the somatic disturbance of function in them will be well enough worked out for the terms "organic" and "functional" to lapse, and only the crudity or transience of the physiological changes remain as a point of difference.

The first or toxic-organic group is large, the chief syndromes in it being neurasthenia, confusion, and delirium and dementia. Such phenomena as apraxia, aphasia, agnosia, amnesia and hallucinosis are fairly frequent in this group.

The second group, comprising three-fourths of the recognisable mental illnesses, includes the insanities or psychoses, and those anomalies, outwardly less alien to the normal mind, commonly called "neuroses". The distinction between neuroses and psychoses is at times convenient, but without substance. To argue whether a dubious case is neurotic or psychotic is like arguing whether a man of medium size is thin or fat: he is both and neither. A genuine decision as to ætiology, prognosis or treatment turns not on whether a case is regarded as neurotic or psychotic, but on more solid findings. Since such words die hard, the best use of them is to term a patient with mental disorder "neurotic" if he has fair insight into his illness, is co-operative and unlikely to need care in an institution, and to term him "psychotic" if the contrary is the case.

The toxic-organic group is divided into diseases located in the nervous system and those affecting it indirectly, as uræmia or lead poisoning may. Some are toxic, *e.g.* delirium tremens; some degenerative (senile psychoses); some inflammatory, *e.g.* encephalitis lethargica; some plainly hereditary, *e.g.* Huntington's chorea or "primary" mental defect; and some privative, *e.g.* pellagra or myxædema.

The "functional" conditions are arranged according to whether emotional disturbance is evident and predominant (affective disorder), or whether there is profound derangement of thought, feeling and contact with the real world (schizophrenia), morbid false beliefs have become fixed without intellectual or emotional deterioration (paranoia), repetitive and seemingly irrelevant phenomena hamper mental activity (obsessional), signs of physical or mental ill-health, especially dissociation, readily appear when an unpleasant situation may thereby be escaped from (hysteria).

As will be seen in the special sections, the personality of the patient may also be a criterion of these groupings, with the proviso mentioned earlier that illness does not only occur in those with the appropriate psychopathic anomaly of personality, nor does the latter by any means regularly issue in definite symptoms. Unless, however, psychiatry takes account of the psychopathic personality, even when not accompanied by symptoms of illness, it cannot study delinquency, disorders of behaviour in children, sexual perversions and other anomalies which touch very closely on psychiatric problems in the stricter sense.

The following is the classification used here; it is much less detailed than that of the International Statistical Classification, to which, however, it can readily be assimilated:

### Organic Disorders:

#### Degenerative and Hereditary Brain Disease.

(Senile dementia, cerebral arterial disease and hypertension, Huntington's chorea.)

#### Syphilis of Central Nervous System.

#### Other Cerebral Diseases.

(Lethargic encephalitis, Sydenham's chorea, disseminated sclerosis, cerebral tumour, cerebral trauma, epilepsy, etc.)

#### Intoxications.

(Alcohol, morphine, cocaine, bromide, etc.)

#### Infections and Exhaustive Disorders.

(Infectious toxæmias, hæmorrhage, etc.)

#### Metabolic, Endocrine and Visceral Disorders.

(Diabetes, pernicious anæmia, pellagra, exophthalmic goitre, myxædema, tetany, pituitary diseases, sexual epochs, cardiac disease, uræmia, etc.)

**Affective Disorder.**

Excitement.

Depression.

Anxiety.

Schizophrenia.

Paranoia.

Hysteria.

Obsessional Disorder.

Psychopathic Personality.

Mental Deficiency.

Mental deficiency, instead of being treated as quite separate from the other classes, might logically be distributed among them. Most of the feeble-minded are probably "sub-cultural", that is, they represent the lower end of a curve of normal distribution of intelligence throughout the whole population, intelligence being here comparable with height. But just as there are dwarfs whose brevity is not a physiological attribute but the consequence of disease, so there are many defectives (almost all idiots fall into this class) whose low intelligence is the result of demonstrable interference with cerebral development, sometimes from hereditary and sometimes from environmental causes. Members of the sub-cultural group, which is by far the more numerous, have it in common with people of psychopathic personality that they are not conspicuously different from the average population, they are not ill, and their troubles are partly due to and manifest in their social relationships, not least during childhood. The pathological groups could be systematically classified according to the disease responsible for their maldevelopment; they differ from the other organic forms of mental disorder only in the age at which the damage has been done. Congenital syphilis, cretinism, cerebral trauma, encephalitis, epiloia, cerebro-macular degeneration, microcephaly, gargoylism, hydrocephalus, epilepsy, Huntington's chorea, congenital diplegia; a long list can be made of the diseases which will interfere with normal cerebral and intellectual growth, if they can begin to act early enough. Custom and convenience, however, are arguments in favour of keeping all mental deficiency in a class by itself.

The above are great clinical groupings, types of morbid reaction, which are as near to a valid and useful classification as we can get at present. There are subordinate symptom-complexes or syndromes, which are likewise innate and preformed, and likewise evoked by circumstances, but which are not limited to any one of the major groupings—they are the web that runs across the psychiatric pattern. The most important of these are depersonalisation, hypochondria, twilight states, stupor and other disorders of motility, and spasmodic attacks and seizures of different kinds. Between symptoms (classified on a psychopathological basis) and the main groupings which best serve clinical purposes, these symptom-complexes have an intermediate place, comparable say, to that of mononuclear leucocytosis or coma in general medicine.

**ORGANIC DISORDERS****GENERAL DESCRIPTION OF TYPES**

The varieties of form and course in organic psychosis are essentially few and simple, in contrast to the causes, which are numerous. In other words, there is no support for the expectation that to each physical disease there corresponds a characteristic mental disorder. It is not possible in an organic psychosis by study of the



mental picture alone to infer its physical cause; for that the methods of somatic medicine are needed. Many different poisons and lesions may produce the same effect on the mental state. Differences depend on the degree and duration of the physical damage and its site, which may determine neurological and other symptoms of a typical kind; *e.g.* in G.P.I. or encephalitis lethargica.

They are the least constitutional of all mental affections, yet even in them constitutional factors are far from negligible. It is due to such factors that one man will show a psychosis with physical illness that in another would lead to no such mental upset, and that one patient responds with a manic extravagance to the cerebral disease that makes another patient depressed. Moreover, hereditary factors can be of great importance in these organic affections, as may be seen in amaurotic idiocy or Huntington's chorea.

The few syndromes commonly met with here, though they are not restricted to organic disease, must be described before seeing how particular diseases colour them and determine their course and treatment. In organic syndromes, a diminution in mental capacity is the central finding. To some extent these syndromes may occur also in patients in whom no structural damage can be found, as might be expected seeing that the available patterns of structure and function are in all cases much the same.

(1) **NEURASTHENIA.**—This term has been over-used and ill-used, like most of the more palatable diagnoses (*cf.* anxiety neurosis), but it need not therefore be discarded now. It denotes a form of irritable, hypersensitive weakness and depression that is not uncommon after infections, exhausting experiences (*e.g.* hunger, lactation, insomnia, worry, hæmorrhage), cranial injuries and chronic poisoning (*e.g.* with alcohol or coffee). It is true that a clinical picture indistinguishable from it frequently arises where physical causes are unlikely and emotional causes are obvious: this clinical finding has the same significance as the fact that the anxiety of exophthalmic goitre is like psychogenic anxiety. Just as the anxiety of exophthalmic goitre or constant fear can pass into delirium, so can physiogenic neurasthenia be aggravated until it becomes plain dementia.

The symptoms are partly somatic—active deep reflexes, increased sensory irritability, feelings of pressure on the head and pains in the muscles and elsewhere, giddiness, vasomotor lability, delayed peristalsis and feelings of fullness in the abdomen, diminished libido, slight clumsiness, and tremor of the muscles of the face, tongue and hands. On the more psychological side, there are feelings of languor, and incapacity to concentrate on any mental work, doubts as to the accuracy of memory, loss of interest, slight depersonalisation, irritability and tenseness, lessened control of emotion, and perhaps slight paranoid, obsessional or hypochondriac trends. This general condition is, when physiogenic, less influenced by a change in mood than would be the case with psychogenic neurasthenia, and the patient is better able to control his motor unrest than his features, which are expressive of his agitation. The chief reliance, however, must be put on the history and physical findings for telling whether the neurasthenia is physiogenic or not; psychological causes which seem adequate to explain the illness may be deceptive.

The course of neurasthenia is towards recovery unless the noxa continues to act; where the noxa persists, extreme chronicity can result. Sometimes an original physical noxa ceases to act, but meanwhile other emotional ones have entered the field, *e.g.* unemployment, domestic fears and frustrations, and so the illness drags on. Treatment depends on assessment of the causes and the possibility of removing them.

(2) **DELIRIUM.**—Delirium, most familiar in fevers, can also be produced by drugs and other causes of acute cerebral disturbance: severe affective disturbance also may be accompanied by delirium. Its characteristics are general malaise, restlessness, irritability and sensitiveness to external stimuli, headache, anxiety and troubled sleep or insomnia. Mild forms of this are met with in so transient an affection as cold in the head. Severe forms are marked by illusions and hallucinations of all the special

senses, especially vision. Anxiety often becomes extreme, and the patient is terrified of his fantastic visions. Thought becomes as chaotic and fleeting as in dreams, activity is incessant and past experiences of daily life are revived, as in the occupational delirium of alcoholics. Attention is weakened, and orientation in time and space much impaired. There are striking variations in the severity of the condition in the same patient: it becomes worse in the evening or when the patient has hardly any external stimuli to keep him in touch (cf. delirium at night and after a cataract operation). The extent to which consciousness is clouded usually corresponds to the amount of perceptual and affective disturbance. Auditory hallucinations occur with clearer consciousness, visual ones very profusely with a clouded mind. The auditory hallucinations are commonly of an elementary, undifferentiated kind—not voices. Vestibular hallucinations may occur, e.g. of floating in the air. Distressing and incoherent ideas pursue each other—ideas of being torn to pieces, burnt, poisoned, buried alive and so on; also ideas of grandeur.

Closely akin to delirium, and indeed shading into it, is the state of clouded consciousness (or confusion) in which thought is very incoherent, but the patient is more eager to get in touch with his environment than in typical delirium. If consciousness is not too grossly clouded, the patient is perplexed and troubled by the disordered perceptions through which alone he can learn what is going on about him. The picture may be indistinguishable from that seen in some forms of manic excitement and in some catatonic states. Differentiation rests, not on the immediate psychiatric symptoms, but on the history and discoverable causes of the illness. The same is true of *acute hallucinosis* in which orientation and grasp are very little impaired, but auditory hallucinations—especially threatening sounds and voices—abound, and there is a tendency to the formation of delusions on the basis of these and other perceptual disturbances. The name "*twilight state*" is applied to another syndrome in which consciousness is changed chiefly because of some powerful affective influence; anger or fear may so overwhelm psychic life that the patient cannot grasp his surroundings, his thinking is interrupted and slow (except where it falls in tune with the affective disturbance), and his motor behaviour is in keeping with his mood. It is as often of psychogenic as of organic origin—one can hardly, for example, by direct observation tell an epileptic twilight state from an hysterical one. Like delirium and the other conditions just mentioned, it is prone to subside and to be followed by amnesia for what happened during it: where there is some recollection, it may be associated with a conviction that the hallucinations and other morbid phenomena were real external happenings.

(3) DEMENTIA.—Of all gross encephalopathic syndromes this is the gravest and most typical. It corresponds to a diffuse cerebral disease, and is made up of intellectual impairment and lessened control of emotion. Its form depends so much on the stage of the patient's development at which it occurs, that it is customary to consider as dementia only those cases in which the cerebral damage has occurred in later childhood, adolescence or adult life, and to regard earlier cases, e.g. cretins, as showing mental deficiency or arrest of development. The distinction is rather artificial, at whatever age it be made. For convenience, only the adult form will be described here. The order in which functions are impaired corresponds to Hughlings Jackson's principle of dissolution: thus, recently acquired memories are soonest lost. There is intellectual weakness—the patient cannot reason, grasp and remember as he could, his attention is less concentrated and sharp, his ideas are fewer, he cannot take in anything complicated or be sure about time and place, he loses himself. His emotions are likewise affected—he weeps over trifles in spite of efforts to control himself, his feelings are shallow and transient, he may be foolishly euphoric, or may burst into anger whenever he cannot get his own way. There are wide variations in the severity of the condition, and its symptoms may be much influenced by the local incidence of the pathological changes in the brain. The extent to which various cerebral func-

tions are impaired may differ widely in the same patient: a man who seems hopelessly demented may be able to play a good game of chess, while another in whom it is hard to demonstrate any intellectual impairment may micturate into his shoes or do something equally stupid and inappropriate; unexpected sexual misdemeanours are not uncommon in demented persons who do not as yet show gross intellectual damage.

Psychological tests have been increasingly used in dementia. Although they are untrustworthy for diagnostic purposes, they can be of value in measuring the degree and progress of the impairment. The most convenient method is that devised by Babcock in which the discrepancy between vocabulary score, which is often well preserved in dementia, and performance on non-verbal tasks is assessed. More elaborate differentiation by means of a wide variety of tests is still in the experimental stage.

Closely connected with dementia are the *amnesic* syndromes, known by the name of Korsakoff. Here the memory disturbance is in the forefront. The incapacity to receive, store and reproduce experience is remedied, as it were, by lying, *i.e.* the patient *confabulates to fill up the gaps in his memory*. These patients are often ready to adopt suggestions, so that one can lead them to tell absurd tales about their recent movements, *e.g.* that they were yesterday in Greenland to see some polar bears. They do not show an intellectual damage or incapacity to deal with ideas that is at all comparable in degree to their memory disorder, but they are always out in their appreciation of time-relationships, especially where the present is concerned. At first blush they often seem to be behaving like mentally healthy people, but one presently discovers that their memory is much impaired, their orientation as to space, time and personal identity correspondingly poor, and their interest and general mood duller than is normal. The disorder of memory is never, as in dementia, a general weakness reaching back even to childhood.

The Korsakoff syndrome is most often seen in alcoholics, in whom it was first described associated with polyneuritis, but it also occurs in a great variety of organic disorders, *e.g.* intoxication with lead, carbon monoxide and other poisons, uræmia, vitamin B<sub>1</sub> deficiency, cranial trauma, cerebral syphilis and arteriosclerosis—apoplexy may precede it and the amnesic syndrome be thus complicated by aphasia. That it should sometimes follow on delirium is not surprising, since in delirium the same memory disturbance is present, but covered up by the concomitant excitement, disturbance of consciousness and hallucinations. Whether a Korsakoff syndrome will clear up depends on the cerebral damage which produces it; the alcoholic form occasionally does so eventually in uncomplicated and treated cases.

Mental deficiency in some of its forms is a special instance of cerebral impairment, as is dementia. It is considered, for the sake of convenience and tradition, in a separate section (see p. 1682).

## DEGENERATIVE AND HEREDITARY BRAIN DISEASE

There is a group of disorders occurring in late middle life and old age, which are clinically and even pathologically near to one another. At the one end of the scale is senile dementia, at the other climacteric anxiety and depression. It includes Pick's presenile dementia, Alzheimer's disease, cerebral arterial disease and arterial hypertension.

The mental disorders of age have displaced schizophrenia and manic-depressive psychosis from their position as the mental disorders of highest incidence. When first admission rates per 100,000 of the corresponding population have been computed either for senile psychoses or for psychoses with cerebral arteriosclerosis, a higher figure has been obtained than for the incidence of all other psychoses

combined; the chances of becoming thus mentally ill, therefore, are higher in the elderly population than are the chances of developing all other mental illness in any age-group of the population. If present trends continue, the number of persons over 45 years of age admitted to English mental hospitals in their first attack of insanity will by 1971 approximate to the total number of first admissions of people of all ages in 1937; more than a third of these admissions will be of people over the age of 65. It is not extravagant to say that nowadays insanity is mainly a disease of old age.

## 1. SENILE AND PRESENILE DEMENTIA

**Ætiology.**—Constitutional factors are obviously the most important. A tendency to become dotards may be evident in successive generations of a family; heredity is held responsible for the wide differences in mental health among elderly people. The symptoms of senile psychosis may not be revealed until the patient is exposed to some sudden stress—the death of his wife, the need to move house, the loss of his occupation, some new set of circumstances. Social factors are of great importance. Senile psychoses are more common in people with lifelong nervous symptoms or psychopathic personality.

**Pathology.**—**PHYSICAL.**—The tissues show the general signs of age, *i.e.* a diffuse atrophy, which makes the convolutions narrower and the weight of the brain less. The nerve cells and fibres are fewer, while the mesodermal and neuroglial tissues are increased; fatty pigment accumulates. There are also, however, in senile dementia striking histological features in the grey matter, especially of the cortex, namely, thickening of the neurofibrils, which are characteristically twisted and aggregated, and there are remarkable plaques, seldom seen except in this condition. The main change is probably in the brain colloids so that condensation and coagulation take place; the plaques and thickened neurofibrils are secondary to this. There is no close correspondence between the kind or extent of the tissue changes and the mental state. Plaques and neurofibrils can occur also in the brains of mentally healthy old people.

**PSYCHOLOGICAL.**—The previous tendencies of the patients may greatly colour the symptoms. Obscure somatic preoccupations and disturbances in time appreciation lead often to fantastic delusions about eternity and what is happening in their body.

**Symptoms.**—Memory is poor for recent events; the extent of the damage may increase until only the recollections of childhood and early adult life remain. People and places are falsely identified with those once familiar, and transient pseudo-memories are invented. Events with a strong affective tone, especially if unpleasant, are remembered better. The memory of the remote past is not entirely spared; even matters of personal identity may at last be forgotten. Grasp and judgement, the capacity to follow a train of thought and to eliminate the irrelevant are faulty. Obstinacy and perseverance go with a rigid adherence to old habits. Prolix and garrulous, the patient does not recognise how little interest there is for others in his repetitive and ill-arranged talk. He may partly cover its emptiness with long and sounding sentences; on the other hand, some patients become monosyllabic, because of their failure to find words to express themselves, and others again will use a word loosely associated with the one they are vainly seeking, or will quite seriously give a punning meaning to a word, and even act accordingly (*e.g.* whistling because "You said I could whistle for my money").

There is a narrow range of interests, in which food, possessions and bodily well-being are prominent. Grotesque hypochondriacal delusions are common. Patients hoard rubbish and are angry if interfered with in this. On the whole, however, their affective responses are greatly reduced; they meet calamities with composure, partly due to their failure to grasp what has happened. Now and then they show depression and resentment at a slight, and may bear a grudge long after. Their activities are

sometimes considerable, on the lines of determined rummaging and collecting; in others a dull inactivity is all. They become dirty and unable to look after themselves. This applies as much to those who are excited and active as to the inert. The former may fight against being fed and washed, and it is not possible to get them to understand what is being done. Delirium and confusional states are prone to occur at night, accompanied by fear and bewilderment. Sleep is bad, and often the patients busy themselves about the place all night long.

Legal difficulties arise through the heightened readiness to accept some suggestions (as in the matter of making a will, or giving away property), the poorer judgement and the lessened capacity to control sexual desire which is sometimes seen in the early stages. Hoarding may lead to petty thieving. Occasionally the patient sets fire to the house during his nocturnal prowlings.

The symptoms need not be obvious. Often the illness has so slowly developed that no one can say when it first passed beyond what is normal in old age. An apparent change of character—a kindly man becoming selfish, a respectable churchwarden assailing little girls sexually—may usher it in; this is not so much a change in character as a release of primitive trends, hitherto controlled. The psychosis may take various forms—depressive, manic and paranoid. In the *depressive* variety there is seldom retardation, the affect is rather empty, the patient is irritable and hysterical symptoms may be commingled with hypochondriacal ones. Ideas of poverty, wickedness and disease are often grotesque in their exaggeration—the patient's urine drowns the whole world, his body is an undying shell of corruption, he is as tiny as a baby—and are monotonously reiterated. The *manic* variety is rarer: pointless activity and a diarrhoea of words, with silly boasting, may be accompanied by a disturbance of memory, giving a total picture of the Korsakoff type: it is sometimes called "presbyophrenia". Many of these patients have always been of hypomanic temperament; their illness may be only slightly progressive and not so severe as to call for hospital care. The *paranoid* variety is especially likely to occur in people who have always been of a suspicious turn of mind. They hide things because they feel surrounded by thieves, and then forget where they have hidden them; their failing senses, especially of hearing, feed their distrust and they project their awareness of sexual impotence or waning intellect. Hallucinations and delusions are mingled—gases are pumped into their room, their food is poisoned, people throw bombs at the house by night, greedy heirs are doing them out of their possessions. Some of these patients barricade themselves against their enemies or call in the police. Whereas the depressive and manic forms are commoner in people with corresponding heredity, this paranoid form is genetically often connected with schizophrenia, though the distinction between the three varieties is not a sharp or important one. The name "involutional paranoia" has been given to the chronic delusional condition of this type that may develop in single women between the ages of 40 and 52.

Bodily symptoms are those of old age, especially in the central nervous system, where it leads to a slow, careful gait, with short steps and legs wide apart, apraxia and poor co-ordination, tremulous rather whining utterance, small sluggish pupils and occasionally epileptic seizures. The disorder of movement is conspicuous in the handwriting—pointed, small or erratic in size, and sometimes jerky and tremulous.

The conditions known by the names of Pick and Alzheimer are to be regarded as atypical senile or presenile psychoses.

*Pick's dementia* consists pathologically of a circumscribed cerebral atrophy, mostly in the frontal or the temporal lobe, or in both; the motor area, however, is seldom affected, nor are Wernicke's zone and the transverse temporal convolutions; other areas of the brain, especially the parietal, may be involved. Histologically, the ganglion cells are swollen and contain argentophil globules. There is a hereditary determinant. It is almost twice as frequent in women as in men—the opposite of what has been found to hold for cerebral arteriosclerosis. The onset, which is

and sclerosis (in which cavities and scars of glial, astrocyte and mesodermal tissue take the place of the necrotic cells) (see also p. 1443). The cortex on the convexity of the brain may show microscopic areas of perivascular gliosis, but no softening. It is not yet possible to correlate the mental and the cerebral changes in these psychoses, except for the focal lesions.

**Symptoms.**—Since "essential" hypertension often precedes definite vascular disease and itself produces mental symptoms, a description of these symptoms serves also to describe the earlier stage of cerebral arterial degeneration. Along with headache, giddiness, tinnitus, faintness and insomnia, there may be disturbance of speech and writing—the former becoming slow and at times indistinct—and transient pareses and apraxia. Certain traits of personality may be intensified: the patient becomes irritable, egotistic, moody and easily tired, his conversation lumbers along where once it moved easily: he is depressed or paranoid; but there may be wide variation in the intensity of these changes, which are by no means always found. Brief phases of disturbed consciousness, lasting up to 3 weeks, may suddenly occur either in a form very like the "absences" of the epileptic, or as twilight states with hallucinations, ecstasy, incoherence, disturbed motility and agitation.

After this stage of neurasthenia and episodic disturbances, the patient with cerebral vascular disease may begin to have trouble in finding words: he perseverates a little, and is at a loss when anything unusual is required of him. His depression and hypochondriacal worries increase, he is distressed by his own slowness and failures, and may attempt to kill himself. Emotional control falls off so that he weeps and storms when he would rather be calm. Nihilistic ideas may abound—his bowels have not been opened for 6 months, his trunk is a hollow cavity. Nocturnal delirium is frequent. Aphasia and apraxia are commonest after a focal complication.

The most important feature is the way the patient continues to look normal and sensible when already mildly demented. Sometimes transfer to the strange surroundings of hospital is too much for the hitherto well-preserved outward normality, and the patient goes to pieces, as he also may if he has to give up his usual work or move house.

**Diagnosis.**—Because a patient has generalised arterial disease, it does not follow that any psychiatric symptoms he may show are due to the cerebral vessels being thus affected. Unless there are definite focal symptoms, or evidence of dementia, it is unsafe to hold the cerebral arteries responsible and to give a prognosis based on this. There is no known means of distinguishing many benign "neurasthenic depressions" and involutional hypochondrias from those due to disease of the cerebral vessels. If there has not been any history of such tendencies until an attack at the age of 60 odd, the probability that it is an organic vascular disease is much higher. The distinction is all the more difficult because so many unstable persons develop arterial disease in later life; especially those prone to anxiety and other affective disorders. *Neurological findings (see p. 1443) may be decisive in a doubtful case. The condition of the retinal arteries is not a reliable guide.*

**Course and Prognosis.**—In definite cases of cerebral arterial disease with mental disorder the prognosis is necessarily bad, though the mental symptoms may only progress slowly, and the patient live another 10 or 20 years. Much will depend on such sudden accidents as thrombosis or hæmorrhage. An episodic confusional state, perhaps even one produced by drugs, may suggest a needlessly gloomy prognosis. In cases of "essential" hypertension, the course of the mental illness is dependent on the general disturbance, and is often quite favourable. Symptoms that are apparently hysterical, occurring for the first time in middle life, are of bad omen.

**Treatment.**—Besides the general medical care of such patients, not a little can be achieved by psychiatric methods. In the early stages, where there is much anxiety and depression, too energetic physical investigation and treatment may do harm: reassurance and sedation can do much good. The less said to the patients about

gradual, can be at any age from 40 onwards, but is usually between 50 and 60. Symptoms depend on the localisation of the atrophy. Memory and affect are not impaired till late; they are preserved at a stage in which the patient behaves stupidly—stealing, lying or otherwise making a fool of himself. Spontaneous attention is poor; at first moody, the patient becomes dull and unresponsive; judgement deteriorates and initiative fails. Stereotypies, echolalia and repetition of empty phrases, monotonous talking and laughing or singing, and outbursts of bellowing or whining appear in the later stages. There may be aphasia. Diagnosis is difficult during life; it may be assisted by an encephalogram showing the shrinkage of cerebral tissue from atrophy or by biopsy. The condition may last from 2 to 12 years.

In *Alzheimer's disease* the senile plaques and neurofibril changes are very numerous. The onset may be between 40 and 60. Women predominate. Indefinite premonitory symptoms (headache, irritability, forgetfulness) are quickly followed by progressive dementia; aphasia and apraxia are prominent, though less coarse and sudden than in cerebral arteriosclerosis. In the earlier stages the patients are in fair contact with their environment, and look as though they grasp much more than they actually can. Their deficiencies are shown up in writing and talking. They may be restless and depressed. As the disease advances they are less open to affective influences: they sink into themselves and say little. Stereotyped words or syllables and movements take the place of embarrassed remarks and gestures. In the aphasia there is a rather characteristic stringing together of syllables like each other in sound, but meaningless. Muscular rigidity may lead to contractures. The progress of this disease to severe dementia is faster than in typical senile deterioration and the onset is rather earlier.

**Prognosis.**—This depends on the previous rate of development of the condition, the general physical health of the patient and any special pathological basis, *e.g.* Pick's atrophy, that may be recognised. Delirious and confusional phases may give a deceptively bad impression, for sometimes, after they clear up, the patient can resume his old routine tolerably well.

**Treatment.**—Since the breakdown of old people is often brought about by their inability to cope with the demands and stresses of a society that is organised for younger people, social measures can do much to delay the time when senile mental changes will make special care necessary. The more satisfying their mode of life, the less will maladjustment and gross failure be the effect of their senility. Although, when senile dementia is clearly evident, treatment will partly consist in providing as easy, familiar and considerate an environment as possible, it would be harmful to leave senile patients idle because they seem listless, or to let them be lonely because they are fretful. Whether institutional treatment is necessary depends not only on the mental impairment but also on the patient's social level and the willingness of his relatives to look after him well enough. Patients often fit surprisingly well into hospital life and routine when this makes due allowance for their infirmities, and provision for their social and psychological as well as their physical needs. Drugs are best avoided, and caution is necessary in letting the patient have the aperients he demands to relieve his—mainly delusional—constipation.

## 2. CEREBRAL ARTERIAL DISEASE AND HYPERTENSION

The characteristic features here are the focal symptoms. All else is indistinguishable clinically from senile and other cerebral conditions; of course, pathologically many senile brains show arterial degeneration too. The early or mild symptoms of cerebral arteriosclerosis are the same as those of "essential" hypertension; and very like those of many benign melancholias of late middle age.

**Pathology.**—Atheroma of the cerebral arteries is accompanied by nutritional changes—softening—in the brain tissue, falling into three stages, *viz.* necrosis, degeneration (with masses of granular phagocytes, containing fats and hæmosiderin)

and sclerosis (in which cavities and scars of glial, astrocyte and mesodermal tissue take the place of the necrotic cells) (see also p. 1443). The cortex on the convexity of the brain may show microscopic areas of perivascular gliosis, but no softening. It is not yet possible to correlate the mental and the cerebral changes in these psychoses, except for the focal lesions.

**Symptoms.**—Since "essential" hypertension often precedes definite vascular disease and itself produces mental symptoms, a description of these symptoms serves also to describe the earlier stage of cerebral arterial degeneration. Along with headache, giddiness, tinnitus, faintness and insomnia, there may be disturbance of speech and writing—the former becoming slow and at times indistinct—and transient pareses and apraxia. Certain traits of personality may be intensified: the patient becomes irritable, egotistic, moody and easily tired, his conversation lumbers along where once it moved easily: he is depressed or paranoid; but there may be wide variation in the intensity of these changes, which are by no means always found. Brief phases of disturbed consciousness, lasting up to 3 weeks, may suddenly occur either in a form very like the "absences" of the epileptic, or as twilight states with hallucinations, ecstasy, incoherence, disturbed motility and agitation.

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The most important feature is the way the patient continues to look normal and sensible when already mildly demented. Sometimes transfer to the strange surroundings of hospital is too much for the hitherto well-preserved outward normality, and the patient goes to pieces, as he also may if he has to give up his usual work or move house.

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**Treatment.**—Besides the general medical care of such patients, not a little can be achieved by psychiatric methods. In the early stages, where there is much anxiety and depression, too energetic physical investigation and treatment may do harm: reassurance and sedation can do much good. The less said to the patients about



their blood-pressure and their arteries the better. They should keep at work and in their accustomed surroundings as long as they can, unless an acute phase of the illness or depression intervene. Emotional upsets oftener aggravate their condition than physical ones, so they should be cushioned against such jolts. Their depression may necessitate hospital care, especially because of the risk of suicide, or because they are too irritable and neglectful to be at home any longer. If there be dementia, even of mild degree, the patient will probably remain in a mental hospital once he has gone there. It is, however, not easy to be sure about mild dementia being present; it can be counterfeited by passing disturbances, *e.g.* emotional ones.

### 3. HUNTINGTON'S CHOREA (see p. 1519)

## SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

Only the mental symptoms will be described here. Hypochondriacal and depressive reactions sometimes follow infection, or the risk of infection: such psychogenic illnesses do not belong under this rubric; occasionally, however, a patient's anxiety lest he be developing neuro-syphilis turns out to be justified. A syphilitic neurasthenia can occur in the early stages of the disease, due to a mild meningitis. The more severe meningo-encephalitis—*cerebral lues*—may be accompanied by disturbance of consciousness, even to the point of delirium or mild dementia: loss of initiative, euphoria or moroseness, poor judgement and impaired memory may persist and the patient be aware of them in greater measure than he is in general paralysis. These conditions are often complicated by the signs of premature arterial degeneration in the brain. The psychoses that accompany tabs are due to syphilitic changes in the brain, often complicated by alcohol, trauma, heart and kidney disease, and other exogenous factors; there are also depressive hypochondriacal reactions to the pains and other disabilities which the patient suffers.

**GENERAL PARALYSIS OF THE INSANE.**—Dementia is the constant sign of this mental picture; the old descriptions of a "classical" course with an expansive onset are fallacious, but general dementia is almost certain to occur in every case that is not treated. All the other symptoms are either neurological and focal, or due to the patient's constitutional predisposition and previous experiences.

The dementia may at first be quite undetectable as such, because it appears under the deceptive guise of a neurasthenia, melancholia or mania; only gradually does the intellectual impairment become manifest. In the beginning of general paralysis, which is seldom abrupt (though it may need a careful enquiry to verify the prodromal symptoms), "functional" syndromes can be so "typical" and organic changes so slight that the most expert psychiatrist is misled; only by physical and serological examinations can he avoid a blunder. A faint degradation of personality, a lapse in social refinements may be the first indication of what is wrong. Then memory for the events of yesterday and last week becomes less trustworthy, what seemed at first a trivial absence of mind becomes serious incapacity, and yet the patient remains serene and outwardly indifferent to his lapses. As in senile and arteriosclerotic dementia, he may be all right so long as he is in an accustomed rut, but a holiday or a change reveals his infirmity. His mood and interests as the illness goes on become dull or labile, his rages are fleeting, his activities fussy; if, however, he is in a manic excitement, with little dementia as yet, the affective changes can be violent, and indeed dangerous, just as in a depressive phase the patient may kill himself. Sleepy and slow, careless about social usages, inattentive and ignorant of what he once knew well, the more demented patient cannot escape recognition as having an organic cerebral affection. Elementary problems in arithmetic and questions of general information are more than he can cope with. He gives easy assurances that he can do them, or

puts his questioner off with airy explanations (*e.g.* that he has not had his spectacles by him lately); when pressed, he makes bad mistakes or becomes angry. The extent of his failure will, of course, depend not only on his dementia, but on his previous intelligence and habits (*e.g.* a bank manager retains the capacity to do mental arithmetic when much else has gone). Inability to receive new impressions and to relate them to earlier memories co-operates with impaired judgement to give a gross but patchy and fluctuating amnesia. Because of these disturbances, and especially the bad judgement, patients may commit offences, ruin themselves by grotesque extravagance and brush aside facts that stare them in the face. They will put up with restrictions on their freedom, forgetting their protests soon after making them; silly reasons are sufficient for their compliance, and a tactfully offered cigarette or joke may divert their thought and feeling from some serious matter that angers them. Their delusions are due to the same disorders of memory and judgement, coloured by their general personality; sometimes they are confabulations, rationalisations for their having forgotten or spoilt something. If the patient had in health tendencies to euphoria and expansive behaviour, grandiose delusions and boasting will be to the fore. It is, however, not uncommon to find a fatuous euphoria, though there had not previously been affective swings and hypomania; in such patients one finds abundant proof of gross impairment of judgement, especially shown as defective insight. The most advanced dementia appears as a helpless, vegetative, bedridden state, sometimes accompanied by gross focal symptoms, such as aphasia and agnosia. The physical symptoms (see p. 1455) are much intermingled with the mental ones, as in the patient's clumsy movements and disturbed speech and handwriting: thus, in his writing he leaves out letters, syllables and words, repeats and transposes them, messes the paper with blots and sputters, writes across the lines, puts in meaningless strokes and leaves his mistakes uncorrected; the tremulous script shows interruptions in the usual smooth alternation and tempo of movement, the letters are of very uneven size and ill spaced. Articulatory and aphasic disturbances may affect the sense, intonation, timbre, rhythm and precision of utterance; they must not be evaluated in diagnosis, any more than the writing disorder may, without regard to the patient's previous normal script and speech and the circumstances under which he was writing or talking, since people, habitually untidy in their enunciation or handwriting, can exhibit many of these symptoms when tired or in a hurry.

Besides the above, atypical mental pictures may be seen either ordinarily or as the outcome of treatment with artificial fever. Paranoid states, hallucinosis, a Korsakoff syndrome, epileptiform excitement, hysterical disorders and catatonic symptoms of every kind (except *flexibilitas cerea*) may occur. Hallucinations are uncommon, except during fever or after malarial treatment; in the latter case they are often of paranoid colouring. Not the expansive form, but a simple progressive dementia is by far the commonest clinical picture; depressive, confusional and hyperkinetic states are almost as frequent as the expansive.

In the "Lissauer" form the slowness of the dementia is remarkable in comparison with the conspicuous focal symptoms, such as the seizures without convulsions or loss of consciousness.

The effects of treatment upon the mental state are of great social moment. In many patients who do well the personality has the edge taken off it, there may be less initiative and force in mental activity, and emotion may be less controlled, especially in the proneness to anger or to frivolous levity, yet the patient is able to return to his former work, even though it is responsible and complex; he could scarcely, however, except in the most favourable cases, learn a new job or adapt to new and exacting situations.

In the "juvenile" form there may be premonitory symptoms of excitability, grizzling, timidity and backwardness at school. Gradually the symptoms of dementia become plain, and if the onset be early enough, symptoms usually found in severe

## OTHER CEREBRAL DISEASES

**LETHARGIC ENCEPHALITIS.**—The mental disturbance of the acute attack may merge into a hyperkinetic excitement, with choreiform and athetoid movements, insomnia, generalised pains, mild delirium and, occasionally, catatonic symptoms: this seldom lasts more than a few weeks. There may be subsequently a neurasthenic fatigue and irritability with headaches and poor sleep. The distinction between what is neurological and what is psychiatric in the symptoms could scarcely ever be more difficult than in this disease. The motor disturbances, such as oculogyric crises, are not merely responsive to emotional and other psychogenic influences, they are inseparable from concomitant mental happenings (*e.g.* the surging up of anxiety or obsessions), and whole patterns of complicated behaviour, *e.g.* breathing, may be involved. The motor rigidity of the patient's Parkinsonian state may be paralleled by a lack of the normal drive and fluidity of thought or behaviour. Memory, however, and grasp are unaffected. The obsessional symptoms sometimes occur quite apart from oculogyric crises, and may greatly distress the patient. Depressive phases may result in suicide, which is fostered, as it were, by the keen appreciation which many patients have of their ruined careers and their almost imbecile appearance, so different from what they were and, indeed, from what they still know themselves to be. Paranoid, and especially schizophrenic, symptoms may develop in the later stages.

The younger the patient the more likely is it that he will develop disagreeable anomalies of personality, and have attacks of restlessness or even be permanently restless. Many children and adolescents after their acute attack become social problems: they play stupid or cruel tricks, they set every one they can by the ears, they may steal, behave sexually in an outrageous way or accuse others of sexual offences against them. Their activity is not always purposive, nor always antisocial; they make the same impression as a monkey might who is sometimes mischievous but always on the move. There may be no Parkinsonism in these cases. The prognosis is not good, and they almost always do better when subjected to the régime of an appropriate institution; they do badly at home or in places where what may be termed normal delinquents and "social problems" are cared for.

**SYDENHAM'S CHOREA.**—The usual mental changes here are lability of affect and irritability. These are seen as naughtiness, outbursts of anger or crying, resentment at sudden noise or light; in others there is lessened spontaneity, often masked by the choreic movements. In more severe cases, especially in older children, these changes are accentuated; in the fleeting phases of anger or terror there may be slight delusional trends. Still more severe forms, with delirium, hallucinations, delusions of persecution and much excitement, are seen in adults, *e.g.* in chorea gravidarum.

The tics and compulsive utterances (Gilles de la Tourette's syndrome) which may follow chorea are evidence of the interplay between hereditary, psychic and structural factors. Chorea is more prone to occur in those whose families show nervous disorders, especially schizophrenia. The motor after-effects, especially tics, appear and disappear under emotional influences; they are also conditioned by the original choreic disturbance of neuromuscular function. The obscene ejaculations of la Tourette's syndrome are dependent on much the same articulatory and respiratory hyperkinesias as are the breathing spasms of encephalitis lethargica, though

they are also dependent on psychological tendencies and experiences. They illustrate how psychological influences work through available bodily structures and functions, whether morbid or healthy. The obsessional element in this affection is comparable to that in encephalitis lethargica.

**DISSEMINATED SCLEROSIS.**—Slight deviations from mental health are frequent, but obvious ones rare in this disease. Affective lability may be conjoined with a slight disorder of judgement, so that a baseless euphoria develops, but this is not universal, and many of the patients are depressed. Acute outbursts of excitement, hallucinosis or delirium occur in a few cases, and dementia in the advanced stages. The most important mental disorder in them is that which appears as hysteria. A hysterical personality has not been present in these patients before the disease began, and the symptoms are in that respect only dubiously hysterical: they do, however, in other respects conform, in that they can be evoked psychologically and removed psychologically; they may centre on, and elaborate, actual anomalies, *e.g.* of movement or sensation, and may still yield to hypnosis or other psychological measures. They can greatly confuse the diagnosis.

**SCHILDER'S DISEASE.**—In this disease profound dementia gradually develops along with the blindness, deafness, aphasia and agnosia and other focal symptoms. In the juvenile cases there may be at first disturbances of behaviour like those of juvenile encephalitis lethargica.

**PARALYSIS AGITANS.**—This may be accompanied by hypochondriacal depression. Sometimes this is an expression of the cerebral disease which also causes the Parkinsonism, and in that case the prognosis is bad; sometimes it is a recurrence of depressive attacks which have occurred at times of stress earlier in the patient's life, and then the outlook is fairly favourable. Senile dementia is, of course, not infrequent in these elderly patients.

**CEREBRAL TUMOUR.**—Apart from any aphasia and apraxia, the mental state here is more closely related to general intracranial tension than to any local disturbance. The size and rate of growth of the tumour are therefore important in this regard. If rapidly growing, there is more disturbance of consciousness, with impaired memory, disorientation, incoherence and, sometimes, hallucinations and confabulation; this clouding of the mind fluctuates a good deal. In more slowly growing tumours, lucidity is preserved and change of disposition is the prominent feature. The patient's earlier tendencies get freer play, unsuspected ones appear, and a series of foolish investments, for example, or homosexual escapades may for years divert attention from the organic disease. The moria, or fatuous wit and cheerfulness, often attributed to frontal tumours but also found in other cerebral diseases, may give the impression of being a hysterical pseudo-dementia; other apparently psychogenic symptoms may prove misleading. A straightforward depressive attack can occur, or indeed any "functional" syndrome.

Hallucinations may depend on a focal lesion, as in the cases in which they are limited to the hemianopic field, or are solely of taste and smell.

**CEREBRAL ABSCESS.**—The mental symptoms are those of tumour with or without others due to meningitis.

**ACUTE MENINGITIS.**—There may be delirium, preceded during the prodromal stage by irritable apathy, and followed by months of moody neurasthenia.

**CEREBRAL TRAUMA.**—After concussion, there is commonly retrograde amnesia, and there may be, later, also amnesia for events following the injury; the extent of this depends on the severity of the damage. Delirium may ensue; it has little that is characteristic, and is more frequent in alcoholic and elderly people. A Korsakoff syndrome may develop. Twilight-states are rather more common; during them acts of violence may be committed, as in epilepsy, and afterwards quite forgotten. Traumatic epilepsy may follow. The later changes in personality are commonly those that may be found lingering after any toxic or other structural impairment of

the brain. But sometimes the disturbance of consciousness is more persistent, the intellectual damage greater, the deterioration progressive; in such cases there is usually cerebral arterial disease, an unrecognised alcoholism, cerebral tumour, general paralysis of the insane, or some other complicating factor. In predisposed persons the cranial injury may be responsible for a melancholic attack, schizophrenia or other "functional" syndrome; the prognosis is usually good even if the illness lasts many months.

Minor symptoms which may be hysterical occur frequently after cerebral trauma. This is partly because of the site of the injury, which favours vague physiogenic symptoms that respond readily to emotional and other psychological influences. Many of these symptoms are, however, produced by psychical rather than physical mechanisms. Not injured cells, but mental attitudes are at the bottom of the tremblings, faintings, weakness, paræsthesiæ and other troubles so often the sequel of a trauma in itself little likely to have such effects. They are not responses to the actual injury, but to the situation created by the injury. It is as unwise to dub all such vague post-traumatic phenomena hysterical as to attribute them entirely to the direct injury. If there is slight amnesia of the typical kind, with difficulty in concentration and headache, it is fairly probable that these are physiogenic residues; if there has been an interval between the actual concussion and the appearance of the indeterminate symptoms, a history of psychopathic predisposition and an adequate psychogenesis (e.g. economic fears and insecurity, or claims for compensation, with repeated medical examinations, and patent uncertainty among the experts) the condition is likely to be neurotic. Much will, of course, depend on the neurological and other findings, including the demonstration of localised lesions; thus, damage to the frontal lobes may much change the personality, and in other sites be responsible for an apraxia, say, or a visual defect. Too rigid and doctrinaire an insistence on discriminating neurogenic from psychogenic residues of the injury can be harmful; the main matter is to prevent neurotic attitudes and symptoms from developing, or if already there, from continuing.

The degree of intellectual impairment can sometimes be measured, and the departure from normality demonstrated, by psychometric methods (see p. 1684). Among the tests employed those which require a capacity to deal with abstract concepts (e.g. sorting objects according to qualities they have in common) are particularly informative.

**EPILEPSY.**—Although the motor seizure is the chief symptom of epilepsy and the decisive one in diagnosis, there are minor or equivalent symptoms, as well as delirium, twilight-states and dementia, to be included among the mental disorders of this illness.

Instead of a major fit the patient may become unconscious; or he may pass into a twilight-state in which for a few minutes or longer he wanders about in a dazed way and does inappropriate things, having afterwards complete amnesia for all this; or there may be a sudden interruption of action and speech, during which the patient remains immobile or makes some automatic or aimless movements. Epileptic furor is a delirious state in which acts of violence may be committed: it lasts often for several days, is accompanied by disorientation and hallucinosis, and is much rarer than is popularly or forensically supposed. All the states of disturbed consciousness mentioned above are most often seen as equivalents for a seizure; the twilight-states, however, may precede the motor attack, follow it, or be accompanied by a few violent clonic movements.

Apart from their seizures, epileptics are prone to swings of mood—towards anger, shallow sentimentalism or depression—which may pass over into a fugue, during which the patient wanders a long way from home.

The likelihood of dementia later cannot be inferred from the symptoms of the epilepsy, except that it is greater if attacks occur very often. Apparent dementia may be the result of intoxication with anticonvulsant drugs, or of the idleness and sterile

in an institution. When there is genuine dementia, it begins as a faint loss of rest and concentration, with increased sensitiveness to supposed slights, then memory falls off somewhat, the trivial and the important are muddled together, and the patient talks with much circumlocution; he is fond of needless system, assumes and parades virtues he has not, *e.g.* an intellectual bias or a devout spirit, and is child-pleased when anyone praises him. Later, a profound dementia may supervene, this is not common; it is unlikely that the changes of character just described are part of a dementing process; many epileptics who exhibit some of the most dis-able features of this sort never become plainly demented, and many severe epileptics are free not only from dementia but also from these traits. There is ground regarding this impulsive, pretentious, fawning and snarling way of some epileptics partly a variable expression of their constitutional predisposition (to which the seizures are likewise due), and partly as a reaction to their situation. Con-sequently it is much less evident, or not evident at all, in those who in spite of their lives live comparatively normal lives.

MIGRAINE.—Occasionally sharp changes of mood, behaviour and personality may take the place of the ordinary attack with headache. It has often been observed that emotional stress may precipitate an attack, and psychological guidance which im-proves emotional stability has been found to lessen the frequency and severity of attacks in many patients.

## INTOXICATIONS

### 1. ALCOHOLIC DISORDERS

Alcohol is so permissible and trusted a poison, so easy of access for those who wish to escape from their troubles, that it is resorted to in excess by maladjusted persons; consequently its effects may complicate or be complicated by the psycho-pathetic anomaly which favoured the taking of the drug, *e.g.* episodic excitement or depression, anxiety, cerebral arterial disease, paranoid states, hysteria. The acute effects of a single dose of alcohol are either the well-known phenomena of intoxication, or an excitement (*mania a potu*) sometimes with clouding of consciousness. The excitement is commoner in people with cerebral trauma, arterio-sclerosis, epilepsy and unstable hysterical personality, and in them may lead to acts of violence; rarely may occur in normal persons who have taken alcohol when they were exhausted and upset.

In chronic drunkards, a dementing *demoralisation* can occur. Their narrowing interest, superficiality of thought, weakness of memory and moral decrepitude are reminiscent of what happens in many epileptics and some early general paralytics. The crudeness and even brutality of their conduct is in ill accord with their maudlin prating about virtues and their pot-house jollity. The mood of these men can be as labile as their abandonment to it is constant: they pass from rage to weeping, and enough soon after, with no shame for themselves and no thought for the miseries they put on their families. Such degradation is, of course, far from being the rule: some chronic alcoholics become only cheap editions of themselves, with their former qualities underlined or smudged rather than defaced; they are perhaps weak and irritable, untrustworthy or lying, but not given to savage fury, nor grossly damaged in judgement and social feeling. Some of them develop delusions, especially of jealousy. They collect, as paranoid people of other kinds do, scraps of alleged evidence which they piece together to prove their suspicions right; complicated delusions of persecution, however, they rarely develop. Sometimes the delusions of jealousy fade as the patient gets more and more facile, but more often they persist as a chronic insanity and are of the greatest danger to the suspected wife; murder is not unknown in such cases.

The nature of the delusions is to be attributed in part to the lessened sexual potency of chronic drunkards and to the domestic wretchedness and aversion they often create, as well as to the same causes as in "functional" paranoid states, where such delusions are also common, especially in middle life.

The symptoms of *delirium tremens* would appear to differ in nothing but severity from the essential symptoms of any delirium (see pp. 1625, 1639). Some observers, however, deny this. The anxiety amounts to terror, mixed oddly enough with euphoria; optic and cutaneous hallucinations are vivid and restlessness can be extreme. There is almost complete sleeplessness, and much disorientation as to time and place, but not as to personal identity. The patient's attention wavers between his hallucinated and his actual surroundings, but can usually be caught and held for a few moments. He is very suggestible, as most chronic drunkards are; pressing on his eyeballs, for example, will very likely make him see whatever one tells him he sees, and he will read aloud from a blank sheet if one wants him to. Among the visual hallucinations may be miniature ones (micropsia), and many illusional perceptions. The content of the hallucinations changes rapidly, and a false perception in one field (e.g. a vestibular one) tends to evoke others (e.g. of sight, touch or hearing). Insight is commonly lacking; afterwards there is patchy amnesia for what has happened in the delirium. The death rate, with adequate treatment, has been about 1 in 7; and of those who die most of the men are under 40, and most of the women under 45.

In *acute alcoholic hallucinosis* auditory hallucinations of a persecutory kind are prominent and consciousness is not notably clouded. It is rarer than *delirium tremens*, and is more prone to follow a bout or orgy of drunkenness. The patient is frightened, but not obviously out of his mind; he is correctly orientated and may be able to go about his business for days. Auditory hallucinations are vivid and insistent, after a premonitory phase in which there are sensitiveness to sounds, and roaring, singing, hissing, etc., in the ears. Tormenting voices, sharply localised but seldom fastened upon bystanders, abuse, threaten or discuss the patient; they may say his wife plays him false, order him to kill himself, describe his every movement, especially at private moments in the bath or lavatory, cast up his more shameful secrets at him, shout his thoughts aloud. There may be many voices of men, women and children, all talking together and perhaps rising and falling in the same rhythm as his pulse. They are so real that the patient answers them; he may be in doubt about the presence of his tormentors and may shout back insults to see if a blow will follow from the owners of these evasive pursuing voices. Hallucinations of sight and other senses are far less prominent than those of hearing; cutaneous ones, e.g. of being sprayed with a cold liquid, are not uncommon. Delusions are usually inconspicuous: they are, as a rule, attempts to account for the hallucinations, and they commonly fade out of the picture or pass into a chronic persecutory disorder. Flight or acts of violence may result from the patient's fear or anger. Usually it is a matter of only 2 or 3 weeks before the hallucinosis clears up, if no further alcohol be drunk; sometimes, however, a delusional state, more rarely a Korsakoff picture, supervenes in predisposed persons. *After recovery, there is little or no amnesia for the events of the hallucinosis. Relapse is to be feared if the drinking goes on.*

The *Korsakoff* syndrome is not invariably associated with polyneuritis. Nor, as stated on p. 1627, is it limited to alcoholism; it can follow other severe chemical and mechanical injuries to the brain. In alcoholics it is commoner in middle life, developing either insidiously in the course of chronic alcoholic demoralisation, or after *delirium tremens*; women are especially prone to develop this syndrome after the delirium. The symptoms have already been described. The disorientation, superficial appearance of clarity, incapacity for initial perception and subsequent recall (extending often to most of the material of memory) yet with retention of some capacity for learning by repetition, along with confabulation, dullness of emotion

and initiative, and grossly impaired judgement making a striking picture. Complete recovery is on the whole uncommon, occurring in less than a quarter of all cases. The mortality rate is higher in women and older people, in those with acute onset and with a red-cell count below 3,000,000, or with a rise in the protein content of the C.S.F. It does not correlate with the severity of the peripheral neuritis.

*Chronic delusional states* have been referred to above; they are sometimes called alcoholic paranoia, but inappropriately so; jealousy is the commonest and most dangerous feature. Alcoholic epilepsy has been described. It is a symptomatic epilepsy, often atypical; sometimes in unstable hysterical patients it may be brought about through overbreathing when intoxicated.

**Diagnosis.**—The diagnosis of alcoholic psychoses must depend much more on a history of drunkenness in any patient than on his clinical psychiatric features, none of which are limited to alcoholic disorder. Since, however, alcohol is far the commonest cause of most of the toxic abnormalities described, it can be safely presumed in some cases in which the certain history of addiction is unobtainable.

**Differential diagnosis**, so far as aetiology is concerned, will turn on somatic findings, including the results of chemical tests. If the form of the disorder is in question, the chief diagnostic difficulty arises with acute hallucinosis and the chronic delusional varieties. A hallucinosis of similar type can occur in schizophrenia and in affective disorders, but in the latter is recognisable by the ideas of self-reproach expressed; the differentiation from schizophrenia is difficult, since in many of the cases the progress of the disorder is towards a chronic schizophrenic psychosis, and one may suppose that in these patients the intoxication had activated, as it were, the same mechanisms as those involved in schizophrenia, or had complicated a schizophrenic illness. This applies also to the chronic psychosis with delusions of jealousy. There is no value in differentiating carefully the clinical varieties of alcoholic psychoses, since they overlap.

**Treatment.**—Social prophylaxis is the main thing. The incidence of alcoholic psychoses in England is less than a third of what it was 40 years ago, and this may be attributed almost entirely to social influences. Individual prophylaxis is scarcely to be considered, save as a by-product of psychiatric treatment, since a great proportion of unstable persons are potential drunkards, and in any case we cannot yet tell which alcoholics will become mentally ill through their drinking. Social prophylaxis is so immeasurably better in forestalling alcoholism and the psychoses and degradation that sometimes spring from alcoholism, that deliberate individual prevention is here negligible.

When alcoholism is itself to be treated, independently of its ill-effects upon mental health, the problem is that of any drug addiction. Absolute removal of the drug is essential in the first place. This may be effected for a time by getting the patient into a hospital or home where he cannot obtain the alcohol he desires, but to ensure that the patient who has had years of excess shall henceforward be able to put aside alcohol while it is within his reach a great emotional upheaval, e.g. bereavement, religious conversion, fear of death, and considerable changes in his human environment are required. These are provided, for instance, by a semi-religious organisation of former drunkards, called Alcoholics Anonymous, which had its rise in America and which has had notable success in the last decade. For the most part, treatment of alcoholism without restrictions upon access to the drug is a failure; the restrictions must at first be imposed from without, not left to the patient's self-control and judgement. Psychotherapy is a necessary feature of the treatment in the many cases in which inner struggles and neurotic disabilities have been the basis for the addiction; it must, however, be conjoined with vigorous social measures (see pp. 1618, 1619).

Methods which aim at "conditioning" the patient to have a distaste for alcohol are sometimes successful. The unconditioned reflex of nausea and vomiting (evoked by emetine) is linked up with the sight, smell and taste of alcohol. Thoroughly



for general paralysis because of the ataxia, tremor, articulatory disorder and other neurological signs. Recovery is the rule when the drug is stopped. Picrotoxin may be needed for acute poisoning. For the addiction itself, essentially the same problems and methods of treatment are in question as with other drug addiction. This applies also to *ether*, *chloral* and *paraldehyde*.

*Mercury* and *lead* poisoning may lead to mental disorder (see pp. 368 and 382); *manganese* to a Parkinsonian syndrome with compulsive symptoms (reminiscent of *encephalitis lethargica*) and a mild paranoid or euphoric dementia; and *benzene* or *carbon disulphide* may cause delirium.

*Acute carbon monoxide poisoning* in rare instances leaves behind severe mental disorder of the amnesic-aphasic kind, which may not become apparent until several weeks after the recovery of consciousness. More commonly, it results in a clinical picture almost indistinguishable from hysteria; this may take months to clear up, and is in no wise benefited by psychotherapy. Chronic poisoning by small quantities of carbon monoxide causes neurasthenia.

## INFECTIONS AND EXHAUSTIVE DISORDERS

### 1. INFECTIOUS TOXÆMIAS

Delirium and a Korsakoff syndrome are the more acute, and neurasthenia the milder, signs of mental disorder due to an infectious fever. In many of the cases, however, in which mental disorder is attributed to "sepsis" or other infection, either the mental changes are unconnected with the infectious process or there has not been an infectious process, as is often found when one enquires into an alleged attack of "influenza" and finds it was nothing of the kind. There are three possibilities: the mental changes are mainly due to the infection; they are independent of the infection; they are partly due to the infection and partly to other, usually constitutional, causes. The depression that occurs in and after many infections is usually of the third category mentioned; delirium instances the first possibility; and the second is often exemplified when some non-organic syndrome is put down to sepsis, *e.g.* in the tooth-sockets.

Wherever a delirium or other mental disturbance of one infection differs from that of another, *e.g.* the delirium of typhoid from that of pneumonia, the difference lies only in the severity and duration of the physical effects of the intoxication and in the peculiarities of the affected person; no mental symptoms specific to any one infection can be demonstrated. Among the individual peculiarities just mentioned must be included a constitutional predisposition or readiness to respond with symptomatic psychoses to mainly physical ills.

There are a few infections that hardly ever cause mental disturbance, *e.g.* tetanus and diphtheria; others do so by their local cerebral incidence, *e.g.* malaria or *encephalitis lethargica*. *Tuberculosis*, from its chronicity and its occasional incidence on the central nervous system, has a special position. Its treatment, moreover, especially in the pulmonary form, necessitates an abnormal, unsatisfying life for a time, and this with the toxæmia seems to be responsible for euphoric or anxious restlessness in which erotic tendencies and irritability are often prominent. *Spes phthisica* is partly attributable to toxic euphoria, in part it is a form of over-compensation for fear.

### 2. EXHAUSTION AND INANITION

These, especially if conjoined with some shattering experience—an earthquake, incessant bombardment, a bereavement—bring about severe mental disturbance, *e.g.* a twilight-state or a delirium. *Hæmorrhage* and *cachexia* may be responsible for "light-headedness", as in advanced carcinoma, or after a severe operation.

## METABOLIC, ENDOCRINE AND VISCERAL DISEASE

## 1. METABOLIC DISORDERS

Various metabolic disorders can similarly, *i.e.* non-specifically, affect mental health. *Diabetes*, for example, which is especially frequent in families with a predisposition to affective psychosis, may be accompanied by transient phases of depression, anxiety or excitement which correspond to changes in the blood-sugar level, or a ketosis may be ushered in by mild delirium. A diabetic pseudoparesis, with peripheral neuritis, may cause slight difficulty in diagnosis. In children, mild hypoglycaemia may be responsible for anxiety, naughtiness and other disturbances of behaviour. Anomalous psychic states may be produced in the rare condition of hyperinsulinism, and be mistaken for hysteria or an anxiety state of the psychogenic sort. *Gout* may occur in people predisposed to affective disorder; often a depressive phase precedes an attack. Alkalosis and anoxaemia may each be the cause of mental disturbance of the organic type. In *pernicious anaemia* there may be symptoms, *e.g.* an acute confusional state, referable to the structural changes in the central nervous system, but more often depression occurs without "organic" features; mania can also occur, and in some cases a chronic paranoid condition. The more "organic" the picture, the poorer the prognosis for a return to mental health. Of deficiency diseases *pellagra* is the one most commonly productive of mental disorder. It must be remembered that a long-standing anorexia, of psychogenic origin, or occurring in the course of a chronic melancholia, may itself lead to a pellagroid condition, so that the symptoms of mental disorder will then be those of the original illness plus those due to the deficiency. The clinical picture is sometimes very like that of hysteria; or the usual organic syndromes may be produced, especially florid confusion with perhaps hallucinations of fire. The nutritional factor in alcoholic psychoses, especially Wernicke's encephalopathy, is prominent.

In the metabolic disorders just mentioned the physical phenomena are relatively coarse and obvious. It is in some cases proven and in others highly probable that less obvious metabolic disturbances are among the primary symptoms of "functional" mental illness, or are its pathological basis. The acid-base equilibrium and the electrolytes of the blood, the metabolism of carbohydrate, fat and protein, and the chemical regulation of the vegetative activities are all, in such forms of mental illness as schizophrenia and mania, subject to changes which have not as yet been used in the pathology or treatment of these conditions, because the findings are not sufficiently constant or specific.

## 2. ENDOCRINE DISORDERS

These play a more prominent rôle in the investigations than in the clinical practice of psychiatry. Many endocrine preparations have, it is true, been administered to schizophrenic, sexually perverted and melancholic patients, either empirically or in accordance with a premature and ill-devised theory, but the good results of all this are negligible. Oestrogen treatment of menopausal neuro-vegetative symptoms is a rational procedure, but the blind use of endocrine substances in psychiatry has had its day.

*Exophthalmic goitre* is more prone to occur in anxious, nervous people, especially after some sudden shock. The usual concomitants—restlessness, tension, irritability, difficulty of concentration and liability to sudden changes of mood—may be complicated by a definite mania or depression and, if the disease be severe or advanced, delirium and confusion may supervene. Though such organic syndromes mean, as a rule, a bad prognosis, they sometimes clear up dramatically after operation. The interaction of constitutional and psychogenic factors with the actual thyroge-

intoxication makes some treatment of the anxiety by psychological as well as other methods desirable in many cases of exophthalmic goitre, either as a preliminary or supplement to partial thyroidectomy.

In adult *myxædema* the slowing of mental activity may sometimes be accompanied by a chronic paranoid psychosis, or there may be a phase of excitement with hallucinations; the variety of syndromes that can occur is referable to pre-existing constitutional tendencies and to the varying severity and rapidity of development of the thyroid deficiency. An apparently "functional" syndrome may precede the overt *myxædema*.

Juvenile and congenital *myxædema* are described elsewhere (see p. 496).

*Tetany* may be signalled by epileptiform seizures, or there may be a proneness to psychogenic fits; thus the patient may spontaneously overbreathe until a convulsion is induced. Hysterics sometimes use hyperventilation in this way. In severe tetany a resistive lethargy or an excited incoherent confusion may occur.

*Pituitary* diseases are more often accompanied by mental symptoms that are a comprehensible reaction to the physical symptoms than by organic syndromes; the latter when they occur may be due to increased intracranial tension. In acromegaly, depression, reserve, touchiness and irritability are not surprising, though some acromegalics remain cheerful as long as their disabilities are moderate, and sometimes there is a blindness to the disease, a lack of insight, even when it is advanced. In *dystrophia adiposo-genitalis* a rather childish placidity may be met. In *adiposa dolorosa* depression may be severe, or hysterical symptoms may develop. Simmonds's disease may be accompanied by depression, severe anorexia, reaction to the psychosexual disturbance, and, in the later phases, by organic syndromes due to the cachexia. Similarly, disorders of pituitary function have been found in some cases of "anorexia nervosa". In Cushing's basophil syndrome depression and other mental disturbances can occur.

*Addison's disease* is accompanied by a neurasthenia of which for a time the physical basis may be quite overlooked (as may also occur in *myasthenia gravis*); in the later stages delirium has been known to occur.

Acute anxiety attacks may occur from a *phæochromocytoma*. Some persons during the course of treatment with cortisone or corticotrophin develop an acute psychosis which clears up if the drug is withdrawn.

*Sexual epochs* may in women be associated with mental disorder of the organic type, e.g. some psychoses of pregnancy and the puerperium. During pregnancy plain psychosis is rare, but hysterical symptoms, depression and anxiety are fairly common, especially if the mother is reluctant to have another baby; a gross psychosis may, however, break out during the latter months of pregnancy. The organic mental syndromes may develop along with polyneuritis, eclampsia or chorea gravidarum. Termination of the pregnancy is called for on account of the mental condition when there are symptoms of organic psychosis which are likely to get worse, a history of suicidal attempts or infanticide in connection with previous pregnancies and a depression again in this one, or if on other grounds there is a clear risk of suicide or other untoward result of the mental illness, should pregnancy continue. The decision is often a very difficult one, requiring an expert knowledge of psychiatry for the careful appraisal of ætiology and prognosis essential in every case. The question must turn mainly on the therapeutic value of terminating the pregnancy, so far as the mother's mental state is concerned, as well as upon the stage of pregnancy reached.

In the puerperium "functional" psychoses often develop in predisposed women; if there be septicæmia as well, a confusional state or a delirium, followed by a period of neurasthenia, may occur. In many cases the delirious puerperal psychosis clears up in a week or two; the more endogenous varieties have sometimes a less satisfactory outcome than their form and onset suggest. Infanticide may occur in a puerperal psychosis, especially if the mother has, while pregnant, felt resentful at

having a baby or been troubled by murderous preoccupations, *e.g.* obsessions. Psychoses of lactation are rare, and seldom of the organic type. Menstruation is apt to be associated with depression, irritability and languor in many women, especially during the few days before the period begins; there are no menstrual psychoses but the liability to suicide and to psychopathic reactions is somewhat higher at this time. There is no satisfactory evidence that the *affective disorders of later middle life* ("involucional melancholia") are caused by the endocrine changes of the menopause; they are certainly not benefited by oestrogen therapy. Puberty and the climacteric are periods of stress during which schizophrenic and affective disorders may occur. The effects of castration are dependent on the age at which the gonads are removed: intellectual development is unaffected, but the emotional and conative activities of those castrated in adult life may be impaired. Neurasthenic symptoms are frequent, and in women anxiety symptoms may appear.

### 3. VISCERAL DISEASE

This may be directly responsible for mental disorder of the organic type. Thus *cardiac* disorders predispose to an anxiety, which at night may take the form of mild delirium, with restlessness, terror, disorientation and auditory and sometimes visual hallucinations. With improvement in the circulation, the mental symptoms disappear, or remain only as a moody unrest. Reference has already been made to arterial hypertension (see p. 1630). The connection between *alimentary disorders* and neurasthenic states is well attested, and is striking in children. Jaundice may be accompanied by severe depression, but seldom leads to delirium, save in the case of acute yellow atrophy. *Ūræmia* may disturb consciousness greatly, in the form of any of the organic syndromes, from a twilight-state to a euphoric dementia; a Korsakoff condition can occur, but is infrequent.

The psychological causes or accompaniments of many visceral diseases have been diligently studied, and the conditions in which they appear prominent are sometimes called *psycho-somatic*. The problems raised are intricate, and the interplay between the physiological and the psychological aspects of the disease processes has not as yet been fully disclosed in any of the major conditions studied, *e.g.* ulcerative colitis, peptic ulcer, bronchial asthma.

### AFFECTIVE DISORDER

This is of three types :

1. Manic excitement and hypomania.
2. Melancholia and mild or neurasthenic depression.
3. Agitated depression and anxiety state.

There is in each case a major and a minor form. Each is related to a more or less characteristic personality, and for each the cause of occurrence may be chiefly environmental or chiefly hereditary. Combinations are frequent (mixed forms), or there may be successive appearance of the different types, often with an interval between the attacks. A benign outcome or periodic course is the rule for the major forms, but not for the minor, which often tend to become chronic. This is partly because the environment can have more influence, whether for good or bad, on the course of the minor than of the major, more explosive and sweeping, forms. It would be a very convenient thing if endogenous cases could be sharply differentiated from psychogenic ones, as in the Krapelinian scheme, but it cannot be done.

*Œtiology*.—INTRINSIC.—Heredity is the most constant single cause. Research has been mainly into the major manic-depressive cases. The genetic factor is weakly

dominant. It may be that more than one gene is concerned, but this is hard to tell, because the predisposition to an affective disorder may be latent in persons who have not been subjected to the stresses that would make it manifest, and consequently the usual Mendelian figures are not to be expected. The present state of knowledge is illustrated by studies on manic-depressive twins, among whom 69 per cent. of those monozygotic (i.e. with identical heredity) were alike affected with the disorder, while the corresponding figure was only 16 per cent. for the dizygotic pairs (i.e. with dissimilar heredity). In the 31 per cent. of monozygotic twin pairs who were not alike in respect of mental illness, the difference must have lain in the environment, thus showing the relative importance of external factors in causing the inherited tendency to become manifest. Although not manifest as illness, the inherited tendency may express itself in bodily and mental constitution.

The bodily habit that is found in a majority (not the overwhelming majority) of those with affective psychoses is called pyknic or eurymorph. It is best seen in men after the age of 30. It is characterised by large visceral cavities (head, thorax, belly), a tendency to fat on the trunk, slender shoulder girdle and extremities, stocky build, a broad face on a short massive neck, thick receding hair and, later, baldness, venules on the cheeks, and a disposition to arthritis, gout, diabetes and especially arteriosclerosis. As this John Bull build is so common in mentally healthy people, it cannot be regarded as a precursor of mental illness, but only as an indication that some of the constitutional and genetic causes, or biological requirements, for affective psychoses are present.

The same is true of the mental constitution or personality. Here there are several groups, shading off on the one side, by way of cyclothymia and other intermediate forms of mild disorder, into definite affective psychosis, and on the other into normal and stable personality. There are those with a pervading gloominess, pessimism and feeling of insufficiency that spoils their lives; others who are for ever anxious, keyed-up, wondering whether something has gone wrong or will go wrong, and whether it is their fault—careworn worrying creatures; while a third group is made up of the lively, enterprising, confident, sociable people, whose euphoria is patent. Irritability may be found in any of these groups, especially the second and the last. Contrasted or different features are often found mixed in the same patient. The most striking characteristic of the personality of manic-depressive patients is their ready responsiveness and lability of mood; they fluctuate with their surroundings, and in many instances pass suddenly and with small occasion from one mood into another far removed from it.

The signs of affective illness may appear in childhood, though major outbreaks of mania, depression or agitation are rare before puberty. When these occur, the phases are usually brief and the environmental influences strong. Milder forms are often regarded as normal, since night-terrors and other fears, mischievous gaiety and sulky gloom are all familiar enough in children; it is the degree, occasion and persistence of the affect which must decide whether it is morbid.

The psychological crises of puberty are only occasionally affective—chiefly self-reproachful depression or agitation—but during adolescence the illness becomes more frequent; it seldom, however, calls for mental hospital care. Each menstrual period may be accompanied by depression or restlessness, usually coming on about 2 days before the period. In the third decade of life the number of cases steadily rises, and there is another peak in frequency between the ages of 45 and 55. The latter, "involutional", cases show the influence of age strikingly, so much so that they are often considered as separate disorders.

There is little to choose between the curves of age incidence for morbid depression and morbid anxiety of whatever degree; for mania the frequency is highest before the age of 30, as also for affective illnesses with a strong confusional flavour. Pregnancy is frequently accompanied by depression and agitation; psychological factors

are mainly responsible. After childbirth, though there be no septicæmia, affective illness can occur, running a typical and often lengthy course.

The female climacteric is a time when anxiety usually mounts, and is accepted as an ineluctable effect of "the change". It may become definite illness, persisting even for 2 or 3 years. It is doubtful whether there is a specific connection between the endocrine causes of the menopause and so-called climacteric insanity; the melancholia then coming on is like the melancholia of 5 or 10 years later, or the melancholia of middle-aged and elderly men in whom the endocrine changes are not the same. The influence of sex as a whole is obscure. Women have this illness more than men, though the manic form is relatively more frequent in men. The reactivity is often greater and the syndrome less clear-cut in women.

*There are geographical differences, sometimes thought to be racial, in the incidence, but the little that is known points to environmental rather than intrinsic causes for this. It has been suggested that affective psychoses are commonly linked with high intellectual gifts; another says they have affinity with mental defect. The former statement has better support than the latter, but both probably are fallacies depending on the material selected for study.*

**EXTRINSIC.—Physical.**—Chronic toxæmia and acute infections, especially influenza and pneumonia, can be responsible for the illness. Various drugs help to heighten the anxiety to a morbid degree, e.g. alcohol in certain circumstances, insulin or hyoscine. Cerebral trauma may provoke an attack. The list of physical factors could be much added to, but it must be borne in mind that wherever a distinctive, rather than incidental, physical cause can be found, the condition passes over into the category of organic psychoses. The most difficult cases in practice are those in which there is a question of cerebral arterio-sclerosis or exophthalmic goitre; the affective disorders indisputably due to these two diseases may be quite indistinguishable from others for which there is no such organic basis. The problem here is clinical rather than fundamental; since vascular, cerebral, endocrine and autonomic functions are particularly concerned in the mechanism of emotional change, certain disturbances of the physical apparatus will necessarily be accompanied by many of the psychological phenomena of these emotional changes. The depression of paralysis agitans and the anxiety of coronary disease are of the same order. The notion that coitus interruptus and other sexual practices produce anxiety is unfounded, but they may contribute to it by psychological means.

**Psychical.**—A recent misfortune, commonplace or tragic, may be the cause. Any calamity to which human beings are liable may provoke an affective breakdown. Sometimes it is induced by the insanity of a close relative. However trivial it seems to outsiders, the event that has precipitated an affective attack has been felt as a catastrophe by the patient; there are no records of great and sudden happiness causing an affective psychosis. The nearest approach to a specific connection between the precipitating happening and the type of affective illness is seen in the anxiety disorders which follow a terrifying experience such as exposure to shell fire and bombardment from the air; morbid depression following bereavement, financial setbacks or degradation is an understandable response, it is true, but to ascribe the type of response directly to the nature of the experience is specious, since on another occasion it may be with hilarious mania that the calamity is met.

Moreover, the experiences of a lifetime will have determined what calamities are most felt; they need not be calamities in other people's eyes at all. Experiences, spread over years, are the common extrinsic cause of the more chronic neurotic forms of affective illness: this applies least to chronic hypomania. In these chronic conditions the patient's own behaviour has so much to do with what happens to him, as it were, from outside that to separate extrinsic from intrinsic is very hard.

**Pathology.**—The physiological changes are characteristic only of emotional disturbance, not of morbid emotional disturbance; and therefore they are not of

diagnostic value. They consist in lability of blood pressure and pulse-rate, abnormal motility of plain muscle, especially in the alimentary tract, carbohydrate disturbances, variations in either direction of the rates of salivary and other secretions and decreased psychogalvanic activity. The changes are variable from patient to patient and are not always discoverable. More significant are changes in basal metabolism, weight, sleep and menstruation; loss of weight is the rule during the illness. Irregularity of menses and then amenorrhœa often occur. Rise in the blood iodine content, changes in the K/Ca ratio, diminished cellular respiration, hypercholesterinæmia and signs of adreno-cortical hyperactivity have been alleged but not conclusively.

The *psychological changes*, in spite of great external differences, have the following in common: the morbid phenomena are in accordance with the prevailing mood, though not wholly derivable from it; thought is less purposively directed to impersonal ends than it would normally be, but more purposively to personal ones; there is a small number of topics of preoccupation in each patient, but his ways of arranging and embellishing them can be many; the whole body (or parts of it) often receives much of the patient's attention, because of more or, it may be, less feeling in it (hypochondria, depersonalisation); misconstructions abound, with consequent ideas of self-reference and persecution as well as misidentification; and there is a feeling of inner tension, unrest and excitement, however apathetic or carefree the patient's demeanour.

The seemingly greater quickness and capacity of manic patients has not been confirmed by psychomotor, intellectual and association tests; hypomanic patients sometimes, however, do better than in their normal state. This can be compared to the effects of increasing doses of alcohol. Patients with affective disorder are more irritable and excitable than is normal. Time appreciation may be grossly disturbed: personal time seems to pass very differently from clock time; time may seem to stand still; no future is conceivable. Perplexity may be conspicuous, and explanations of this in terms of Gestalt psychology, conditioned reflexes and toxæmia have been proffered.

The effects of experience in bringing about this illness cannot be explained in terms of a logical and coherent system, unless one accepts the premises of that system and infers what cannot be observed. Consequently, as there are several such psychological systems, there are several explanations. They state the conjectured ways in which instinctual energy or libido may become misdirected because of environmental conditioning, frustration and loss.

**Symptoms.**—**SYMPTOMS OF EXCITEMENT (MANIA).**—There is excitability of mood and movement. The *mood* is mostly one of jollity, rather infectious, but likely to become boring or overbearing; occasionally it turns to anger and resentment. It is labile; tears will flow readily on some trivial occasion, to pass into laughter in a twinkling.

*Thinking* is apparently rapid. There is flight of ideas, with successive words and phrases loosely connected only by similarities of sound or chance associations. Consequently, the patient wanders from the point; whether he can come back to it depends on the severity of his condition. Jokes, self-praise, flighty comment on his surroundings and facile optimism make up the tenor of his exuberant conversation. Nevertheless, the number of topics he touches on in the course of the day is often more limited than if he were in normal health: he reverts to a few matters over and over. He may criticise himself, with cynical bitterness or humour, as he criticises others; he may talk a lot about bodily disturbances, e.g. his varicose veins or his sore throat. His mood and expression are consonant with what he says. He is distractable, herein seeming at the mercy of his sensations and of every small detail, whether it be inside himself or, as is more common, connected with things about him. Judgement is impaired.

*Delusions* are less common than *distortions* and misstatements. People are wilfully

called out of their names, events misrepresented, bodily sensations exaggerated, and accusations of ill-treatment or persecution irresponsibly preferred and sometimes long persisted in. The more confused and excited the patient, the more likely to be deluded and even hallucinated. Most of the seeming hallucinations are *façons de parler* or illusions; sometimes the patient is, as it were, pretending or acting the part of a hallucinated person.

*Activity* is exaggerated, and in severe cases incessant. Its object may change from moment to moment, but sometimes the main end is kept pertinaciously in view. The patient, if tactlessly thwarted, gets angry, sulky or violent. He feels very strong, and seems untiring. He has many schemes, of an optimistic cast, and, in the course of putting them into action, may be extravagant, inconsiderate or interfering. Sexual excesses or drunkenness may occur and bring much harm, especially when the patient is a young woman. Troubles with the police arise through silly pranks or self-confident exploits.

*Sleep* is brief but deep. In the early and mild stages the patient looks exceptionally well, but after weeks or months of over-activity and little sleep he looks exhausted, with sordes on his lips, hoarse voice, drawn skin and perhaps less total activity but many unfinished little movements. Food is welcomed in the mild stages; when the activity is great, the patient does not give himself time to eat, but plays with his food or is continually diverted to something else. Sexual desire is at first heightened but potency less.

The symptoms vary widely in degree. Mild hypomania may be an enviable time of well-directed expansive energy, unencumbered by some habitual restraints; gross mania may be a delirious, hallucinatory condition, with incoherent talk and little free activity.

**SYMPTOMS OF DEPRESSION.**—In the early stages or milder forms, the patient finds concentration and recollection difficult, he has less interest and pleasure in life, he feels that this world is unreal and himself changed, he dreads effort or responsibility.

The *mood* is one of grief and misery, looking in every direction for material to feed on. The past supplies peccadilloes or graver lapses; what is wretched in the present is dwelt on inordinately; the future is foreseen as hopeless ruin. Anxiety is mixed with it, often in extreme degree. Weeping is less common in the extreme forms. The patient's expression usually conforms to his affect.

*Thinking* is more difficult. This "retardation" in thinking shows itself as incapacity to deal quickly and purposively with impersonal topics, while brooding on personal matters goes on, with a press of inner activity, a ceaseless roundabout of painful thought. The making of decisions is dodged. Conversation may become meagre, even monosyllabic, though some patients are ever ready to tell their troubles. The content of their thought is *sombre*—the product of ruthlessly unfair examination of their frailties and misfortunes. Some criticise themselves remorsefully or with *cynical detachment*; some bewail their losses; others abandon themselves to resigned and world-shunning despair. There are many varieties of misery, and melancholia knows them all—as many varieties as can be made from the experiences, character and imagination of a human being. Consequently they reflect the moral, economic or hygienic standards of what is good and bad that are imposed on us by modern society and our particular education.

*Delusions* occur in proportion to the depth of affect; they are the extreme form of the doubts or preoccupations just mentioned. Patients often fluctuate between uncertainty and conviction about their troubles even during the same day or the same conversation. Insight may be good and judgement sound, when the affect is not overwhelming. The delusions are the product of the depression, which is primary; they are not its occasion, though often adduced as that. Most of them concern the future as well as the past; anxiety is prominent. Wickedness to be visited with damnation; secular crime to be punished in this world; loss of property that will



mean starvation and beggary for one's family; mortal or corrupting diseases—these are the common substance of delusions and are often commingled. For example, some patients blame themselves for having caught venereal disease which will expose them to the loss of their job and of their hope of salvation, exclude them from decent society and do loathsome damage to their bodies; no evidence, no argument shakes the erroneous belief. The delusions may be grandiose in that the patient affirms himself the chief of sinners, no one has ever been as wretched or wicked as he, he alone has done the unpardonable sin; or they may be of a minimising sort—nobody cares about him, he is of no account, let him go into a corner to hide, people despise him. This last belief is often understandably associated with ideas of reference or persecution—people make contemptuous gestures or remarks as he passes, they set detectives to watch him, they tell each other how bad he is. He accepts this almost always as his desert, though occasionally there may be overt resentment. Apart from this resentment, his beliefs derive understandably from his affective state. There are, however, features that betoken undercurrents at variance with the professed attitude or delusions. Thus many depressed patients, professing humility, are importunate in their demands on those around them.

Such hallucinations as occur are in keeping with the patient's affect and are of much the same nature as the delusions, though expressed more in perceptual terms. People are making derisive remarks, his body gives off foul smells, food has a different and disagreeable taste—it is often the mode of expression rather than of subjective experience that decides whether these are hallucinations or delusions. This is notably the case with bodily preoccupations, when, for example, patients report their food to be stagnating in their belly, their skin dull or fetid, their eyes impaired, their head empty. Much of this depends on depersonalisation, in which the body as a whole feels bereft of life and feeling, and emotional deprivation or emptiness is translated into bodily experience. In mild forms of depression there is no question of delusion or hallucination, and often no recognisable content to the gloom; the patient cannot say why he is sad. In the more chronic forms a settled and partly justified conviction about ill-health, present troubles, and the dark future prevails; the ideas may be obsessional and partly divorced from the prevailing affect.

*Activity* is limited, thus contributing to the "retardation". The more severe the depression the less does the patient do, unless the concomitant anxiety makes him restless. It is possible, however, for a patient to be depressed without "retardation". In typical cases facial expression is rather fixed and movements delayed, as though done against resistance; more or less complex activities, dressing, say, or writing a letter, take unduly long. The most extreme form is stupor or lack of all spontaneous activity; it is seldom absolute. Patients rarely become wholly indifferent to cleanliness in defaecation and micturition.

*Suicide* is the greatest danger in depression. Whereas manic patients thoughtlessly do themselves harm or get into a fight but do not try to get hurt, depressive patients are often bent upon doing away with themselves. The risk is not proportionate to the degree of depression; many very retarded and melancholy patients make no attempt, while in depersonalised mild cases a fatal outcome is not uncommonly brought about thus. There is consequently much risk during the phase of improvement—often more risk than during the preceding severe "retardation". Deliberate self-mutilation is rare.

*Sleep* is bad—hard to come by, light and unrefreshing. The *appetite* is bad too: food may be constantly refused for this reason. Commonly also the patient eats too little because of feelings of fullness and other discomfort in the abdomen, or because of delusions about his bowels or his food. Mild constipation is common, but is often given much exaggerated importance by the patient. The *weight* diminishes, chiefly, but not wholly, because of insufficient intake of food. Daily fluctuation in the general condition, with improvement towards evening is common. The skin

may be dry and sallow, and in some severe cases pigmented, as it is in pellagra. Menstruation may lessen or cease; sexual desire is much less. There may be autonomic disturbance, generalised or limited to a single system.

Here, too, there are wide variations, between the mild "neurasthenic" and the grossly deluded melancholic who craves death. There is every gradation between the two extremes, and a single patient may during the course of the illness exhibit them all.

**SYMPTOMS OF ANXIETY.**—The *mood* ranges from uneasiness to panic-stricken terror. It may be an abiding or a recurrent state. Though chiefly turned to the future, as fear must always be, it rests on past experience, often painful and largely repressed, and it reverts to the past to account for the troubles in store. Herein, as with rationalisation and some other psychological devices, there is evident a strong desire to make things understandable in a causal nexus—a tendency to be found not only in patients but also in those who observe them. The patient's expression varies with the strength of his fear.

*Thinking* is troubled, the disorder showing itself in speech somewhere between frightened dumbness and the voluble talk that seems designed to cover up embarrassment and disquiet. The patient can seldom follow a train of thought for long without a limited number of preoccupations forcing themselves in. How far this interferes with daily life or set tasks depends on the amount of anxiety, as does also the impairment of judgement and insight. The content of thoughts is as manifold as in depression, every normal matter of human concern enters into it. Fears centring strictly on a few special topics, e.g. the fear of being run over in the street, may be to the fore; the fear of insanity is particularly common.

*Delusions* are frequent in the grosser forms, which are most strikingly though not exclusively seen in patients of late middle life. They may say that their bowels are stopped up and their bodies about to rot; their enemies are waiting to tear them to pieces; their families will be tortured; their names abhorred for ever. Hell, they are certain, awaits their souls though their bodies cannot die; time stands still and no redemption is possible. There are many delusions less extreme than these mainly hypochondriacal and nihilistic ones; e.g. beliefs that employment will be unobtainable, or that the patient will be victimised for having had such an illness. Hallucinations can occur: at the height of fear every sound and sight and smell may be misinterpreted as meaning some pain to come; but most of this is illusional colouring of actual percepts. Depersonalisation is common with all degrees of anxiety.

*Activity* is much disturbed. There may be sudden attacks of panic in which the patient rushes blindly out into the open, or aimless wandering, ceaseless agitation, with movements especially at the small joints—wringing of the hands, rubbing the face, picking at sores, pulling out hair. Starting many tasks and finishing none is as characteristic of anxiety as of mania. Anxious people are distractable: their eyes follow a trivial movement—a fly walking on the window-pane—though they only comment on it when some interpretation that chimes with their mood can be fitted; their ears are sharp for hints of alarm. During an attack of anxiety with strong somatic repercussions activity may be completely interrupted—so-called collapse—while the patient, terror-stricken, expects his death; alternatively he may run for air or help. Very agitated patients may lie or sit in semi-stupor, with starting eyes and parted lips, incapable of speech unless under some strong stimulus.

*Suicide* is uncommon in those with episodic, highly somatic attacks of fear, and in those with chronic mild hypochondriacal anxiety, but not infrequent in the grosser forms and in those mingled with depression.

*Sleep* is bad: in the mild forms the patient may be afraid to fall asleep because of his horrifying dreams and the terror into which he suddenly awakes.

Sudden highly somatic episodes of anxiety are common: the patient feels his

heart palpitating, his bowels turning over within him, he sweats, his limbs tremble, his mouth is dry, he feels he will fall or collapse or die; he turns pale, his pulse-rate changes, usually becoming more rapid, his blood pressure rises, he may want to open his bowels or pass his urine. When anxiety is long-standing and severe, such attacks are rare. It is possible for parts of this general affective disturbance to be isolated, and to occur with little conscious anxiety, as in muco-membranous colitis, effort-syndrome, aerophagy, neurotic indigestion, enuresis, impotence, ejaculatio præcox, psychogenic asthma, hyperidrosis. The factors determining such special emphasis on one or other system are partly physical (some organic defect or innate functional anomaly) and partly psychological. In anxiety thyroid enlargement can occur; weight falls off; menstruation is irregular or ceases; the deep reflexes are very active.

**Diagnosis.**—Typical cases are easy to recognise. The common errors of diagnosis lie in: (1) Missing organic disease (e.g. general paralysis, cerebral arterio-sclerosis); or the converse (e.g. mistaking the more expansive manic patient for a general paralytic). (2) Forgetting how mixed the symptoms of mania, melancholia and anxiety may be, so giving rise to atypical pictures that may be mistaken for schizophrenia, if too superficial an examination or too static and rigid a diagnostic criterion be used. (3) Forgetting the influences of age, general personality and milieu on the content of a patient's mind, e.g. his having lived among spiritualists may lead to deceptively fantastic statements. (4) Expecting to be able to diagnose solely on presenting symptoms, without regard to previous history and constitution; the reverse is also to be avoided. (5) Expecting diagnosis always to lie between distinct entities which could not possibly be mixed together in the same person, as though hysteria were incompatible with affective psychosis, or both of these with schizophrenia; in fact, they often are mingled. This is not to make light of diagnosis, which gives the psychiatrist much knowledge that he cannot gain from study of the individual case before him.

Nothing in the mental state of a patient with affective disorder may enable one to exclude an organic basis such as general paralysis or cerebral arterio-sclerosis. This decision must turn on the physical findings. The problem becomes simpler when signs of dementia supervene (see p. 1626).

From schizophrenia, diagnosis depends on a picture of the whole illness, on the presence of characteristic thought-disorder, incongruity of affect and bizarreness of behaviour, as well as on the previous personality and constitution, rather than on any positive features of affective psychosis; the remoteness and unconvincing manner of the schizophrenic, so hard to describe but almost conclusive when recognised, may help. Later, when complaints have become empty and repetitive to the point of stereotypy, and catatonic symptoms mix with the anxiety, diagnosis is easier. As between schizophrenic and manic excitement, the setting in which the excitement occurs is almost more important than the *prima facie* symptoms. In young people schizophrenic features may often be found without their being of much significance; in the elderly what seem to be catatonic features may rest on an organic cerebral basis. The more easily one can get in touch with the patient, enter into his mood and understand what he says and does, the more is it an affective, not a schizophrenic disorder. The range of benign affective phenomena is wider than a textbook description can convey.

There is no need, except for administrative purposes, to try to diagnose affective psychosis from psychogenic depression, cyclothymia, anxiety neurosis, neurasthenia, or involutional melancholia; these are only subdivisions of it, in which the age of onset, reactivity, severity or chronicity of the condition is being stressed. Periodic recurrence is sometimes made the hallmark of affective psychosis; this historically interesting point of view is hard to apply, because so many patients have only one definite attack in their lifetime, and because periodicity can be striking in other conditions, such as obsessional disorder and schizophrenia.

From obsessional disorder the diagnosis may be difficult when there is localised anxiety or depression with sharp content and good insight; so closely alike are the conditions, that some authorities have proposed to include obsessional disorder also in the manic-depressive group, thus disposing of the diagnostic problem. It is best, however, to keep them distinct, and to discover in a particular case whether the characteristic subjective rejection of the obsession occurred at its first appearance; often the anxious or depressive patient at the beginning has accepted the thought which accords with his affect, though later he struggles against it and may disclaim it. Genuine obsessions, however, are common in affective psychoses.

**Course and Prognosis.**—The varieties of outcome and sequence are many. They depend on the balance between particular intrinsic and extrinsic causal factors in each case, and on the extrinsic factors which are brought to bear on it in the form of treatment. The more typical the illness, the surer the recovery in favourable circumstances.

A history of definite affective psychosis in a parent or grandparent points to recovery from the attack, but it is unsafe to infer the course of the illness from hereditary data alone. A well-adapted personality and a pyknic build, a history of similar illness followed by complete recovery, a fairly sharp and fairly recent onset, and precipitation by external troubles which will not be likely to continue are all of them points to the good. Advancing years make the prognosis poorer, but a first attack of melancholia in late middle life, if there be no vascular disease, eventually clears up in two-thirds of the cases; convulsant treatment has further improved the prognosis for this group. Bodily changes are often the best indication of coming recovery. Improved appetite and regularity of the bowels, cessation of anxiety symptoms, clearing of the complexion, increase of weight and return of menstruation may be noted, even before any increase of activity and long before any admission of feeling better can be got from the patient.

A first attack of excitement or anxiety will seldom be the only one; of depression it may. Periodic depression and anxiety is less likely to cease in middle life than periodic excitement. The occurrence of hallucinations or delusions is in itself of little consequence prognostically. A transition from anxiety to depression or mania, and from mania to depression, or vice versa, is commonly gradual. Only in predominantly reactive attacks can one surmise how long the illness will last, or when another attack is to be feared. After recovery complete insight into what happened during the illness may not be attained, especially by resentful manic patients, melancholics who are sensitive and suspicious, and agitated patients who feared personal harm.

Generalised somatic disturbances, e.g. loss of weight, especially if acute and brief, are of good prognostic import, other things being equal. The more the somatic preoccupations or symptoms are diffused over a period of time and localised to one system, the poorer the prognosis; this, however, does not apply so much to children as to adults. Hypochondria and depersonalisation suggest a long illness, as do nihilistic delusions (e.g. denying that one's bowels are opened at all), and, to a far less extent, admixture of hysterical or schizophrenic features. The more the psychogenic causes have been obviously operative for a long period, the greater the tendency to chronicity. In the more chronic forms or after a series of attacks, there may be impaired initiative and judgement, irresoluteness, dullness and social deterioration—none of them conspicuous. Puerperal and pregnancy psychoses have a good outlook. The milder forms of anxiety and depression, if not already chronic, respond well to treatment, especially to psychotherapy.

Death may occur from suicide, insufficient food and intercurrent disease, especially pneumonia.

**Treatment.**—PROPHYLACTIC.—Genetic prophylaxis is occasionally possible, as when two persons with definite affective disorders marry each other and are advised

not to have any children. Rules of thumb do not apply in this matter; it is wrong to tell a patient he should marry or not marry, procreate or not, unless one has been able to weigh the dubieties of our genetic knowledge, the pedigree of the patient and all his transmissible qualities with an informed and cautious judgement.

Individual prophylaxis is not usually practicable until after symptoms have appeared which bring the patient to the doctor; social prophylaxis and child guidance may, however, have value in staving off or mitigating affective illness, especially in those who are temperamentally very responsive to adverse circumstances, *e.g.* in their domestic life, their upbringing or their employment. No satisfactory evidence is forthcoming that such measures can forestall the grosser affective disturbances, necessitating mental hospital care, which occur in highly predisposed persons. In so far as one finds that environmental factors (*e.g.* heavy responsibility, unemployment, or sexual frustrations) have been important in provoking an attack, advice on these matters may be helpful; it may be practicable by psychological and social treatment during the healthy interval to do much good in this way. But some cases, in which intrinsic factors seem all powerful, are proof against such measures, and in any case it is not easy to persuade the patient when he is well again to put himself for a long time in the doctor's hands.

**TREATMENT OF THE ACTUAL ILLNESS.**—It is convenient to consider separately the acute major forms, and the minor more chronic cases.

For the former, the treatment other than by convulsions is directed to safeguarding life, relieving distress and providing the best conditions for the emotional disturbance to subside; the situation is like that in tuberculosis or typhoid fever. Exhortations to "pull yourself together" are as out of place as advice to take a voyage or an argument about the delusions. If the attack is sufficiently severe to unfit the patient for ordinary duties, treatment at home is probably inadvisable. Although in such attacks all argument is futile and active psychotherapy harmful, yet the loss of relation between current experience and emotion is never absolute; there is virtue in separating the patient from real trouble and distressing associations, reassuring him, giving him firm, kind management. The essential combination of these, and especially the last, is rarely obtainable at home. The patients, however boisterous or suicidal, usually recognise their need of treatment and are willing to enter hospital voluntarily. They should not transact any business if it can be helped; their judgement may be too much disturbed, they lay up trouble for themselves. Continuous narcosis sometimes curtails an attack; it demands experience and care.

Convulsant treatment is valuable; most of all for involutional conditions, least for mania. Among involutional patients those with baseless suspicion and resentment respond less well than the self-reproachful and agitated. It is still uncertain how much benefit can be obtained in younger patients with acute affective disorder; many of the figures purporting to show that in manic-depressives (thus distinguished from involutional melancholics) the recovery rate after convulsant treatment is also high, have been compiled from a series of patients the majority of whom had reached later middle life and might therefore have been properly classified as involutional. It is, moreover, difficult to evaluate recovery rates for this purpose in a condition in which recovery is often obtained by other therapeutic methods, such as would probably have been employed along with the convulsant treatment. Whereas in the depressive conditions of late middle life there can be little doubt about the general superiority of convulsant treatment to any other available method, in the affective disorders of earlier life it is only by the effect on the duration of the attack, and the subsequent frequency and severity of attacks, that the efficacy of convulsions can be judged; the restricted information available does not give any conclusive general answer, though it is evident that, on the one hand, some young patients have their attacks of depression promptly cut short by this method of treatment, whereas previous attacks not treated thus had lasted for many months, and on the

other hand some of them soon relapse. For manic patients it is on the whole disappointing.

Convulsant treatment by the electrical method has superseded chemically induced convulsions. It is important that the psychiatrist should not use subconvulsant doses if he can help it. The number of fits required varies from patient to patient but it is unwise ever to give a total of more than twenty fits. Patients with circulatory or pulmonary disease should only be allowed to have convulsions after the risks have been fully weighed. In order to lessen the chance of spinal or other fracture, a relaxant is administered, usually in conjunction with barbiturate intravenously.

For the depressions of middle life convulsant therapy has enough success to justify calling it a specific method of treatment. By the electrical method, fits lasting less than a minute are induced three times a week; not more than ten fits are usually required. A relapse may necessitate repetition of the treatment. *Fragile bones or vertebral deformity may preclude use of the method, unless special precautions are taken and the dangers made known to the patient or his responsible relative.* The treatment should not, except in very special circumstances, be given as an outpatient procedure. It is capable of causing temporary, and perhaps permanent cerebral damage, though, as a rule, the forgetfulness or disturbance of consciousness which may follow the fits soon clears up. In spite of the simplicity of the actual procedure—hardly more complicated than turning on the wireless—the tiro can do great harm with it by selecting patients who are unsuitable on either mental or physical grounds, by giving too many or too few fits, and by neglecting methods of preventing fracture and other complications.

Patients with severe and long-standing agitated depression sometimes are much improved by frontal leucotomy; the longer they have been ill the less good is the operation likely to do.

Prolonged baths—for 8 or 10 hours daily at a constant temperature of 96° to 98° F.—have much value in allaying restlessness, whether of the manic or the anxious kind, especially the former. They have the further merit of diminishing angry contact with other people, permitting fairly free movement and lessening dirtiness, besides promoting sleep.

*Drugs* are indispensable. The fear of habit formation should not prevent hypnotics being given when there is persistent insomnia. Barbiturates or paraldehyde often suffice: it is well to ring the changes and to diminish the dose without the patient's knowledge. For severe anxiety opium (e.g. as papaveretum) and hyoscine may be helpful; the risks are obvious. Continuous narcosis is valuable, but must be used with caution. Food must be given in adequate quantity and kind. The induction of mild hypoglycæmia by insulin each morning may be helpful in inducing a willingness to take more food. Artificial feeding, preferably by nasal tube, may be necessary because otherwise the patient would die of starvation. The presence of acetone in the urine and a falling weight curve are strong indications that nutrition must be attended to promptly. A good nurse may sometimes, by unusual patience and sense, get over an obstinate refusal to take enough food and drink, but often nothing prevails against it. Apart from hydrotherapy, rest in bed, fresh air, attention to the bowels and other measures of general hygiene are desirable.

*Suicide* is of the first importance. Prevention of it can be better ensured by close knowledge of the patient and his day-to-day condition than by mechanical precautions, but if he is bent upon it, these may be unavoidable. It is possible to make them unobtrusive without nullifying them. Certain it is that excessive use of bolts and bars can defeat its own ends, and excessive supervision aggravate a patient's misery, his fears or his resentment. Two good rules are: (1) to discredit the maxim that those who talk of suicide never commit it, and (2) to remember that most suicides are surprises. Convalescence from melancholia is a risky time.

Occupational therapy is good, as soon as the patient can be got to co-operate;

but it is not rational treatment to pester a melancholic, to encourage the fretful restlessness of the agitated, or to give the manic patient more things to muddle himself with and destroy. Still, it is often surprising to find how soon, under tactful guidance, these patients will enter into ordered activity of a more or less simple sort, and how helpful it can be to them. During the stage of improvement the same is true of recreations and social activities. Patients should not leave hospital till recovery is assured, unless it is obvious that the hospital surroundings and the absence from home and work are an actual cause of their persistent anxiety or dejection.

To revert to the *milder* forms, which tend more to become chronic. Here manipulation of the conditions in which the patient lives at home and at work may be conjoined with psychological treatment (individually or in a group), depending on an appraisal of the causes of his illness. There is nothing distinctive (though much that takes account of the individual patient's needs) in the psychotherapy and social treatment called for (see pp. 1618, 1619); danger signals must be recognised as they occur. Zeal must give way to the real needs and resources of the patient, which are often not appropriate to a drastic or very lengthy treatment. Simple measures of enquiry, explanation and reassurance, together with small environmental changes, may have much effect. A fixed régime imposed in detail by the doctor is helpful; this becomes more and more necessary as the affect dwindles in long-standing cases. Hypomania does not usually respond to causal treatment of any kind; it seems to run a largely autonomous course. Anxiety may yield very satisfactorily to patient psychotherapy and environmental adjustment.

## SCHIZOPHRENIA

**Definition.**—The forms of illness under this name are so diverse that many efforts have been made to distribute them, so far in vain. What is common to them all is a detachment from the world without, and a breaking up of normal psychological connections within. The personality is not integrated as in normal people; thinking, emotion and conduct are discrepant and morbid, yet there is no impairment of formal intelligence such as is found, for example, in organic dementia. The obsolescent name "*dementia præcox*" is not a synonym for schizophrenia, but a reminder of its recent history. At the end of the last century a large number of patients in mental hospitals were found to have begun their illness before they were 30, and to have passed ultimately into a deteriorated state that looked like dementia; their illness was closely studied, delimited and called "*dementia præcox*". When the same clinical picture, however, came to be found in cases that had not such an outcome or onset, the latter criteria were waived in favour of a descriptive analysis of the actual symptoms, and along with this larger conception came the new word "*schizophrenia*", which betokened a more psychological approach, and a more elastic and generous notion of what might be included. Theories of causation, psychopathology and clinical boundaries are implicit in any view of what "*schizophrenia*" really is; consequently, it is still possible for two experts to disagree about what should properly be included under this name, yet over the diagnosis and prognosis of any particular patient they will attain a measure of agreement and certainly surprising to those who know the condition only from reading or limited experience.

**Ætiology.**—**INTRINSIC.**—The intrinsic factors are very important. Studies of the incidence in twins and in the members of a family demonstrate a hereditary factor in a majority of cases. If one of a monozygotic pair of twins be schizophrenic, the other is also in 76 per cent. of cases, whereas the corresponding percentage among dizygotic twins is only 14. The nature of the mode of transmission is still in doubt; the most recent observations suggest a single recessive factor which must be inherited from both parents. Variations in the manifestation of the disorder may be in part

dependent on a non-specific character controlled by a multi-factorial genetic mechanism.

The constitutional features that betoken an innate predisposition to this illness are more of the psychological than the physical kind. The bodily attributes have been said to be an "asthenic" or "ectomorph" (weedy and lank), "athletic" or "dysplastic" build; but, since these are found in much the same proportion among healthy people as among schizophrenics, and the correlations between habitus and diagnosis are not convincing, there is little to be said for them here. It is, however, certain that "pyknic" build (see p. 1646) is uncommon among schizophrenics. More significant, however, are the features of personality, commonly called "schizoid"; they are to be found in a large number of cases, though not by any means in all. The patient is reported to have shown slight peculiarities from his earliest years; he has been quiet, shy and solitary, a "model child", given more to daydreaming or abstract speculation than to ordinary interests and activity; sometimes he has been unduly submissive and sentimentally affectionate, or touchy, suspicious, obstinate, and resentful of advice and control. A single "typical" schizoid personality is a myth. It is, moreover, to be stressed that a "frozen" description of the schizoid varieties of personality does not do justice to the true state of affairs: characteristic deviations from the conventional norm of behaviour can always be understood better if the patient's way of dealing with his circumstances is viewed historically as a biography of individual tendencies and experiences, rather than described as a bundle of traits. By paying heed to the development of faulty as well as healthy habits of response, the psychiatrist can often see the march of events that led up to the patient's illness, and escape too artificial a sundering of inherent tendencies from the external happenings by which these tendencies have been evoked and given shape and substance.

**EXTRINSIC.**—The illness sometimes breaks out after childbirth or an acute infection. None of the efforts made to inculcate some specific infection have succeeded, nor has intoxication in general been found to play any considerable part in the causation of schizophrenia. The same is true of cerebral trauma. There are, however, many instances of a chronic schizophrenia supervening on an intoxication, and of schizophrenic symptoms, especially of the catatonic sort, appearing in the course of an organic disorder, such as G.P.I. or encephalitis lethargica. In these, the same structural and functional systems must be supposed to have suffered impairment as in the "endogenous" forms of schizophrenia, and it has been particularly urged that in the chronic paranoid conditions that may follow an acute alcoholic psychosis, it is really a matter of schizophrenia that happens to be associated with alcoholism, if not partly activated or released by it. It is further to be remembered that certain intoxications, *i.e.* with mescaline, lysergic acid or adrenochrome, produce a mental disturbance that is in some respects similar to schizophrenia, and that any chronic hallucinosis comes in time to look very like a long-established schizophrenia, probably because the possibilities for abnormality of any human mind are few, the deprivation symptoms almost uniform, and our methods of clinical examination imperfect. Endocrine disorders, especially of the gonads, have been held responsible, but are more probably manifestations of emotional disturbance; findings are not consistent and the relation between endocrine and psychological events still rather obscure.

Recent mental stress may sometimes be the starting point of an attack, but in a considerable proportion of these cases the reported overwork, disappointment in love or other painful experience, is found to have been a product of the already existing illness, or the last of a long series of disturbing events. No recent experience is ever sufficient to account for the illness without regard to intrinsic causes. Nor is any remote experience either. No matter how searchingly the patient's life be resurrected and analysed, it is scarcely ever possible to discover that anything happened to him which would have led to his adopting a schizophrenic way of shunning daily life unless he had been somehow disposed to it from the beginning; although, of



course, much may have happened to him that has strengthened and fostered the disposition.

Among contributory factors, age and sex are noteworthy. An onset after the age of 40 is uncommon. In three-quarters of the cases that later exhibit the characteristic chronic syndrome, the illness begins between 15 and 25. The condition may become overt in children before puberty. Men are more often affected than women—in the proportion of 113 to 100, according to the largest available statistic; the matter is dubious, however, because of the different standards of diagnosis used.

**Pathology.—PHYSICAL.**—Histological changes in the brain are not characteristic; it is doubtful if they are even frequent. A cellular loss in the third and fifth layers of the cortex, with lipoid accumulation, has been found, but it occurs in many other conditions. Swelling of the oligodendroglia has been described in brain tissue obtained at biopsy. Many claims about cerebral pathology, and the chemical and physiological changes in schizophrenia have now been discredited, so that all findings in this difficult field have come to be matters of suspicion. Variations in the same individual may be wide. Investigations have purported to show: a disturbance of the acid-base equilibrium towards the acid side, with a diminished excitability of the respiratory centre to carbon dioxide; lowered rate of oxygen consumption; polyuria; diminished gastro-intestinal motility; poor response to epinephrine, insulin and dinitrophenol; and to vestibular stimulation by cold water or rotation; abnormal heat regulation; abnormally variable sugar, creatine and non-protein nitrogen content of the blood; anomalous capillaries; decrease or sluggishness of total blood-volume; and slowing of the arm-to-carotid circulation time. These findings, indicative of a defect in adaptive capacity, have not so far been controverted; they represent disorders of metabolism and regulation which may be partly a concomitant of the characteristic mental disorder, and partly an effect of it, *i.e.* they may be essential physical disturbances in the illness, or may be secondary to the abnormal, often inert, life the patients have led since they became ill; thus evidence of hepatic dysfunction in catatonic patients is of nutritional origin and may be corrected by changing to a suitable diet.

Some inferences have been drawn from the similarity of catatonia to the extra-pyramidal syndrome that can be produced in animals by bulbocapnine; the argument from analogy cannot be pushed further than to say that certain functional systems are available in the brain, disorders of which are sometimes evident in schizophrenia, as they also may be in poisoning or in encephalitis lethargica, G.P.I. and other diseases.

Very significant are the well-attested metabolic findings in the rather rare cases of cyclical catatonia. In these the nitrogen balance varies periodically; with alternating phases of retention and over-excretion, corresponding to the mental change from excitement to stupor or vice versa. By means of thyroxine a thorough emptying of the patient's nitrogen store can be brought about and subsequent nitrogen retention prevented, thus leading to clinical improvement. The correlation between metabolic happenings and clinical condition in these patients is now established.

**PSYCHOLOGICAL.**—The large and inconclusive literature on the psychopathology of schizophrenia derives from:

- (1) Minute description of the phenomena observed, and abstraction from them of general principles of disordered function.
- (2) Experimental study, using projective, sorting, reasoning and other tests, as far as possible under controlled conditions.
- (3) Studies of artificial hallucinoses (*e.g.* mescaline intoxication) and parallel experiences.
- (4) Comparative study of animals, children, poets, primitive people, etc.
- (5) Intuitive or speculative interpretation.

It will be obvious that these methods overlap and that they differ widely in

acceptability and usefulness. The findings of almost all can sound plausible, when stated in general terms; discrepant or abstruse, when stated in detail. Their exposition touches on the most intricate problems of normal and morbid psychology, and therefore is highly technical and unsuitable here. A working hypothesis for clinical purposes is that in schizophrenia there are inherent faulty dispositions, whose manifestation depends, in severity and persistence, on upbringing and other external circumstances. It is characterised by, among other things, a perversion and failure of synthesis, so that there is an inco-ordination, "intrapsychic ataxia", as it were, a splitting up of the mental life, which justifies the name "Schizophrenia". The whole psychic life of the patient, cognitive, emotional and conative, may be changed in a way that is alien to normal understanding. We can observe the change but to enter into it or describe it adequately in terms of our own experience is far more difficult than if we try to do this for depression, manic excitement, hysteria or obsessions. It shows itself also as a turning away from the contacts and realities of daily life, a preference for what the mind can supply from its own stores, however, morbidly, rather than for the current experience that the outer world affords.

**Symptoms.**—Schizophrenia may be regarded for clinical purposes as a form of maladaptation in which there are characteristic defects of inner harmony and consistency in behaviour, thought and emotion. These are rarely seen in childhood, but from puberty onwards they may appear in varied combinations (often in persons who for years have been introspective and unsocial). There is discrepancy between mood and utterance, disturbance of conduct (briefly summed up as catatonic or hebephrenic), self-absorption and incapacity for sustained thinking along normal lines. A guarded or artificial demeanour may conceal these essential features, whereas they may be conspicuous in a florid or "deteriorated" case. Hallucinations and delusions may fill out the picture; affective or other morbid types of reaction may complicate it.

The onset is not always abrupt. There is often a long history of preliminary symptoms in which it is arbitrary to decide where personality has merged into illness. Complaints of headache, weakness, anxiety attacks, loss of appetite and dysmenorrhœa may have accompanied slight oddities of behaviour, such as rudeness or apparent absence of mind and indecision. The patient may have felt an alarming change in himself, in his capacity to think and feel normally, and been notably depressed and anxious. Ideas of persecution or of exaltation may occasionally escape him, or he may have become stilted in his talk and shown other affectations and mannerisms. The more gradual the onset—and in many cases it has spread over many years—the more unlikely is it that it will have been recognised as morbid.

The commonest or basic symptoms are: (1) Disorder of thinking. (2) Emotional incongruity. (3) Hallucinations. (4) Disturbed impulses or conduct. From these can be derived most of the other symptoms, such as delusions, feelings of influence, autism, catatonic phenomena, anomalies of speech, negativism and the rest.

The *disorder of thinking* is a characteristic and central feature. The patient cannot command the whole range of an act of consecutive thought; he misses the point, fastens on details and brings in irrelevant associations which are correct in themselves, but which divert him from the main end of his original process of thought; consequently his thinking is incoherent, rambling and jumbled. He brings together the most far-fetched topics, so that the connections are sometimes so superficial as to be empty of meaning, and at another time profoundly influenced by symbolism and highly individual values. The usual logical sequences are ignored: cause and effect are interchanged; temporal, spatial, verbal and accidental relationships are unduly turned from abstract to concrete, treated as grounds of identity, played with or flouted. Things linked only by analogy and chance association are taken to be the same. The condensation of several conceptions in one, or transference of a set of attributes to some inappropriate object, may become a matter of course, so that only the closest knowledge of the patient and his surroundings will enable the psychiatrist

to follow his meaning. It is not necessary, however, that such extreme incoherence be evident in the patient's talk; he may not show any at all when speaking, or may suddenly obtrude a startling lapse from normal ways of thought which he then ignores, justifies or explains away. Inconsistent thoughts can be present together in a way impossible for normal people; and the same object or notion can appear to him in several interchangeable guises, each of which would normally exclude the others. The patient himself is often aware of his disordered thinking, and may describe it: he feels his thoughts are suddenly taken out of his mind, other thoughts, foreign to him, are put into his head, his mind is not his own, his thinking is suddenly interrupted, some external power controls it.

The thought-disorder is illustrated by the following characteristic remarks of patients: "There were bats and bees coming through the window; of course that was because my brother-in-law kept teasing me. He said I had bees in my bonnet." "If I should return during my absence, keep me here until I come back." "I have a lot of forced thoughts. My thoughts are all drawn-out words, they ought to be pin-pricks. There is an unnatural stoppage in my thoughts, too. . . . I have heard voices say, 'He is conscious of his life' . . . To get my feeling back to normal I feel like changing motor-cars into battleships, to be superior to them."

This disorder may only be demonstrable when the patient gets on the topic of his delusions; in other matters he may seem quite sensible. It is not essentially different from what normal people experience during states of altered consciousness, e.g. in dreams, or when falling asleep; the schizophrenic, however, has it with clear consciousness, so that a listener often feels that the patient is making fun of him in giving such transparently absurd answers with an air of knowing exactly what he is about. A chronic well-preserved schizophrenic has been known to make his living as a comedian, the audience much enjoying the allusive, half-comprehended nonsense, with its background of innuendo and symbolism. Autism, i.e. immersion in his own fantasies and preoccupations, may account for much of the oddity and detachment the patient shows; it accounts also in part for his "negativism", in that he resents any stimulus that interferes with his daydreams.

Delusions arise mainly out of the thought-disorder. They are often bizarre; they may occur to the patient with a suddenness of conviction that puts them beyond all argument; and they are egocentric in that they commonly bring indifferent happenings or people into a special relationship with the patient—e.g. he suddenly knows that when his cousin yesterday said he had been reading about Napoleon's divorce of Josephine, it was a subtle way of telling the patient that his wife was committing adultery with this cousin, whose name is Joseph. The delusional ideas may not be firm conviction, but fleeting notions, readily given up, and based upon some casual instance of the thought-disorder; sometimes they are schizophrenic ways of saying something commonplace—e.g. the patient declares his wife has poisoned him, but when he is further questioned says airily that he means she gives him ill-cooked food which is bad for his digestion.

Fixed delusions are, however, common, and are usually of a paranoid complexion; they may develop out of more or less ephemeral ideas of reference. They are often intermixed with hallucinations. The patient gets into a state of mind in which he feels there is meaning in everything, something is going on behind the scenes, he is perplexed by all this, and mystified, it has to do with him in some uncanny way. Presently, he begins to "see through it all", sometimes he gives it some religious or cosmic significance, especially if he has much anxiety as well—the Last Judgement is at hand, he is to be responsible for the regeneration of the whole world. The delusions are not always enacted on so grand a stage; there may be homely fancies about neighbours who whisper and sneer, or about some bogey like the Jesuits or the Jews or the C.I.D. Often, the patient complains that people work on his mind, hypnotise him, influence him for his own good, set about to drive him mad or ruin

him. Delusions of grandeur may be linked up with these paranoid ones (*e.g.* he is being persecuted because he is the Messiah), and may be likewise pedestrian or lofty, according to the patient's previous education and interests, the severity of his disorder, the copiousness of his fancy and the amount of normal mental function still in evidence. Here, as elsewhere in psychiatry, the symptoms are a mixed outcome of impaired or perverted function on the one hand, and of normal function on the other, the latter either reacting to and modifying the disorder, or obtaining freer play through it. If, for example, a patient feels his thoughts being controlled by some external influence, and he has queer tinglings in his body, his conviction that he is being hypnotised, and that someone is playing an electrical instrument on to him, must be regarded as a normal attempt to find the cause of an almost inexplicable happening. The delusions are sometimes about past events, which are falsified retrospectively, *e.g.* the patient relates details of his having been a changeling or a predestined hero. Delusions about bodily transformation or disease are frequent, and may be complicated and bizarre.

Patients often do not act in accordance with their delusional beliefs, especially when these are fleeting or chronic; they may, for example, be friendly towards a nurse whom they believe to be persecuting them cruelly. But this is, on the whole, unusual in the early or acute stages of the illness: a patient will then act on his beliefs violently or in terror; he may go to the police or be driven to suicide.

Constantly the matter of a patient's delusions will be found to be intimately dependent on his experiences, his emotional attachments and sufferings, his struggles and frustrations; it is impossible, however, by any such analysis and derivation of his delusions to account for the fact of their occurrence, *i.e.* for the patient's choice of this way of dealing with the experiences in question. The same is true of the general thought-disorder: *e.g.* interruption or "blocking" of the train of thought may take place only when some emotionally weighted topic, some complex, is touched on. This accounts for the place where "blocking" occurs, but not for the "blocking" itself; that, like the other fundamental disturbances of function in schizophrenia, eludes a wholly psychological explanation.

Intellectual defect does not occur, though the patient may find it difficult to form concepts necessary for abstract thinking. There is usually no clouding of consciousness. Intellectual laziness or evasion is often conspicuous; the patient may repeat questions in a musing way, or profess ignorance. Orientation and memory are not, as a rule, diffusely impaired, though hallucinations, delusions and lack of interest may interfere with them, and consciousness may be disturbed in stupor or excitement. Many a patient who has long borne the appearance of gross dementia will suddenly show that his intelligence is still a sharp instrument: drugs, *e.g.* sodium amytal or insulin, and intercurrent disease or shock can thus dramatically reveal how little ground there is for calling this illness a dementia. Schizophrenics often do the unexpected. Amnesias, and deliria, when they occur in schizophrenia, may be hysterical; obsessional and hysterical symptoms, like anxiety and depression, are compatible with schizophrenia, and are often an intimate component of the illness.

The speech and writing of the schizophrenic betray the extent of his thought-disorder. Stiffness, pedantry, fantastic euphuisms, words of his own coining, queer symbols and grammar, stereotyped repetition and infantile twists like speaking of himself always in the third person may be conspicuous features of the patient's use of language. There may, of course, on the other hand, be little or nothing outwardly amiss in his conversation and writings. In florid or chronic cases the patient may talk in an unnatural voice, or without any modulation. Writing may be set forth as though it were painting, and the converse: in subject and matter the patient's insanity may be patent, but his treatment of his matter, however odd, is seldom odder than some forms of art, and it cannot be called typical of the illness. These anomalies of symbolical representation are as open to psychological explanation as are the

delusions mentioned above; the neologisms, for example, can be analysed up to a point; and these phenomena have enriched our knowledge of the psychopathology of schizophrenia.

The *emotional incongruity* is the chief, but not the only, sign of disturbed affect. Often the patient himself notices in the beginning of his illness that he is less moved by habitual affection, or even feels hatred towards a parent he has loved. The strongest and rarest of human passions are not infrequent in this illness: ecstasy, mystic communion, despair, horror, agony of death, limitless abandon, apotheosis, salvation, are approximate names for these exceptional states that are probably indescribable in the current language of normal people. Apart from these, and much the commonest of the affective changes, is apparent emotional shallowness: the patient receives moving news without any sign of being touched by it, or his response is perfunctory; he smiles or looks bored when talking of a recent tragedy in his own family. This shallowness and incongruity of affect is, however, not to be taken at face value. What the patient says, and what he means with his words, may be very different; so may what we say be very different from the meaning the patient attaches to it. It is unsafe to assume that the patient's words have reference to what is mainly going on in his mind at the moment, or that his outward expression is a trustworthy index of his emotional state. Violent emotional outbursts—of anxiety, rage, love, misery—can certainly occur in a patient who has lately seemed empty of all affect. The schizophrenic patient is undoubtedly different from normal people in his emotions, but not in so negative a way as his seeming apathy and lack of affective rapport would suggest. His attitude towards the same person may change quickly, in accordance with conflicting or opposite tendencies in himself; this ambivalence is often understandable in the light of his earlier history. Sometimes the illness leads to a blunting of ordinary reserve, a lack of reticence, or a levelling down of the gravest matters, so that frivolous or cynical indifference and imperturbability are signs of the patient's morbid condition.

*Hallucinations* are not so frequent as superficial examination of patients might suggest; many of the patient's assertions about queer sights and sounds are not the expression of vivid perceptions but of passing fantasies, imagined more plastically than is normal; this is particularly true of many of the so-called visual hallucinations, or of cases where the unreal perceptions occur in several senses together. Hallucinations are nevertheless extremely common and persistent in schizophrenia; auditory ones occur most often, diffuse somatic ones not infrequently, those of smell, taste and sight more rarely.

The "voices" are sometimes so closely linked with the thought-disorder that it is difficult to tell whether the patient is relating what he has heard or what he has thought. He may show the intermediate stages between the two, declaring that people repeat his thoughts or that everything that passes through his mind is spoken aloud inside his head; his actions are described publicly, he cannot go to the lavatory without shameless comments. What the voices say may be abuse or encouragement, trivial repetition or threats and commands; this content can usually be accounted for by the psychiatrist, when he knows the patient and his history well. The voices may come from strange places, *e.g.* from inside the patient's own chest or abdomen, and are then often accompanied by curious somatic hallucinations, indicative of morbid attitudes, both physiogenic and psychogenic, towards parts of the body. The latter often occur independently. Queer sexual feelings, or distortions and impossible growth of various organs, may be reported. They are usually bound up, as any schizophrenic symptom is likely to be, with delusional and emotional components, which are partly derived from the patient's experiences and psychological development. The visual disturbance, like the gustatory, is more often illusional than hallucinatory, *e.g.* people's faces look fiendish or artificial or transfigured.

The *actions and bearing* of the patient are often characteristic. Abruptness or

lack of grace in movement may be seen early; it can be indistinguishable from the fidgety self-conscious hobbled-hoy stage of adolescence. The patient may pull faces at himself in the mirror, or may be unaware of his grimaces. Asymmetrical movements of expression, twitchings, mannerisms, queer rituals and tic-like gestures are to be met with. The meaning of the patient's movements can usually be worked out, but after they have been present for long their sharpness is rubbed off, as it were, and the empty stereotyped movement at last gives little clue to what was once a significant emblem of experience and feeling. The movements often seem to become automatic, like the "verbigeration" of empty phrases in the patient's speech. Negativism, talking and acting beside the point, and bizarre escapades may be seen at any stage of the illness.

There may be a suspension of movement, or the reverse: akinesis or hyperkinesis. Both may occur in the same patient, who may lie for weeks or months in a catatonic stupor, from which he suddenly emerges into swift action. He may carry out some impulsive action and then promptly return to bed and stupor; or he may become wildly excited and imperil his life by his blind and raving activity. During catatonic stupor, patients may adopt strange postures, *e.g.* holding their head off the pillow all day, pursing their lips. They may be indifferent to cleanliness about faeces and urine, or actively dirty in this regard. Waxy flexibility is rare, but many patients are automatically obedient so that they keep up an imposed posture.

The variety of schizophrenic anomalies of conduct is too great to be described here. They must not be assessed absolutely, but always in relation to the setting in which they occur. Then they have meaning in the individual case, and are not merely so many examples of "ambivalence", or "mutism" or "negativism". It is, however, true in this matter also that understanding the content of an anomaly does not make its occurrence likewise understandable. Much of the schizophrenic's conduct is so close to certain disorders of movement in organic disease of the central nervous system and its connections, that *somatic mechanisms* may be assumed to have suffered damage in this condition. There are three main things to be done with any schizophrenic symptom: (1) to search out its psychological origins, and its meaning for the patient in his present situation; (2) to link it up with the other functional disorders that he shows and (3) to consider its background of physical structure and function. It is not always practicable to attempt all three, nor is it as yet possible to do them well, but none can be ignored without detriment to a full analysis.

Often the most significant yet intangible effect of the illness is upon the patient's *personality*. After florid symptoms have died away, or when there are no definite symptoms at all, a change in the patient's ways is remarked by his intimates. Not only is he outwardly different—more "peculiar", less understandable and predictable, rather shut-in upon himself, remote, with queer values and impulses—but in many cases he is also aware of this change, and may complain of an inner perversion of himself, a loss of that unity which we take for granted when we say "I", or "me". Insight in schizophrenia, in this respect and more generally too, may be penetrating and just, as many self-descriptions attest. There may also be varying degrees of impairment up to gross lack of insight.

None of the *bodily symptoms* are characteristic of this illness, though many occur. Besides the *somatic complaints* and preoccupations already mentioned, patients, especially if young, show vegetative anomalies. Thus, vasomotor disturbance may take the form of cold bluish extremities, exanthems or oedema. Seborrhœa is common. Abnormal growth of hair occasionally occurs in women. Loss of weight in the acute stages, and fatness in the chronic condition, interruption or irregularity of menstruation, and fluctuations of temperature may also be observed, especially in catatonic cases; of the schizophrenic states, stupor is the richest in demonstrable bodily changes. Fleeting neurological signs, *e.g.* pupillary anomalies, may be found.

In states of acute excitement attacks of unconsciousness may occur, but epileptic seizures are very rare.

**VARIETIES.**—There are three main forms—catatonic (with acute outbursts); hebephrenic and simple (early onset, chronic course); paranoid (fairly late onset, delusional). They are not exclusive categories, and it is usually profitless to try and appportion a doubtful case to one or the other. They do not correlate closely enough with outcome or effective form of treatment to be of much use clinically.

In *hebephrenia*, the least common variety, delusions and hallucinations are inconsiderable, but abnormal conduct is to the fore: the patient may be silly and mischievous, abruptly eccentric or inert and without initiative. The illness may progress without acute episodes ("dementia simplex"), or be interrupted by phases of excitement or obvious insanity, which subside, leaving the patient worse than before. In *catatonia*, the most favourable variety, the symptoms are plain even to the layman: akinetic or hyperkinetic states may appear and subside quickly, sometimes for good or for several years. There are usually, also, characteristic disorders of thought and emotion, which may clear up when the stupor or the excitement does. In the *paranoid* form, generally rather late and insidious in its development, but less damaging to the personality than the hebephrenic, partial systematisation of the delusions is common in the earlier stages, but may be later swallowed up in the general thought disorder and deterioration ("dementia paranoides"). The more bizarre the delusions, the more likely is affective emptiness to replace gradually the initial resentment and distress, but sometimes the patient passes into a chronic paranoid state, obviously schizophrenic to the psychiatrist, but compatible with ordinary life outside an hospital. Hallucinations and luxuriant delusions may, however, be conspicuous in the paranoid form (paraphrenia and "dementia phantastica").

**Diagnosis.**—The chronic and advanced cases—"typical dementia præcox"—that abound in mental hospitals, are easy to diagnose: but early or inconspicuous cases often extremely difficult. The chief positive points to look for are: characteristic thought-disorder, a qualitative change of affect, and other evidence of "intra-psychic ataxia", as well as feelings of being under external influence. Catatonic symptoms are of limited diagnostic value, because of their frequency in organic and symptomatic psychoses. More important than any single feature is the impression of the cases as a whole, the development away from normal interest and response to the real world, and the establishment, instead, of "autistic" self-satisfactions so that the patient's personality is twisted awry, as it were, and withdrawn from easy contacts.

It is unsafe to lay much weight on the diagnostic help afforded by projective and other psychological tests. The intuitive element in the interpretation of Rorschach and other findings of this kind is greater than is consistent with a reliable diagnostic procedure. The psychological data may suggest schizophrenia but should not be the decisive factor.

From organic syndromes—syphilis of the central nervous system, alcoholic psychoses, disease of the cerebral vessels, encephalitis lethargica, etc.—the differentiation turns on the physical findings, more than on the mental state: a schizophrenic syndrome may appear in an organic condition, because the brain, as Kraepelin said, is like an organ whose stops give out the same sound, whoever works them. Often it is not a matter of deciding whether the syndrome is organic or schizophrenic, but whether, being schizophrenic, it has a discoverable somatic basis or not. Alcoholic delusional states are an instance of the complicated relationship that may be found (see pp. 1638, 1639). If, after consciousness has become clear again, the other phenomena of toxic confusional psychosis persist, then schizophrenia is the more probable diagnosis.

Diagnosis of schizophrenia from an affective syndrome is difficult, because both are often combined in the same patient. Some of the significant points have already been referred to (see p. 1652). Catatonic excitement differs from mania in

that the speech and acts of the latter are intelligible as expressing a general affect and are conformable to the situation in some measure; the onset and cessation are not so abrupt as in catatonic excitement; and there are usually characteristic features which make the distinction easy. Melancholia becomes suspect when delusions are repeated without the appropriate effect, and there is a readiness to project responsibility for the illness, to complain of external influence. The inertia of the depressive is not so complete as that of catatonic stupor, nor so likely to be abruptly broken through. States of severe agitation are not always easy to distinguish from schizophrenic excitement, but a more frequent problem is that of deciding whether some bodily fear or conviction of disease is schizophrenic or not. Whether in regard to a preoccupation or a delusion, the chief point to consider is the appropriateness of the affect to the alleged hypochondriacal notion; the more bizarre the bodily change described, the more likely to be schizophrenic. Depersonalisation is sometimes at the bottom of these somatic complaints; what is significant is not the depersonalisation, but the way it is elaborated and regarded by the patient.

*Hysteria can offer great difficulties, largely because hysterical mechanisms are so often operative in schizophrenia.* Plain motor or sensory disturbances commonly give less trouble than hysterical dissociation, stupor and pseudo-dementia. The previous history, the relationship of the outburst to a particular set of happenings, the behaviour in the intervals, the demands upon the attention or response of bystanders must be taken into account. The mistakes and oddities of the hysterical pseudo-dement may be theatrical, in accordance with his ignorant notion of what insanity is like; the deliriously dissociated hysteric does not identify correctly the people around him, as the schizophrenic usually does, even when in a dream-like state; the hysteric who is acting some imagined scene does so without discrepancies or gross interpolations, whereas the schizophrenic is seldom so consecutive and persistent. The degree to which the patient is being influenced by his immediate surroundings is, however, the chief guide, apart from definite schizophrenic features.

*Obsessional states offer difficulty when the patient is in doubt as to whether his alien thought or impulse comes from within his own mind or is imposed upon him.* If he shows indifference as to the occurrence and content of the compulsive ideas, it is suggestive of schizophrenia; but careful examination of the development of the symptom, and the patient's attitude towards it, permits a clear diagnosis in most cases. Complicated rituals, odd obsessions and chronicity make an obsessional illness look very like schizophrenia; as does intoxication of an obsessional patient by bromides. Obsessions may develop into schizophrenic symptoms (see p. 1679).

**Prognosis.**—Schizophrenia is always a serious condition. Though some recover, the tendency of this morbid change is to do permanent damage to psychic life. In the individual case, however, pessimism is not justified. It is certainly never possible in the early stages of the illness to be certain that recovery is out of the question.

**Heredity** is a poor guide to the prognosis, except in the rare cases in which an identical twin of the patient has for some years had a schizophrenic illness, or in which one parent is schizophrenic, and the other has schizophrenic relatives; even then it is difficult to prognosticate with assurance regarding the present attack. If one parent has had an affective illness the prospects of recovery are brighter, but this can better be assessed from the patient's own bodily and mental constitution. If he is of pyknic build, the outlook is much better. Similarly, the patient who has for years tended more and more to withdraw from his surroundings, to be careless of social requirements, to lie late and live alone, given up to day-dreaming and eccentricity—such a one should he become overtly schizophrenic, has a poorer chance of doing well than the active, suspicious and impulsive man, or the self-conscious, introspective worrier who similarly falls ill. A narrow and rigid previous personality makes deterioration more likely than if there had been wide interests and possibilities of adaptation.



The more abrupt and stormy the onset, the better the outlook. This is one of the most reliable guides. When the onset has followed upon a recent painful experience, and the content of the patient's talk and his behaviour refer to this, or when a physical damage appears to have provoked the symptoms (*e.g.* influenza or head-injury), the outlook is rather better than when the provoking factors are obscure; but this is by no means always the case. If the attack occurs during puberty or adolescence, prognosis must be cautious, because of the difficulty of distinguishing between the transient upsets of this period of adjustment, and the progressive schizophrenia that may then show itself plainly. The earlier history is of great help.

The nature of the symptoms is not a safe guide. Very severe departures from normality may clear up, yet an outwardly mild condition be of grave omen. Symptoms such as stereotypies of movement and speech, which indicate that the illness has been going on a long time, and that there is a general narrowing and fixity, are grave; as are also hebephrenia, and a long-drawn-out stupor, with negativism, impulsive violence and vasomotor changes. The more manic or depressive features, the better. Previous attacks, with an interval of normality between them, are prognostically favourable. If the patient first falls ill after 30, he will scarcely go downhill in the tragic way young people sometimes do. He may develop fixed delusions, which are often rigid and encapsulated, so to speak, and therefore he may be able to return to ordinary life, with reservations; or it may be that his morbid beliefs absorb all his mental powers, and compel institutional life. The more the psychiatrist can discover healthy modes of response in the illness itself, as well as in the previous personality, the happier the outlook. Many patients, after an attack, do not return to work, but have narrower interests, and less spontaneity than before; they are more easily tired, and may be hypochondriac, or show other symptoms thought to be "neurotic". Such patients have sometimes made a poorer recovery than others who return to work and can meet most social demands, though careful enquiry reveals definitely schizophrenic sequelæ in their thinking and emotions.

The simplest rule is that an abrupt onset of the illness, an adequate cause for its occurrence and a well-adapted non-schizoid personality are the criteria of good prognosis. Sensible early treatment may avert disaster.

**Treatment.—PROPHYLACTIC.**—This, whether eugenic or individual, is limited and uncertain. Even if effective, it can reach only a minority at present, and its effectiveness is a matter of faith. Probably child guidance and other measures of mental hygiene do good in averting potential schizophrenia, but no one can be sure of this. Such treatment aims at diverting the child into social activities and keeping him out of situations in which he will be mortified or otherwise troubled emotionally. However wordily or abstrusely the prophylactic treatment be described, it is essentially a matter of trying to make an unusual child into an average one, or changing his surroundings to suit him.

**TREATMENT OF THE ACTUAL ILLNESS.**—There is no one treatment of the disorder that has manifest superiority over any other. Insulin has striking results in some early cases, but is neither a specific nor a panacea. Pains-taking attempts at readjustment of the patient's outlook and behaviour by means of suitable psychotherapy, occupation, games, etc., are the most systematic and rational ways of making a permanent change for the better. The co-operation of the patient is here necessary, and also the help of a social worker desirable, who may do much to modify and arrange the patient's circumstances in the interests of his mental health, *e.g.* getting him suitable occupation, and schooling his relatives in a sensible attitude towards him. Such treatment is not practicable for those acutely ill, but for the mild, the convalescent or the imperfectly recovered case it is of great value. By means of it many patients can be discharged from hospital before they have settled into apathy, or become unresponsive to the claims of the external world; it is better not to keep a schizophrenic patient in hospital waiting for complete recovery, but to get him back

into ordinary life as soon as possible, provided conditions there are not too adverse for him, or he too abnormal to cope with them.

Treatment in a psychiatric clinic or mental hospital is usually necessary at some stage of the disorder, and must be decided chiefly by the severity and social risks at the time. For the large number who become permanently in need of institutional care, much of the deterioration formerly customary may be averted by the energetic use of occupational therapy and recreation which make the patient's life less sterile. The term "total push" has been applied to a programme having this object, and attaining its social end in proportion to its vigour in using all available means of stimulating and encouraging the individual patient.

There are few conceivable ways of altering a human being that have not been tried in this illness. Many of them have been those believed to be efficacious in other illnesses; some have been intended to shock the patient somehow. Of the former may be mentioned thyroid and other endocrine preparations (in large doses), transplantation of gonads, removal of supposed septic foci, induction of fever by malaria, etc., injection of human serum, manganese salts, production of aseptic meningitis, hypothermia and continuous narcosis. Of the latter, *i.e.* shock-methods, many of the procedures of a bygone time are examples; the whirling chair, precipitation from a height, immersion in ice-cold water and so forth. The most recent methods which entail a profound disturbance are those which use insulin or a convulsant (see p. 1621). The convulsant method has been of value in some acute stupors and conditions in which, along with the schizophrenia, there is a considerable affective admixture.

The value of insulin treatment is variously assessed; some believe that it should be given to every schizophrenic as soon as his condition is recognised, others that it benefits those who would get well with other forms of treatment, if administered with equal zeal. The former say that it shortens the duration of illness and increases the number of recoveries; the latter insist that this improvement is seen to be largely spurious if a "follow-up" enquiry is made into the later course of the patients' lives. That such extreme views can be held by responsible observers relying on large series of cases is due, not only to their prejudice and temperament, but to the difficulties of judging therapeutic success in an illness which is sometimes difficult to diagnose with certainty in its early stages, is often accompanied by another more benign mental illness, and has anything but a uniform prognosis; moreover, it was believed to be hopeless by many psychiatrists in pre-insulin days, so that they did not try to treat it by methods then available which would have yielded full permanent recovery in a quarter of the cases, if selected on the same basis as is now customary for insulin treatment. It was the general experience before the advent of insulin that a third of the schizophrenic patients who were admitted to an active psychiatric hospital within a year of the onset of their illness got better with general treatment and remained capable of life outside a hospital; mass figures from a heterogeneous collection of psychiatric hospitals showed less satisfactory results. This partly accounts for the discrepancy between those who report remarkable improvement in the proportion of schizophrenics who recover now that insulin has been used for their treatment, and others who cannot discover any statistically recognisable difference in efficacy between conservative treatment and the insulin method, under comparable conditions of case-selection and management. An additional cause of discrepancy in results lies in the different methods of administering insulin treatment. Some aim at giving the lowest dose of insulin that will produce coma, others prefer the highest dose that can be given without endangering the patient's life; some let the comas continue for 3 or 4 hours, others terminate them earlier, and there are even advocates of comas protracted up to 15 hours for patients unresponsive to milder measures; hypoglycæmic convulsions are regarded by some as therapeutically valuable, by others as harmful. Insulin and convulsant treatment have demonstrated beyond dispute

that in the present state of psychiatry the value of a new therapeutic procedure should be assessed not by the reports of enthusiastic pioneers, invaluable though their efforts and observations are, but by the outcome of a planned therapeutic trial in which uniform standards have been employed in the selection of cases, the method of administering the treatment and the assessment of outcome; also due regard must be paid to the choice of those "control" cases with which the beneficiaries of the new method are to be compared.

The insulin method consists in the induction of hypoglycæmic coma daily, for not longer than 3 months. It is seldom desirable to exceed sixty comas. The coma is allowed to last a variable period, according to the clinical condition. If unduly prolonged, it may be difficult to terminate it by the usual method—the administration of carbohydrate through a nasal tube or intravenously. Persistent or "irreversible" coma is the chief danger of the treatment; about a sixth of those who pass into such a state die. Because of this and other complications, mostly avoidable, the insulin method should only be used by experienced persons, in a hospital adequately organised and staffed for the purpose. The treatment is most effective in cases which would have a good prognosis for the attack if treated by other methods. In a series of more than a thousand patients treated with insulin, 13 per cent. recovered and were still well 2 years later, at which time there were also 14 per cent. much improved. Such figures are so much influenced by the choice of patients that they cannot easily be compared with the results of other methods. In the main, however, they speak in favour of the insulin method, if applied with discrimination, skill and willingness to use other methods also, during the administration of insulin or afterwards. Frontal leucotomy has been employed in otherwise intractable cases, and some patients thus treated have become easier to look after or fit to leave the mental hospital.

The details of treatment, whether in hospital or at home, must be individual; even in such matters as the allaying of excitement no uniform procedure, *e.g.* continuous baths, or narcosis, can be a routine measure. When excitement is extreme, disturbances in water metabolism and loss of salts may be combated by giving 5 per cent. saline intravenously, 300 ml. every other day, alternating with forced fluids. During stupor, general measures for ensuring adequate food (in some cases feeding by tube), cleanliness and evacuation of urine and faeces must always receive attention. It has been found that various chemical agents, such as carbon dioxide inhaled in a 30 per cent. mixture with oxygen, and sodium amytal, will temporarily interrupt a catatonic stupor; this finding accords with the metabolic changes reported in the condition, but its therapeutic value is slight.

## PARANOIA AND ALLIED STATES

The words "paranoia" and "paranoid" are used loosely by many. Kraepelin gave paranoia its modern meaning, describing it as the endogenous, insidious development of a permanent and unshakable delusional system, with complete preservation of clarity and order in thought, will and action. If the illness cleared up, if it showed symptoms of an organic, affective or schizophrenic syndrome, or if it was provoked by external happenings, it could not be paranoia. Thus delimited, the condition is exceptionally rare; so rare, indeed, that there is no use in having such a category. Moreover, cases that Kraepelin himself called paranoia have since become obviously schizophrenic. The same is true of paraphrenia. There is now no profit in thinking of paranoid states as syndromes in their own right, so to speak, and of the same order as schizophrenia or affective disorders. They are on the same subsidiary level as stupor, hypochondriasis, anxiety and depersonalisation. When met with, they must be distributed according to the accompanying symptoms and the

general trend of the illness; and their prognosis and treatment must be assessed accordingly.

Besides the paranoid beliefs and attitude referred to in previous sections, there are a number of instances of this unhealthy relationship between the patient and his surroundings, which may be mild in their outward form, easily understandable in the light of the patient's history and fairly responsive to treatment. Some deaf people become distrustful, misinterpreting what they cannot hear plainly, and construing it into a jeer or an insult. Sensitive and shy people are often troubled by doubts and shame as to their physical or moral worth; and, by projection, attribute to others the dislike or contempt they do not acknowledge in themselves. This occurs in youths who masturbate, and suppose others to remark it, and in old maids who believe men to be pursuing them; but there are many varieties of shame and desire, besides the sexual, which lead to such ideas of reference or persecution. The development of paranoid reactions of this sort is usually plain. So is that of the querulous, resentful type of reaction, e.g. in the man who believes himself done out of his rights and who becomes a persistent litigant or writer of memorials. Before judging such a man psychopathic, the extent of the injustice he has suffered must be compared with the degree of his resentment and his relevant conduct. Commonly the injustice is found to be fanciful or trifling, and the man's sense of grievance immoderate, so that he comes to believe there is a veritable conspiracy to wrong him, and devotes most of his time to useless appeals or threats. He may persuade his wife or his children of the justice of his complaints, inducing delusions in them, i.e. *folie à deux*, etc. Many such patients, however, never become deluded: they are contentious about their wrongs, and waste years, perhaps, in proclaiming them or seeking redress, but they are well aware how other people regard them, and what has actually happened. Many claimants of compensation, "grouzers", "old soldiers" and unstable adherents of more or less cranky movements, are to be placed here. There is no sharp dividing line between these psychopathic people, and the more or less normal, often socially precious, leaven who detest injustice and are willing to do much to defeat it.

## HYSTERIA

In hysteria, symptoms of illness are represented by the patient for the sake of some advantage, without his being fully conscious of this motive. The form of representation will vary widely according to the circumstances that have provoked the illness, the patient's experience of what the symptoms are that he is trying to represent, and his somatic resources. These factors, presently to be discussed, bear on the hysterical symptoms that simulate physical disease. But it is impossible to restrict hysteria to this physical form. The illness that is represented by the hysteric may be a mental one; moreover, it is not possible to consider hysteria without regard to the mechanisms of its occurrence which manifest themselves in the personality and are mainly psychological. Hysteria is the most psychogenic of all illnesses. Its recognition is therefore a double problem: (1) exclusion of what may be called "genuine" illness, i.e. of a recognised morbid pattern and (2) discovery of an adequate motivation. To ignore either of these requirements is to court error, since hysteria may occur along with physical or mental disorder, elaborating upon it and mimicking it, and, on the other hand, some physical diseases give rise to symptoms indistinguishable in their form and apparent psychological mechanism from those of hysteria.

**Ætiology.**—A hereditary factor is probable in many cases. Thus, a group of hysterics who were pathological liars were compared with the average population in respect of the proportion of their brothers and sisters who were in mental hospitals: it was five times as many; and of the parents of the group, a sixth were psychopathic. From these and similar figures it is not possible to tell the mode of transmission or

the nature of what is transmitted, but only to infer a hereditary factor. The occurrence of hysterical mechanisms in children, and their frequency in healthy adults, especially after calamities or in unendurable conditions, such as may occur in war, suggest, however, that hysteria is potentially present in most people and that environment is more important here than heredity. The combination of heredity and environment may result, long before actual illness occurs, in a *hysterical personality*. This is not found in all patients who show hysterical symptoms, but nearly all people of hysterical personality show hysterical symptoms. Many of the features of this personality are socially obnoxious, but other features are not, and it is wrong to use "hysterical" as a depreciatory epithet for a set of qualities that one dislikes. These people are unduly responsive to the situation they are in, especially if by their excessive response they can fulfil wishes of which they are hardly aware, or evade what is painful in the situation, instead of meeting it and disposing of it adequately. Unsatisfied with their own capacities, they seek to cut a better figure than their endowment warrants, and are constantly posing and pretending. This, like all their behaviour and aims here described, is not done with full consciousness, but with a more or less sincere ignorance or ambiguity of purpose; it is not a question of deliberate deceit, of studied histrionics or malingering. In thus responding to situations and turning the response to some inadequate end, the hysterical person is characterised by a lack of inner stability and of constant standards of behaviour, and also by a lability of affect and an exuberant fancy. The fantasies normal in childhood are here seen in physically mature adults, who, like children, can temporarily live their fantasies, absorbed in this unreal compound of past experiences and longings, yet not so wholly divorced from their real surroundings as might appear. In an attenuated form, this is evident when they almost unwittingly manufacture some situation, according to their needs—literally "making a scene"—and enter into it emotionally with a rapidity and fervour impossible for more stable people. Egotism and untruthfulness (*pseudologia phantastica*) may be pushed to the point of delinquency. There may be a longing for prestige, sympathy, love or some other emotional relationship, which leads the hysteric to behave in a way strikingly out of keeping with his demeanour on other occasions; the inappropriateness of his behaviour even at the time may be obvious to a detached onlooker, but is not always so. Many of these people can use illness or well-acted fantasies of illness to satisfy their hardly conscious needs; they may also gain their ends by forgetting what it would be painful to remember. Here again the onlooker may find it hard to tell how genuine or complete is this forgetfulness, but the question is of little moment compared with discovery of the motive for the hypomnesia. Hysterics are often regarded as unduly suggestible because they respond so readily or violently to situations and to people with whom they develop an emotional relationship, often unrecognised by themselves as such. The emotional attitude of a hysteric towards others is often influenced by sexual factors. Hysterical personality is believed to be commoner in women than in men, and may be associated with psychosexual immaturity. Coquetry and frigidity are not uncommonly allied in hysterics; there may be much flirting and sexual excitation, stopping short of coitus. It is, however, juster to say that the sexual lives of hysterics show instability and inadequacy than to specify any particular aberration.

Hysterical personality can be recognised before puberty; in younger children, however, it must be extreme to be recognised, because of the great frequency of such mechanisms normally then (e.g. behaving as though fantasies were real, counterfeiting illness, somnambulism). Some of the grossest instances of hysterical behaviour have been recorded in girls not yet adolescent, cf. the Salem witches. Much of the work of child guidance clinics is taken up with the treatment of hysterical tendencies, not perhaps taking the form of definite symptoms but plainly evident in the child's personality.

The precipitating factor for the onset of hysterical symptoms is usually a situation,

emotionally charged, out of which the patient's symptoms will bring him more or less overt, but unacknowledged, gain. This gain need not be material and obvious, and may run directly counter to such accepted values as health and ability to work. One of the plainest instances of a partial unsubstantial gain is that created by an injury, and the resulting insecurity and claim for compensation or pension; hysterical symptoms flourish in such a soil, and are usually influenced for the worse by repeated medical examinations. Hysteria occurs among soldiers under active service conditions, and can readily be fostered in them by injudicious measures.

**Pathology.**—This is almost wholly a matter of psychopathology. It is true that disseminated sclerosis and many other organic diseases of the brain may be accompanied by hysterical symptoms, but the association is not a constant one. The psychological changes can usually be traced further back than the happening that provoked the illness; often they are the continuation of normal tendencies of childhood that have been fostered and extended by ill-judged upbringing. The hysterical symptoms that appear as motor or sensory phenomena show the patient's readiness for the translation of experience into bodily symbols; this is a special instance of the universal tendency for somatic representation of experience, converting it into action. It is the facility and exaggeration, not the existence, of this "conversion" mechanism that is characteristic of hysteria. What is thus translated or "converted" into physical terms has been something painful and unacceptable; the partial exclusion of it from consciousness, "repression" of it, is therefore understandable; in its physical, symbolic form it is tolerable and may even be prized. Identification with other people is responsible for the frequent imitation of symptoms and for the epidemics of hysteria. Clearly the mechanism need not be limited to the production of physical symptoms, though bodily structure and local weaknesses may conduce to this. There can be hysterical phenomena, such as the dissociation seen in fugues and so-called splitting of personality, which are instances of the exclusion of recent and remote painful experience from clear consciousness. The wishes and fears that deviously attain outward expression as hysterical symptoms do not derive solely from the recent past, though much of their strength may come from it. It must be admitted that there are some hysterics in whom this psychopathology cannot be demonstrated, and that such cases are among the most intractable.

**Symptoms.**—These may be divided into: (1) sensory; (2) motor, including fits and (3) quasi-psychotic.

The symptoms can be like those of any conceivable affection of which the patient has a notion. The cruder his notion, the less will his symptoms be like those of the simulated condition, but after he has been demonstrated to a class or repeatedly examined he may better his notion, and consequently his symptoms come closer to those of organic disease. Or, if he has had opportunity of seeing insanity, his pseudo-insanity may smack less of the stage than it otherwise usually does. The range of hysterical symptoms is so great that to describe them all in detail would take inordinate space, and there is no need to do so.

The sensory or, more properly, the *perceptual* symptoms include *clavus* and *globus hystericus*, blindness, deafness and *anæsthesia*. The two former are so common in all sorts of mental disorder, especially those accompanied by anxiety, that they are of little specific importance in hysteria; enquiry as to their presence will often in these rather hypochondriacal patients lead to their occurrence. The difficulty in swallowing reported by hysterical women may be associated with a strong disinclination to eat—*anorexia nervosa*; it should not be confused with depressive *anorexia* or that of pituitary *cachexia*. Any cutaneous disturbance of sensation that the patient has a notion of can be presented, e.g., *anæsthesia*, either mono- or bi-lateral, or of stocking and glove distribution, and *analgesia* of any part. The *anæsthesia* seldom corresponds to any nerve trunk, nerve root, or spinal segment, unless the patient has had special opportunities of knowing. With an *anæsthetic* hand objects may be

identified, and any test which the patient does not recognise as referring to this disability he will perform satisfactorily. Such tests are not a means of "catching the patient out" as though he were a malingerer, but of ascertaining whether the symptoms express only his notion of some illness. The tests for a malingerer, it is true, amount to the same thing, though one assumes the malingerer to be clearly conscious of his purpose; consequently any distinction between hysteria and malingering must depend on the observer's impression as to the patient's honesty and self-knowledge; certainly it cannot be decided by tests. The tests for blindness (*e.g.* using a stereoscope with a supposedly blind eye), deafness (*e.g.* effect on pulse, respiration and psychogalvanic reflex of exciting remarks addressed to the patient), and for other forms of perceptual defect all depend on the physician's greater knowledge of what should or should not accompany the symptoms of which the patient complains; they are not intended to discover hysterical "stigmata" or characteristic anomalies. The ovarian and other hyperæsthetic spots, the pharyngeal anæsthesia and the concentric limitation of the field of vision formerly used diagnostically, were all products of suggestion or, as in the last instance, phenomena that may occur in normal fatigue, in hypochondria and in certain cerebral lesions.

The motor symptoms are paralysees, paræses, spasms, contractures and tremors. Hysterical paralysis or paresis never affects individual muscles, but always movements. By various devices it can be shown that the patient can still use the affected muscles, as long as he does not know that the movement in question requires their use. The paralysees affect chiefly the left side of the body, are common in the legs (preventing proper walking or standing), and often occur in limbs or other structures that have earlier been the seat of an organic disability, *e.g.* trauma or paresis. If the paralysis be flaccid, no loss of tone or of reflex response is found, and the patient, through his ill-informed notions of what should happen, behaves otherwise than a patient with organic paralysis would—*e.g.* if asked to rise from the supine to the sitting posture, without using his hands, he keeps his paralysed leg flat on the bed. If the paretic part be kept stiff, the antagonists will be found to come into action first when the patient is asked to perform the movement he says he cannot; and if the movement has to be made against resistance, sudden removal of the resistance reveals how much of the apparently tremendous effort was going into associated irrelevant or antagonistic movements. Passive movement to overcome the spasticity or subsequent contractures cause the patient to be more upset than could be accounted for by any pain he may complain of. The varieties of abnormal gait are numerous; many of them fantastically elaborate and, from the look of them, exhausting. Not only the musculature of the limbs may be affected but of the trunk (leading to curvatures and odd postures) and indeed any voluntary muscles, *e.g.* of the tongue, larynx, pharynx or eye. In hysterical aphonia the voice may sink to a whisper, or there may, more rarely, be complete mutism; the voice can, however, be used normally for coughing and similar purposes. The aphonia often comes on after some local inflammation that has caused hoarseness, or after a fright. Stammering, usually of the exaggerated kind, may also occur. Spasm of the external ocular muscles, leading to a convergent squint, may accompany a spasm of accommodation. Ptosis and blepharospasm sometimes occur. Many of the tics and spasms that used to be thought hysterical are now recognised to be often physiogenic, *e.g.* residual symptoms of encephalitis lethargica and chorea; spasmodic torticollis, for instance, is far less often psychogenic than used to be supposed. When a spasm or paresis has long been maintained, trophic disturbance may follow: blueness and œdema, shiny skin, fibrosis of periarticular structures and similar effects of rigidity and disuse. Tremor may occur and is often gross, as in many of the war cases. It is variable in degree and rhythm, and often disappears when the patient's attention is turned from it; this, however, is not a safe criterion.

Hysterical fits commonly occur in patients with obviously hysterical personality.

responded to psychotherapy. Psychogenic fugues are not invariably hysterical; they may be symptoms of a reactive depression in which despair and perplexity are conspicuous.

"Pseudo-dementia" covers the large group who behave as though insane. It may occur, as in the so-called Ganser syndrome, in prisoners awaiting trial. Whatever the circumstances, its motive is escape from a disagreeable situation. It is likely, however, that it is mainly those with a predisposition towards severe mental illness, especially schizophrenia and the high-grade defectives, who have recourse to this kind of hysterical behaviour. It sometimes comes on after brain injury. The patients' behaviour corresponds necessarily to their notion of insanity, which is usually far enough removed from anything the psychiatrist knows as such. Occasionally, however, it is very near the buffoon-like conduct of some schizophrenics. The patients say that they do not know their own age, affect not to understand simple remarks, give absurd answers which nevertheless indicate that they know the right answer (e.g. by inverting the correct order of the figures in a sum). When asked about some simple matter, they look as though they were making terrific efforts to remember (herein behaving differently from the schizophrenic). The most characteristic thing is the disparity between the patient's alleged deficiencies and his general alertness: he says he does not know anything about his own past, he cannot read or spell or do the simplest arithmetic, and yet he may be behaving quite naturally and adapting himself to the situation in a way which would be inconceivable if he had actually so advanced a dementia.

Some hysterics go to great lengths in their representation of ideas of illness. They will allow themselves to be put among grossly insane people, or submit to repeated operations, such as amputation. Self-inflicted injuries, e.g. keeping wounds and sores open, are not uncommon (cf. dermatitis artefacta). In some such cases masochistic tendencies can be recognised, but by no means in all. Suicidal attempts are not infrequent. They often have as their purpose revenge, the satisfaction of some spite, and the patient may leave behind a lying, fantasy-coloured letter, indicting someone. Frequently the suicidal attempt is in the nature of a theatrical demonstration, carried out in such circumstances as make it unlikely to be fatal; and if the patient kills herself, it is more through bad management than intention.

**Diagnosis.**—It will be plain from what has been said that diagnosis must be both negative and positive—negative, by excluding any organic cause for the symptoms; positive, by finding motives and relating the symptoms to them. Neither method is alone sufficient, because of the occasional concurrence of structural disease with psychogenic symptoms. As to the former, *i.e.* the negative method, it is unnecessary to enter here into all the differentiating points. Many of them have been mentioned in the foregoing description of symptoms, and all turn on the disparity between what experience tells us would occur if these symptoms were of organic origin, and what the patient knows about such matters. Consequently a doctor who has hysterical symptoms is extraordinarily difficult to diagnose, in this negative sense. The method of arriving at a diagnosis by suddenly taking the patient unawares, and seeing if his symptoms persist, is to be deprecated; it antagonises him. Likewise undesirable is the procedure of seeing whether one can suggest new symptoms to the patient.



of some physical disease. It is, however, in neurology that the most difficult cases of all arise, e.g. in disseminated sclerosis, carbon monoxide poisoning, cerebral vascular disease or encephalitis lethargica; here there is more likelihood of the organic disease being overlooked than of its being wrongly diagnosed. The patient's previous personality, any provocative situation or emotional disturbance, the previous occurrence of organic signs, e.g. transient diplopia, and the age of the patient must be considered. Hysterical symptoms appearing for the first time in middle or later life in someone whose personality has been stable, are probably not solely psychogenic. If the symptoms diminish when little or no attention is paid to them, they are more likely to be hysterical.

**Course and Prognosis.**—This depends mainly on the patient's personality and social setting, and on the treatment employed. A long history of hysterical traits prior to the illness, a continuance of circumstances favourable to the symptoms and inadequate or excessive treatment are all unfavourable. This is, however, an illness that sometimes confounds prediction, patients recovering when many adverse factors have been operative and the symptoms have been present for years. In children the prognosis is fairly good if treatment can be undertaken promptly; it is best if the hysteria is monosymptomatic and has come on after a fright. In all cases in which the situation which provoked the illness persists, the outlook is bad; for example, in compensation cases for which no medical treatment is of any avail—for obvious reasons—until the litigation is settled once and for all. Similarly, during war, psychotherapeutic successes are often dazzling while the hysterical soldier is under treatment in hospital, but the symptoms come again when he must return to duty. There are many varieties of outcome, chronic invalidism being the commonest. A few patients later become schizophrenic, and a few become involutional melancholics. The prognosis in respect of the patient's hysterical personality is more important than that of his hysterical illness; it is, however, no more to be assessed by rules than the general future of any human being's life and personality. Patients do not necessarily tend to become anti-social; delinquency is certainly a likelihood in some hysterical people, but bravery and self-devotion may be conspicuous in others.

**Treatment.**—Too much treatment is worse than too little. Injudicious physical or psychological treatment of hysterics often makes their symptoms worse and their illness intractable. Recondite methods should be eschewed by all but experts. Common sense is as important as psychological understanding; and social usefulness more to be aimed at than removal of symptoms or attainment of self-knowledge. In short, it is not the hysterical illness or the mechanism of repression and conversion that calls for remedy, but the patient's inadequate way of dealing with difficult situations. Consequently, the whole treatment must aim at the patient's return to ordinary conditions of life as soon as possible, and at a re-education of his ways of meeting difficulties. To this end it is profitable to go over with the patient the situations, emotional disturbances and motives that led up to the illness, and to do this without implying moral judgement or social indifference—certainly without teaching the patient one's psychological theories. It is a matter of general psychotherapy (see p. 1619); and it may entail a far-reaching analysis of the patient's past life, her emotional development and her instinctual tendencies. It is questionable, however, whether anyone without special psychiatric experience is wise to enter lightly upon this way of benefiting the patient. For, on the one hand, he may be misled into a wilderness of fantasy masquerading as once-repressed, now-recalled psychic trauma; and, on the other, he may be at a loss how to deal with the attachment and dependence upon him which the patient will come to show, and which may in fact be the chief influence in bringing about her precarious recovery. A great deal may be achieved—perhaps as much as by more thoroughgoing methods—if the physician, himself mature and with impartial insight into the psychological motivation of the symptoms, leaves aside in his dealings with the patient any very detailed enquiry into the more remote

causes of the illness and the purposes it served; and, instead, directs her towards a better social adaptation, by advising her to avoid when possible the situations that, as he sees, favour the production of symptoms, getting her into a disciplined way of living, and stepping in with explanation, support and advice whenever fresh difficulties arise. His success in getting rid of individual symptoms at the beginning may be an important factor in establishing the necessary relationship with the patient. Such a line of treatment is not heroic or dramatic, and it demands a great deal of the physician; but it avoids some of the commonest blunders and may be strikingly successful. For this, or indeed any treatment, admission to hospital is not essential; but it will help when there are adverse factors in the patient's situation and, of course, will be essential if there be such symptoms as self-injury, suicidal attempts, pseudo-dementia or gross paralysis. The danger of the patient's picking up new symptoms in hospital should also be weighed. Isolation is usually inadvisable.

Many of the symptoms of hysteria will not wait upon general treatment, but demand energetic intervention. Anorexia, for instance, cannot be allowed to go on to an avoidable inanition, nor a paralysis to the stage of contracture; a mute patient, or one who is deaf or blind or ignorant of his own identity, offers such practical obstacles to almost any kind of treatment that the symptoms must be tackled and disposed of early. For this purpose suggestive measures are valuable and appropriate physical treatment may be called for, *e.g.* supervision during feeding, or even tube-feeding in anorexia nervosa, physiotherapy for paralysis, voice-exercises. Suggestive measures need not take the form of hypnosis; suggestion in the normal waking state has many advantages over hypnosis, though those expert in the latter are sometimes very successful in their treatment. Suggestion, like almost every form of treatment of hysteria, has pitfalls, and its triumphs, like those of every other method, sometimes prove vain, but in the hands of a physician who is at once confident and cautious, this method may result in a satisfactory recovery. If, in using suggestion, such physical devices as faradisation can be avoided, it is better to do so. As a means of demonstrating that the illness is not due to local disease, however, such methods sometimes take their place in a detailed plan of treatment. Motor and sensory symptoms can usually be got rid of if the physician is patient, determined and confident in the use of persuasion and suggestion. Intravenous injection of a barbiturate, such as sodium amytal, may facilitate such treatment, and may help the patient to disclose motives and happenings he had been reluctant or unable to talk about; disclosures of this kind, however, must be received and utilised with caution, and lasting benefit is not to be expected from such catharsis alone.

The choice of occupation, the settlement of any social cause of illness (*e.g.* claims for compensation) and the obtaining of a healthy attitude—neither complaisant, much-enduring nor harsh—on the part of the patient's relatives and friends, are all important factors in treatment. The hysterical reactions to injury call for special mention because of their frequency. Though often of transparent motivation, they are not by any means to be regarded as outright malingering; for the patient's feeling of illness may be sincere, his symptoms distressing, his anxiety typical and his irritability and insomnia symptoms that he would gladly get rid off. But they are none the less psychogenic. It is often assumed that so far as an illness is psychogenic, it must be treated only by psychotherapy. This is false theory. There are few mental disorders in which psychotherapy alone produces such small benefit as in the hysterical conditions due to the compensation or pension situation that may follow an injury. Putting an end to the situation early and the resumption of ordinary activity as soon as any physical injury has been repaired are the most potent measures in the earlier stages. Even if the symptoms have been present a long time, the ending of disputes about claims and the return to ordered routine and regular occupation achieve more than do frequent medical interviews. Psychotherapy is then an adjunct, not an essential feature, of the treatment.

Marriage should never be recommended as treatment for hysteria; the superstition about this has resulted in lamentable troubles, especially for the person the hysteric marries. This is not to say that every hysteric is to be dissuaded from marrying; there are more things than treatment to be considered then. Married hysterics, however, should not be recommended to have—or to adopt—a child. Contrary to popular notions, pregnancy and puerperium more often aggravate than benefit hysteria. Moreover, hysterical women are not usually satisfactory parents, and commonly induce psychopathy in their children.

### ANXIETY STATE

As already stated, the emotional syndrome so called is part of the group of affective disorders, in which depression and manic excitement are also included. It is there described. It would be indefensible to put into a special category all the forms of mental illness in which anxiety is conspicuous, for it can be severe in the most diverse conditions, ranging from delirium tremens to schizophrenia. The outwardly mild form, tending to chronicity and often largely psychogenic, responds well in the less advanced stages to psychotherapy; it is therefore important that its recognition should not be delayed because of a doubt as to physical disease. Yet often the correct diagnosis is overlooked while the patient is being investigated or treated for some local disorder. This arises partly because of the quasi-physical signs of fear which he may show—dizziness, tremor, nausea and vomiting, indigestion, diarrhoea, palpitation, a sense of oppression in the chest, rapid pulse, flushing, sweating, frequent passage of urine, etc. It is still more due to the patient's anxiety turning on his health, especially his physical health, and leading him to ask for more and more medical opinions, radiograms, laboratory investigations, etc., the favourable results of which, however, do not allay his worry. Over-cautious advice as to régime, based on a possibility that there may be some early physical disease, can be harmful to the patient's mental health in that it restricts his normal life, and may constantly recall and reinforce his anxiety. The converse error of mistaking some early symptoms of physical illness for hypochondriacal anxiety is equally to be avoided. Physical investigation of doubtful cases is, in short, indispensable, and should be prompt as well as thorough. When it fails to confirm the presence of a physical disorder the patient should not be treated as though he will still be in danger of the physical illness unless he takes special precautions in diet, exercise, etc. This is well illustrated by such a condition as effort-syndrome, where care taken to avoid any damage to the heart intensifies the illness. The patient should be fully investigated on the psychological side and treated accordingly; this does not mean that he should be treated only by psychotherapy. The discovery of a possible psychological cause for the symptoms does not prove that there is not also a physical cause for them, but it makes it less likely. The converse is also true. For aetiology, diagnosis, prognosis and treatment see section on Affective Disorder (pp. 1645 to 1651).

### OBSESSIONAL DISORDER

**Definition.**—In this condition the characteristic feature is that, along with some mental happening, there is an experience of subjective compulsion and of resistance to it. Commonly the mental happening (which may be a fear, an impulse or a pre-occupation) is recognised, on quiet reflexion, as senseless; nevertheless it persists.

**Ætiology.**—**INTRINSIC.**—The hereditary factor is strong. A third of the parents of obsessional patients, and a fifth of their brothers and sisters, have themselves shown pronounced obsessional traits; the proportion is in each case higher if all forms of mental abnormality be included, since both schizophrenia and affective illnesses occur

some forgotten alarm, and take a queer form, such as a phobia of lavatories or of one-legged men. It is loose usage to give the name "phobia" to every case in which an individual develops fear that is excessive or inexplicable; the essential features of an obsession, already mentioned, should also be present. The term "claustrophobia", for example, is often loosely applied to a fear or dislike of being in an enclosed place, which is not obsessional. Fears of dirt or infection are very common phobias; they are symbols of moral, usually sexual, taint, and they lead to much washing, etc.; thus, a patient who has blamed himself for masturbation may be constantly washing his hands, or following a complicated ritual of touching nothing with his bare hands for fear of contamination. Often the rituals and defensive precautions seem grotesque when compared with their ostensible purpose, as in the case of a patient who is perpetually putting himself to the greatest trouble in order to ensure that he never steps on a worm inadvertently. Ludicrous as his behaviour may seem, it is often tragic in the distress, and indeed ruin, it may cause him. Another phobia is that which has fear as its object, i.e. the patient is afraid of any situation in which he may feel fear; some such patients do not leave their homes for years, because they fear they may have "agoraphobia" once they get outside. Obsessional rumination usually takes the form of endless questioning or search. The patient has to ask himself "Why" with pointless insistence about all manner of problems beyond his or anybody's grasp; or he has to keep casting round in his mind after some forgotten name or word which he could easily do without. Religious scruples sometimes fall into this category, as when a penitent is continually running to his confessor with some venial trifle he has come upon in his interminable self-questioning and doubt.

Obsessional patients are in most cases depressed; their illness is a depressing one. Besides this secondary depression, however, there is frequently an association of a more intimate kind, in which depression—or mania—is the essential or the main part of the illness, and the concurrent obsessions seem to be symptoms of this affective disorder. In such cases the obsessional illness is very often cyclical in its course. Anxiety is a common accompaniment of obsessions; in phobias it is most conspicuous. The anxiety is inseparable from the patient's struggle against the subjective compulsion which is so alarming to his feeling of integrity in self and mind, such a shock to his belief that he is a free agent. Schizophrenic symptoms may be in the offing, or actually present, when the obsessional ideas are of the magical kind, e.g. the patient feeling that the effect of his obscene thoughts upon others may be averted by some gesture, or when his rituals are carried to bizarre lengths, e.g. having to save the last drops of his urine because of some recurring doubt. Depersonalisation may occur in the course of an obsessional illness.

**Diagnosis.**—If the essential features, i.e. feeling of subjective compulsion and immediate resistance to this, be kept in view, it is seldom difficult to distinguish between obsessions, on the one hand, and delusions, hallucinations, ideas of reference or self-reproach, feelings of being influenced and schizophrenic stereotypes, etc., on the other. The only difference between obsessions and many schizophrenic phenomena towards which the patient retains insight and which he regards as alien to him, lies in the nature of the compulsion he experiences: in obsessions it is subjective—he feels that it comes from within his own mind, whereas in the schizophrenic phenomena he feels that it comes from without, it is imposed upon him. It is a difference, however, that may be obliterated, i.e. what was once obsessional may become schizophrenic, but this is an uncommon outcome when the obsessional disorder is definite and well-established. In differential diagnosis it must be remembered that obsessions may occur in the course of almost any mental illness in a person of obsessional tendencies, and that the psychological mechanism for the production of obsessions, like that for hysterical symptoms, is present in almost everybody in varying degree. Consequently, an illness is not to be regarded as obsessional unless obsessions are the chief symptoms.

**Course and Prognosis.**—The outlook for recovery is worse if obsessional symptoms have been present since childhood, if they now fill up most of the patient's time, and if he is weakly resigned to his illness. The best outlook is when the obsessional illness comes on suddenly in a person who has not had conspicuous obsessional traits or who has had previous benign attacks. A cyclical course is not uncommon. The situation is ominous when the ritual gets more and more systematised and remote from what previously occasioned it. The development along schizophrenic lines, already mentioned, is more to be feared in such cases and in those with bizarre obsessional thoughts; the great majority of gross obsessionals, however, do not become schizophrenic or anything else than obsessional. About half the cases recover from an attack, which may, however, last for a year or even more. Many people are subject to brief attacks, lasting only a few days, and largely due to fatigue or physical illness reducing their mental health. Intercurrent happenings influence the course of the illness, *e.g.* some men were free from symptoms during their period of war-service, with its routine and lack of responsibility or need for decision. The content of the obsessions is of little use prognostically. Old age is not in itself an adverse factor, but attacks in childhood suggest a strong constitutional bias and are therefore unfavourable on the whole. Few obsessionals give way to anti-social impulses, *e.g.* to suicide, homicide, delinquency. It is true that obsessionals who are also depressed may kill themselves, and that obsessionals who are irritable and angry may injure others; but obsessionals rarely yield directly to an impulse they have resisted, or need to have "irresistible impulse" urged in extenuation of a crime. Sexual offences and perversions are rarely obsessional.

**Treatment.**—Patients should be encouraged to continue at their occupation and not to test themselves, or try to overcome their obsession, by repeatedly putting themselves in a situation in which it will occur. So long as their impulses are not likely to get them into trouble, they should be dissuaded from "fighting" them; external restrictions are more helpful than reliance on "will-power". The physician should aim at getting a patient well by putting an end to his anxiety and struggle; if that is not wholly attainable, the patient must be educated to deal with his obsessional tendencies by acknowledging their existence, their psychological origins, and, often, their harmlessness in those very respects in which he thought them most harmful, *e.g.* obscenity. Frank recognition of obsessional tendencies, which everyone has in some degree, is an important step in learning to control them. In some patients the obsessional attack is so cyclical and almost self-limited that a brief rest and general care are all that are needed. In others, whose affection is chronic, recovery is out of the question, but advice about the management of their lives, varying according to their individual circumstances, helps them greatly. In some such patients frontal leucotomy lessens or removes the distress that formerly accompanied their obsession. Obsessional patients, so prone to rumination and endless questioning, often clamour to be psycho-analysed. There is no evidence that psycho-analysis, however prolonged, benefits them more than methods that are not so exigent of time and money. Obsessional children who may be beset with fears of contamination and religious scruples, usually respond well to changes in their human environment, advised after the physician has enquired into the family and school situation; temporary separation of the obsessional parent or treatment of the latter often proves remarkably beneficial. Discussion of his problems with the child is an important adjunct, just as it would be with an obsessional adult.

## PSYCHOPATHIC PERSONALITY

who do not regard themselves as ill, nor do others think them is abnormal enough to upset or puzzle other people, and

sometimes themselves. In this it is like mental illness, and calls similarly for psychiatric understanding and treatment. But since they are not ill, their behaviour must be attributed to abnormal personality, much as an aberration like alkaptonuria must be attributed to abnormal physical constitution. All abnormality of personality that does not amount to manifest illness may properly be called "psychopathic personality". The term does not connote an evaluation of character, according to how useful such a person is to society, nor is it a prediction about the likelihood of subsequent illness of a particular type; it is a descriptive term. But people of abnormal personality will often come into conflict with organised society and with individuals more normally constituted; they will be on the whole more vulnerable to stresses; their peculiarities, intensified into symptoms of illness or proofs of delinquency, will earn them pity, contempt, dislike, punishment or compulsory treatment. It is therefore common for "psychopathic personality" to be used as a pejorative term, limited to those who will afflict society in some way—the "anti-social psychopath", the "psychopathic tenth", are significant phrases, akin to "psychopathic inferiority" and the still earlier "moral insanity"; or the term is used to denote those who stand in danger of insanity—the "schizoid psychopath", for instance. It is, however, wrong to apply to the concept "psychopathic personality" so shifting and subjective a criterion as social disapproval, nor can mental illness be assumed to be a certain outcome in even pronounced aberrations of personality. Among mystics and poets, men of action, scholars and scientists are some who have properly been classified as of "psychopathic personality", their abnormality consisting nevertheless in unusually high, rare and valuable if peculiar qualities, rather than in a blemish or handicap. St. Teresa, Joan of Arc, T. E. Lawrence, Cavendish, Cellini, Tolstoy, Mozart, Michelangelo—any hurried list of famous people that have been cited as examples of psychopathic personality, testifies to this. Apart therefore from any judgement about the good or harm they do to society, people are said to have a psychopathic personality if they fall outside the wide range agreed upon as normal—not quite the same thing as healthy—yet are not ill. Society being ordered as it is, the majority of such abnormal people will at some time come into conflict with it or fail to meet its demands and their conduct will often rightly be called anti-social. The anti-social group of persons with psychopathic personality is large; its size will vary according to the culture in which they live and the allowances or opportunities it makes for them. This is obviously true if their adjustment as adults to the demands of the community is the measure of their "anti-social" trends; it is true also of their development and the way in which social influences may be such as to foster their smooth participation in a very diverse pattern of human relationships, or may mar them, giving neither free play nor direction to their peculiarities. Success in preventing many of these abnormal people from becoming a nuisance or a danger is, therefore, a test of the educational methods, the pliancy and the psychiatric hygiene of a community. This is not to ignore the hereditary and narrowly individual factors which determine psychic constitution, but to stress the social causes of later social failure, should it occur; such failure, however, need not be regarded as inevitable in people of psychopathic personality.

Classification of psychopathic personality can be (1) arbitrary, (2) psychological or (3) psychiatric. The first picks out what seem serviceable characteristics that occur often and conspicuously; thus, one well-sponsored list is made up of the excitable, the unstable, the impulsive, the eccentric and perverse, the quarrelsome, the anti-social, and the liars and swindlers, and makes further reference to aesthetes, scatterbrains, enthusiasts and fanatics. The second, which is the ideal method, is based on the varieties of normal personality. Unfortunately, the types, trait-clusters and other classificatory groups so far proposed do too little justice to the complexity and range of human personality to be satisfactory or lasting. The third, or psychiatric, classification, is likewise provisional but it has the advantage of grouping

these non-morbid abnormalities in the same categories as the severe, morbid ones (with which there is reason to believe them genetically connected). To do this begs some fundamental questions, but it is for the present useful to recognise schizoid, affective, paranoid, obsessional, hysteric and perhaps epileptic varieties of psychopathic personality. This list is open to the objections that must be made to any attempt at stating types of personality, and it is wrong to suppose that any of the varieties mentioned must always precede, or indicate proneness to, the illness from which its epithet is derived. Nevertheless, they give the psychiatrist a familiar frame of reference and they leave room for manifold combinations of traits and attitudes within each class, so that the individual drug-addict, the sexual pervert, the hypochondriac and the fanatic can be included. If this psychiatric classification were to be judged by as rigorous a standard as the psychological, it could not stand; it will no doubt eventually give way before a surer psychology of personality and a surer psychopathology, as indeed it would have to now if the psycho-analytical conception of the structure of normal and morbid personality were accepted as final. For the time being, it is convenient to use these derivative terms, such as schizoid, and to give them no more weight than the bare labelling of personality deserves. Understanding a psychopathic person's motives and conduct, of course, requires full consideration of his development, circumstances and traits and goes beyond their classification for clinical purposes.

Besides the hereditary and social causes of psychopathic personality, anomalies of cerebral structure may contribute to the condition. But in childhood and even in maturity damage to the brain, by infection, poisoning, malnutrition or trauma, can lead to changes in personality, such as occur after encephalitis, carbon monoxide intoxication, pellagra, operations and accidental violence to the brain. They do not conform to a single pattern, and may be complicated by intellectual impairment. They depend to some extent on the part of the brain affected; in perhaps the most striking group—encephalopaths whose emotional control is much reduced so that they easily become violent when they cannot get their own way—the hypothalamus and other structures in the rhinencephalon are suspect. Electro-encephalographic data have recently been added to the clinical, psychological and experimental evidence for this. Some writers believe that most of those with psychopathic personality characterised by violent outbursts have an innate or acquired cerebral abnormality, and even, though on inconclusive grounds, that there is a kinship between the aggressive psychopath and the epileptic. It would, however, be a mistake to attribute psychopathic personality, even when marked by excitability and impulsive acts of violence, mainly to anomalies of cerebral constitution; emotional deprivation or insecurity during childhood, parental mismanagement, and in adult life severe frustration and adversity constitute psychological causes which are often in evidence.

Any description of forms of psychopathic personality must be lengthy, as must also any consideration of their psychopathology and treatment. Crime, juvenile misbehaviour, habitual or sporadic drug-taking, peculiarities of sexual desire and practice, incapacity for certain occupations and public duties (e.g. school teaching, military service), the temperamental concomitants of inferior intelligence and, at the other extreme, some of the characteristics of genius; these are intimately linked with the problem of psychopathic personality, and their exposition would demand a fuller treatment than space allows.

## MENTAL DEFICIENCY

As already stated (p. 1626), there is nothing in principle to separate these from other forms of mental anomaly save that they occur at an earlier stage of life. Like mental disorder, they shade into normality; no man can say where stupidity ends

and feeble-mindedness begins. Again, as with mental disorder, the same clinical picture may be due to a variety of causes ranging from heredity to trauma. They are, moreover, delimited rather by social than by other criteria, and they are not definitely associated with any constant pathological findings, except in the numerically limited group of special clinical types. In that they are capable of only limited improvement when well established, and that the intellectual functions are more obviously damaged than any others, their similarity to cerebral impairment in adult life is easily seen. They are not by any means cases of purely intellectual defect; they represent, it is true, one extreme on the scale which has people of great intellectual ability at its other end; but they are also examples of a general impairment of mind, affecting the emotional and conative functions, and often associated with a more general impairment of the whole organism, which may be seen in its physical structure. Since the milder forms are indistinguishable (except on an arbitrary reckoning) from what may be termed normal stupidity, it is difficult to use rigorously the official definition of mental defect, as a condition of arrested or incomplete development of mind existing before the age of 18 years, whether arising from inherent causes or induced by disease or injury; but the description is serviceable. It should be recognised that, just as "psychosis" differs from "neurosis" only in a rough social sense, turning on the need for special care, and "neurosis" from "normality" only in respect of the limitations the former imposes on one's daily life as a social organism, so does the distinction between normality and feeble-mindedness, and between gross or certifiable deficiency and the lesser forms, turn on the social adaptation of the person in question. To complete the points of similarity there is recognised a "moral defectiveness", which has its parallel in some kinds of "psychopathic personality". The effects of encephalitis lethargica, parenchymatous syphilis and thyroid deficiency upon the mental state and development at different ages, or the varying results of amaurotic familial idiocy in the infantile and the delayed juvenile form, illustrate how important is the stage of growth or maturity at which damage is done.

**Ætiology.**—The customary division is into primary (hereditary) and secondary forms, but a less dogmatic distinction is between those who represent the lower extreme of normal variation (the "subcultural" group) and those in whom a gross structural pathology is discoverable. The former group is a large one, making up approximately three-quarters of all cases of mental defect. This is an estimate arrived at by independent workers, but it may have to be changed as we acquire better methods of determination and fuller knowledge of the subtle interplay between environment and heredity. The grosser the deficiency the less important the hereditary factor, except in some rare well-defined anomalies, such as amaurotic idiocy. Familial concentration of a given form of defect is specific for each clinical type. A combination of several genetic factors is probably responsible for all but the special types: the mode of transmission of amaurotic familial idiocy and of phenylketonuria is recessive; that of epiloia dominant.

The environmental causes are prenatal, congenital or infantile; they include birth injury to the brain, meningo-encephalitis, hydrocephalus, cerebral syphilis. Various poisons and deficiencies may be responsible, as in the well-known instance of cretinism, as well as certain malformations of the cerebral tissue, e.g. microgyria and porencephaly, and of the cranium, e.g. oxycephaly. The influence of maternal rubella and other exanthemata, and of Rh incompatibility upon the fœtus have lately been studied in this connection. Sensory defects, as in a deaf-mute, may greatly impair mental development. It is possible that some cases of schizophrenia beginning in the first few years of life are indistinguishable from mental defect and are diagnosed as such.

**Pathology.**—In many cases there are no significant findings; this is particularly the case with high grade defect. It is probably impossible from the histological appearances to infer the extent of hereditary or exogenous causation. Develop-



mental anomalies, such as general hypoplasia and microgyria may, however, be mingled with evidences of a past lesion, as in porencephaly or hemiatrophy, or with signs of a disease actually present, as in amaurotic idiocy, cerebral lues and tuberosc sclerosis. Localised lipoid deposits in the brain are found in amaurotic idiocy, Schuller-Christian's disease, gargoylism and Niemann-Pick's disease.

**Symptoms.**—The usual classification is into idiots (who are too defective to be able to guard themselves against common physical dangers like falling into the fire), and imbeciles and feeble-minded persons (who need to be looked after because of their incapacity to manage their affairs or to profit by instruction). Imbeciles cannot earn their living; the feeble-minded cannot get on in an ordinary school, but may learn a good deal in a special school and be able to earn a living. The criterion is in each case mainly a social one; the same is true of "moral defect", *i.e.* mental defect coupled with strong vicious or criminal propensities. Although these terms are defined in an Act of Parliament, they are vague and of administrative rather than medical use. An attempt has been made to render them more precise by psychometric means: the customary tests for mental age (usually the Stanford-Binet) are

applied, and if the subject's intelligence-quotient  $\left( \frac{\text{mental age}}{\text{actual age}} \times \frac{100}{1} \right)$  be less than 20,

he is called an idiot; if it be between 20 and 50, an imbecile; if between 50 and 70, feeble-minded. It must, however, be recognised that though mental defect is mainly a matter of intellectual capacity, it is not solely this, and that intelligence tests, however valuable and trustworthy, cannot give a complete indication of the degree of mental defect. Even the intellectual defect may be uneven, showing much more in some tasks than in others, and it would be a gross error to suppose that a mentally defective person with a mental age of, say,  $9\frac{1}{2}$  years is mentally in the same state as a normal child aged  $9\frac{1}{2}$  years.

The *physical* symptoms are chiefly due to lesions of the central nervous system: birth trauma may have led to paralysis, spasticity, athetosis; or there may be evidence of an inflammatory condition of the brain and its membranes, as from syphilis. The whole clinical picture may be greatly coloured by the motor disturbance, *e.g.* continual rocking and twisting movements, grimaces and abnormal posture. The special senses may be affected, as the result of an independent anomaly, *e.g.* coloboma, misshapen ears; or from a common cause, *e.g.* interstitial keratitis, the retinal changes of amaurotic idiocy. It is dubious whether the "stigmata of degeneration", such as a "Gothic" palate or a Darwinian tubercle, occur any more frequently among defectives than in the rest of the population: at all events, there is none that can be used diagnostically, except in the case of mongoloid idiocy. There are, however, some correlations between somatic anomalies and mental defect. Thus, there are more physical defects among these people than in the average population, and this becomes more evident as one looks lower in the scale of mental defect, in which skeletal and cardiovascular anomalies may fairly often be found, sometimes, but not always, due to thyroid or pituitary disorders. The mongoloid variety is described below.

The *mental* symptoms are lack of intelligence and of the normal exercise and control of primitive tendencies. This may be extreme, as in idiots, who cannot be taught to feed themselves and keep clean or who can only just recognise their companions and make their elementary needs known—they are, indeed, much less intelligent than an animal. Imbeciles are usually incapable of learning and remembering any but very simple matters. They may, however, be able to do automatically what they cannot understand or put to independent purpose: thus, "idiots savants" are especially clever at doing mental arithmetic, recalling dates and other such operations. What imbeciles manage to learn they cannot utilise in any but the most familiar circumstances. Abstract concepts are too hard for them, and their judgement is as poor as their grasp or awareness of what is relevant in any situation. Though in many

ways suggestible and accessible to flattery, they may be obstinate and egotistical, and readily fall into anti-social courses, *e.g.* prostitution, vagrancy, crime. Crude sexual offences or murder may be committed as lightly as some minor deception. The personality of imbeciles varies widely: some are docile and kindly, others rough or deceitful and vindictive. It depends much on their upbringing. It has been found that in satisfactory conditions only about 8 per cent. of defectives show anti-social or troublesome behaviour. But though the deviations of personality may not lead to delinquency, it is common to find in mentally deficient persons defects of temperament and character, as well as of intelligence, which are reflected in social inefficiency. This is most important in the feeble-minded, who have intelligence enough to learn an occupation; whether they can earn their living by it will depend on their character and the way they have been brought up.

Many persons who are high-grade defectives, when measured by formal tests, are not taken to be such because of their social adaptability, their fluency and capacity for keeping their heads above water as long as economic and other stresses are light. There are instances of people classed as mentally defective during childhood, because of their backwardness in school and their low score in tests, who later in life amass money by their own efforts, or even hold responsible positions. A majority of high-grade defectives, however, live dependent and often troublesome lives; at most they do simple repetitive work. Many of them are unstable creatures, whose psychopathic personality may be sufficiently anti-social for the term "moral deficiency" to apply to them. Hysterical trends may show themselves in crude phenomena, *e.g.* convulsions, counterfeit insanity or fantastic lying; and religious and artistic pretensions may take in gullible followers and even lead to the founding of ephemeral movements.

Defectives are prone to disturbances of mood, sometimes arising out of awareness of their inferiority and its social consequences. Sudden outbursts of excitement may show similarity to manic or catatonic hyperkinetic states; they may be accompanied by a paranoid hallucinosis, mainly auditory, which clears up with startling rapidity in a day or two. In respect of these psychotic episodes, defectives are like epileptics and juvenile encephalitics, in whom a cerebral impairment has likewise occurred before the attainment of maturity. Some of the morbid phenomena, especially in idiots, are very similar to the disorders of motility seen in schizophrenics, because, it may be assumed, the same bodily mechanisms are implicated.

The *mongoloid* type of defect is characterised by striking physical features. Probably the outcome of intra-uterine conditions, it is most frequent in last-born children in a large family, or in children born of elderly mothers; parental syphilis may occasionally be the cause. In many cases the brain-stem and cerebellum have been disproportionately small, and other signs of maldevelopment have been reported. Cerebral metabolism is abnormally low. It is likely that hereditary factors of an irregularly dominant nature also play a part. The condition is usually present from birth; physical growth is slow, and has stopped by the time the child is 15. Defective growth of the skull, leading especially to abnormalities of the base and the orbit, are responsible for the peculiarities of cranial shape. The pituitary gland has been reported as showing an increase in eosinophil cells and deficiency of basophil cells. The appearance of these usually happy idiots and imbeciles is rather suggestive of a Mongol or of a fœtus. The skull is small and round, and the junction of occiput and back of neck flat; an epicanthic fold across each inner canthus, narrow tilted eye-slits and lids without lashes, red cheeks, fissured and often protruding tongue, stubby depressed nose with nostrils looking forward, irregular late-appearing teeth, coarse hair on the scalp, small facial bones and occasional neurological anomalies, such as nystagmus, make the head of every mongoloid a disagreeable but ready index to his disorder. That the disorder is a general one the rest of his body testifies; his limbs are lax and over-mobile at the joints; he has broad, clumsy feet and hands (with short fingers, a special pattern between the base of the third and fourth fingers, and a crease

depending as they do to some degree on the subject's attitude and situation at the time, about which the group-tester will know little or nothing, and they cannot be trusted when a low score has been obtained. In all instances where a decision must be taken that depends partly on the results of the test, any puzzling or unduly low score on a group test should be reinforced by an individual test, such as the Binet or Bellevue. It must, however, be admitted that the inexpert administration of individual tests can yield as rich a crop of wrong conclusions as can the uncritically accepted group test. The truth is that "no mental test score should ever be accepted at its face value, nor trusted in the same way as physical measurements are trusted. . . . No one ought to use tests who is not willing to familiarise himself with the underlying principles which must be understood if tests are to be applied and interpreted properly, and with the literature which bears on the particular tests that he employs. In skilled hands, testing provides a far surer and more accurate tool for the assessment of abilities than do subjective impressions or the ordinary examination paper. But human nature is far too complex to be measured in the simple and direct ways in which physical quantities can be measured, and the over-enthusiastic but unskilled tester is only too likely to make serious mistakes."

**Treatment.**—**PROPHYLACTIC.**—Eugenic measures are desirable for the rare hereditary conditions, like amaurotic idiocy, and in the case of those imbeciles and feeble-minded in whom genetic rather than environmental causes have been responsible for their maldevelopment and who are capable and desirous of procreating; idiots do not procreate. Voluntary sterilisation for eugenic reasons has been recommended by a Departmental Committee, but has not yet been explicitly sanctioned by law. Birth control, therefore, is the eugenic measure to be advised in cases in which defectives seem likely to transmit their defect; unfortunately few such defectives can be relied on to observe contraceptive precautions effectively. Segregation may indirectly serve the same end. Well-managed partition and treatment of parental syphilis are the only other practicable ways of forestalling defect.

**Educational and social.**—Much improvement may be attained by the training of defectives: it is work for experts. Many high-grade defectives who would otherwise spend their lives in an institution can be prepared by suitable graduated work under sheltered conditions for an independent life in the general community. Where there are special disabilities, *e.g.* of the senses, or of such capacities as reading and writing, attention to these may lift the child out of the class of mental defectives altogether; so may education designed to promote emotional stability and self-confidence. Whether a child lives at home or in a colony or institution will depend not only on the degree of his intellectual and social deficiency, but also on the adequacy of his home circumstances. There are many kinds of provision for the care of some of the 300,000 defectives in England and Wales, ranging from special schools and statutory supervision to mental hospitals; an eighth are in certified institutions, and a thirtieth more in public assistance institutions. Well-run colonies providing adequate psychological and occupational as well as psychotherapeutic and other clinical services succeed in socialising many defectives hitherto vicious or violent, who can then go out and live usefully in the community or in hostels. Some, however, prove intractable, especially those who have epileptic fits.

**Physical.**—The bodily disturbances, *e.g.* contractures and paresis, call for orthopaedic treatment, which sometimes benefits the mental state. The treatment of the forms due to thyroid deficiency or syphilis is described elsewhere.

AUBREY LEWIS.

## APPENDIX

Histoplasmosis	page	i
Toxoplasmosis		v

## APPENDIX

### HISTOPLASMOSIS

**Definition.**—An acute, subacute or chronic infection of man and certain animals by the fungus *Histoplasma capsulatum*, giving rise to three main clinical types of disease: (i) the disseminated form, where the parasites invade the reticulo-endothelial cells in many parts of the body; (ii) the primary pulmonary form confined to the lungs and adjacent lymph-nodes; (iii) a localised infection of the skin or the mucous membranes of the mouth, tongue or pharynx.

**Ætiology.**—The fungus exists in two forms: (i) a mycelial phase which is found when it is existing as a saprophyte or if it is cultured at a temperature of 22° C.; (ii) a yeast-like phase which occurs when it is living as a parasite or if it is grown on enriched media at 37° C. Infection from natural sources is probably due to the mycelial phase, but it is the yeast-like phase that is parasitic and invades the tissue cells; change from one form to the other readily occurs.

The fungus has been isolated from the soil in many areas and some twenty species of animal have been found to harbour the parasite, the bulk of natural infections being found in dogs, cats and rats; it has also been found in a high proportion of skunks and opossums, but only small numbers of these animals have been examined. Birds have not been found infected with *Histoplasma*, and seem to be highly resistant to it, though the fungus can be found in profusion in their droppings and in the litter of poultry houses. A number of small epidemics have occurred on farms in the United States, and amongst builders working in lofts where birds roost, caused probably by inhalation of infected dust. The adoption of the deep-litter method of poultry farming in this country suggests the possibility of similar outbreaks arising, particularly in the more humid western counties. Both sexes are susceptible at all ages, the highest incidence being either during the first year of life or in the later adult years. Amongst adults, males are infected seven times as frequently as females.

The chief portal of entry is thought to be the respiratory tract, but the disseminated form may originate in some part of the gastro-intestinal canal. Primary skin lesions also occur but they are uncommon. Special precautions seem necessary in laboratories, as already 41 cases of infection, with clinical illness, have been reported amongst laboratory workers who had been handling *H. capsulatum*. The incubation period is not known with certainty but is thought usually to be from 4 to 6 weeks, with a range of from 2 weeks to 3 months. *H. capsulatum* has a world-wide distribution although clinical cases occur somewhat sporadically outside North America. In Great Britain at least 15 cases have been diagnosed with certainty, but it is thought that in the majority the infection was acquired elsewhere. The principal endemic centre is in the United States of America, where the greatest incidence is found in an area extending from the Great Lakes to the Gulf of Mexico, in the valleys of Ohio, Missouri, Arkansas and Mississippi rivers.

**Pathology.**—The fungus invades and multiplies within the reticulo-endothelial cells and in the disseminated form it may be found throughout the body or confined to a single organ; the suprarenal glands often being the principal or only organ involved. In acute disseminated infections with a fatal termination, intra-cellular organisms may usually be found post mortem in stained sections of tissue from the lung, liver, spleen and suprarenal glands. The gastro-intestinal tract is often affected, and the bone marrow almost invariably. The organism produces greyish-white nodules, usually multiple, varying in diameter from 2 to 3 mm. up to several centimetres. Extensive areas of necrosis may be found surrounded by granulomatous

tissue. Superficial or deep ulcers may be seen in the small or large intestine and nodules have been found in the submucosa and deeper layers of the intestinal wall. Caseation of the suprarenal glands may cause almost total destruction of glandular tissue, and a recent review of 103 fatal cases of histoplasmosis revealed that 35 per cent. were found post mortem to have some damage to suprarenal glands. Infections commencing in the mouth, pharynx or larynx show localised necrotic ulcerations and enlargement of the regional lymph nodes.

In the benign pulmonary infections multiple, small, discrete, fibrotic nodules may be found in any part of the lungs, and early enlargement of the tracheo-bronchial and hilar lymphatic glands is usual. The central portions of the nodules become caseous and later calcify: these residual lesions are often seen in a routine radiograph taken months or years after the infection occurred. When the lung is involved in the disseminated form of the disease there is usually an extensive, bilateral, interstitial pneumonitis in the early stage of the illness with diffuse or localised areas of consolidation. At times abscess formation occurs, which may be followed by cavitation. Where healing takes place, fibrosis with contraction often causes deformity of a section or lobe, and a clinical diagnosis of chronic tuberculosis or bronchiectasis is not an uncommon error; where it occurs near the lung roots it may be mistaken for a bronchogenic carcinoma. Occasionally the infection is confined to the mediastinal lymph nodes and a picture almost indistinguishable from Boeck's sarcoid or lymphoma is presented.

**Clinical Features.**—(i) *Disseminated histoplasmosis.*—This may be an acute and rapidly fatal illness and this form is most common in infants, in the aged, or in those debilitated by tuberculosis or malignant disease. More commonly it runs a sub-acute course, the illness extending over many months, with a fatal termination in most instances, although arrest of the disease and ultimate recovery have been recorded a number of times.

There is no characteristic clinical picture. Common early features are debility, loss of weight, low-grade fever, sweating, joint and muscle pains, abdominal discomfort and diarrhoea. Leucopenia and progressive anaemia are almost invariable and enlargement of the liver and spleen are usually found. Involvement of the suprarenal glands may destroy so much glandular tissue that Addison's disease results, and histoplasmosis should always be excluded when such a diagnosis is made. If the infection spreads to the lung it will usually give rise to a pneumonitis, with an abrupt onset accompanied by fever around 103° to 104° F., but seldom any clinical features to distinguish it from a viral pneumonia. Symptoms may be limited to occasional chest pain and a dry unproductive cough. The physical signs are seldom of any diagnostic value. By contrast a radiograph shows an extensive bilateral interstitial pneumonitis, miliary or patchy, together with enlarged hilar lymph nodes. The acute stage lasts for 7 to 10 days, followed by gradual subsidence. The radiographic signs, however, do not reach their maximum for 2 weeks; after 6 weeks a fine nodular fibrosis may be seen, and after 3 months nothing abnormal may be detected. More often though, when recovery takes place, contraction follows the fibrosis with marked deformity of the affected lung section.

(ii) *Primary pulmonary histoplasmosis.*—This form is very often asymptomatic; it may cause mild catarrhal symptoms and malaise, and suggest influenza or bronchitis. Spontaneous recovery is the rule and the disease is seldom recognised before this has taken place. It may be months or years before the residual lesions are seen in a radiograph, as the examination is nearly always made either as a routine or for some other condition.

**Laboratory Findings.**—The fungus may usually be found in the cytoplasm of the reticulo-endothelial cells and in the macrophage cells, in the form of round or oval yeast-like bodies varying from 2 $\mu$  to 4 $\mu$  in diameter. Smears stained by Giemsa's method show chromatin irregularly condensed within a refractile capsule. The

organism is found most easily in smears obtained by sternal or splenic puncture but may also be seen in smears from the lesions, where these are accessible, and at times in the cytoplasm of the mononuclear blood cells. Very occasionally in heavy infections a direct sputum smear will show the organism.

**Culture.**—If the infection is scanty, culture will be necessary and this is the method for definitive diagnosis. Cultures should be made on enriched blood agar to which small quantities of penicillin and streptomycin have been added. Infected material such as blood, bone marrow or sputum should be rubbed over the culture medium, the plates then being closely sealed with "cellophane" tape. It is essential to incubate some of the plates at room temperature as at 37° C. only yeast-like bodies are produced. At room temperature an abundant aerial mycelium is formed consisting of septate hyphae with numerous microconidia attached to their sides or growing on short lateral branches. In addition there are the rounded tuberculate chlamydospores which are characteristic of *H. capsulatum* and their presence makes diagnosis conclusive. The material used for culture must be fresh and the cultures should be observed for 6 to 8 weeks before they may be considered negative.

**Histoplasmin Skin Reaction.**—The histoplasmin skin reaction develops within a few weeks of infection. 0.1 ml. of a 1 : 1000 dilution of standardised histoplasmin is injected intracutaneously. The reaction is read after 48 to 72 hours in the same way as for the tuberculin test. A positive reaction is found not only during the clinical stage of the disease but in many healthy persons living in endemic areas. As such reactors have an unusually high incidence of pulmonary calcification, it seems probable that a past infection with *Histoplasma* has healed spontaneously without causing any recognisable illness.

**Complement Fixation Test.**—In acute infections, complement fixing bodies appear in the blood towards the end of the third week of the illness and increase during its course, gradually diminishing as recovery sets in. In chronic pulmonary infections they may persist at a high level for many years. The complement fixation test is a valuable aid to diagnosis and should be employed whenever infection by *H. capsulatum* is suspected. The test may become negative in the terminal phase of the disseminated form of the disease but the fungus can then usually be identified readily by blood or bone marrow culture; or by the examination of tissues obtained after biopsy has been performed. The antibodies produced cross with the antigens of other fungi, particularly *coccidioides immitis* and *blastomyces dermatitidis*. These cross reactions do not, however, invalidate the complement fixation test as the titres of the homologous antigen are significantly higher.

When biopsy is possible, sections of enlarged lymph nodes or of tissues from superficial lesions may show endothelial cells packed with *H. capsulatum*. Caution is necessary, however, when considering biopsy, since two recent case histories have revealed that shortly after a biopsy was performed, each patient having been previously in good health, generalised symptoms typical of the disseminated form of histoplasmosis arose, followed by death a few months later. The diagnosis was confirmed post mortem and it appears possible that the organism was disseminated into the blood-stream when the biopsy was performed.

**Prognosis.**—In the past histoplasmosis was often considered to be an almost invariably fatal disease. More recent knowledge indicates that the mortality is probably extremely low, since it is considered reasonable to assume that a positive histoplasmin skin test indicates past invasion of the tissues of some part of the body by the fungus, and such positive reactions have been obtained from several millions of persons in the United States. Such persons often have scattered calcified areas in the lungs such as are found after histoplasmosis. It is thought, therefore, that the majority of infections are overcome without any noticeable disturbance of health, or the disease passes unrecognised, as the illness is of short duration and spontaneous recovery ensues.

Where the diagnosis is made during the clinical course of the disease, it may be

said that in primary pulmonary histoplasmosis, recovery nearly always occurs spontaneously and the prognosis is excellent. Localised infections are more serious, and run a much more prolonged course. They usually progress by localised extension, and unless the disease is arrested they tend to be ultimately fatal. There are, however, a number of records where the disease has continued for many years without any serious disturbance of health to the persons affected.

More than one-quarter of the fatal illnesses occur in infants under 1 year of age. In these, the disease is nearly always in the disseminated form, and up to the present time it has been found that over two-thirds of all cases of disseminated histoplasmosis have a fatal termination.

**Treatment.**—It is fortunate that the great majority of cases recover unaided, since despite favourable initial reports on a number of new compounds, there is not yet sufficient evidence to consider any of them curative.

Most of the established antibiotics and sulphonamides have been tried and they have all been reported to be ineffective, although recent laboratory trials have shown that several sulphonamide compounds do have a pronounced action on *Histoplasma* and are capable of overcoming infections in mice previously inoculated with lethal doses of *H. capsulatum*. Sulphanilyl thiourea is by far the most active of the many compounds tested, possibly because, unlike most of the other sulphonamides, it is only partially inactivated by *p*-aminobenzoic acid. The yeast phase of the fungus is far more sensitive to the drug than is the mycelial phase, and this may explain its efficacy in histoplasmosis in mice, which is usually a very acute and rapidly fatal infection. In the more chronic infections, common in humans, the mycelial phase of the fungus may predominate, making its eradication much more difficult. Further clinical trials of sulphonamides seem necessary.

The use of cortisone and related compounds should be avoided in histoplasmosis, as it has been found that the initial improvement that often occurs following their administration is temporary, and rapid extension of the disease often follows. When the suprarenal glands have sustained such severe damage that Addisonian crises occur, cortisone will be necessary to tide over the crisis, and to prevent their recurrence small maintenance doses together possibly with DOCA should be given.

Ethyl vanillate received favourable reports when first used, but later trials failed to confirm its value. Stilbamidine, and more recently 2-hydroxy-stilbamidine have been used, and they have appeared to have a favourable influence upon the course of the disease, although the response to their administration is somewhat uncertain.

Two drugs still undergoing laboratory trials have given encouraging results, combining powerful anti-fungal properties with low toxicity for many different species of animal. One, nystatin (fungicidin), is an antibiotic which has been marketed under the trade name of Mycostatin. In laboratory animals it has proved to be highly effective in all forms of infection, whether fulminating, moderately acute or chronic, and the therapeutic doses have not been toxic. In contradistinction to sulphanilyl thiourea, nystatin is more active against the mycelial phase of *H. capsulatum*. If the preliminary reports on these two drugs are substantiated, treatment with a combination of the two may prove to be highly effective.

The other drug, MRD-112 ( $\beta$ -diethylaminoethyl fencholate) also has marked anti-fungal properties combined with a low toxicity. In human infections it has been given by intravenous injection, commencing with a dose of 50 mg. daily, later increased to 150 mg. daily, the duration of treatment being 24 to 28 days. The higher dose may cause drowsiness at first, but clinical improvement has been apparent soon after the commencement of treatment, although radiographic studies have shown very little change in the lungs throughout this period. It should, however, be remembered that in cases with an acute pneumonitis, due to histoplasmosis, the radiographic signs in the lung do not usually reach their maximum for 2 to 3 weeks after the onset, although subsidence of the infection often commences after 7 to 10 days.



## TOXOPLASMOSIS

**Definition.**—An uncommon disease of man and animals, of world-wide distribution, caused by a small protozoon, *Toxoplasma gondii*, which may be transmitted to the foetus *in utero* by an infected mother or acquired by some means as yet unknown in childhood or in adult life. The majority of infections probably pass unnoticed but the parasite may give rise to a wide variety of symptoms and signs, of differing severity and variable duration, depending partly upon the age of the person when infected, which tend to be so grouped that four main clinical types of illness may be recognised.

1. **CONGENITAL.**—This form is characterised by encephalomyelitis, cerebral calcification, hydrocephalus and choroidoretinitis; with symptoms either apparent at birth, or appearing soon afterwards.

2. **ACQUIRED.**—

- (i) *Cerebrospinal*—most frequent in children in whom the most typical manifestations are those of an acute meningoencephalitis;
- (ii) *Lymphatic*—characterised by the enlargement of one or more groups of lymphatic glands, with at times fever of several weeks' duration and marked constitutional disturbance;
- (iii) *Exanthematous*—the form most frequently found in adults, presenting as an acute febrile illness with a widespread maculo-papular rash, a diffuse interstitial pneumonitis, myocarditis and at times meningoencephalitis;
- (iv) *Latent*—where infection by *T. gondii* gives rise to no symptoms or signs of the disease, and diagnosis can only be made by means of laboratory tests. Latent infections are found only in adults, and are probably always acquired after the age of childhood.

**Ætiology.**—The causal organism was first discovered in 1908, in a small North African rodent, the gundi (*ctenodactylus gundi*), and it was named *Toxoplasma gondii* Nicolle and Manceaux. It was thought to be a protozoon and was classified as one of the sporozoa, but there is still much doubt about its true position. Although many species have since been described, *T. gondii* is considered the only species occurring in man and animals, all other forms described being considered strains of a single species, since both morphologically and immunologically they all appear to be identical.

*T. gondii* is an intracellular parasite found usually in the endothelial cells, the mononuclear leucocytes or the tissue cells. Free living forms may also be found in the tissue fluids of the host. In this free extracellular form, the parasite is a slender crescent-shaped organism, with one end rounded and the other pointed, measuring from  $4\mu$  to  $6\mu$  in length, its breadth being around  $2\mu$ . Intracellular forms often lose the crescent shape, becoming pear-shaped, oval or rounded when they may readily be confused with *Leishmania*. In dry films stained by Wright's or Giemsa's methods, the cytoplasm is blue, the granular nucleus, which is single and fills about one-quarter of the cell, stains a reddish purple and will be seen near the rounded extremity, whilst towards the pointed end there is a small deeply staining red granule, the paranuclear body. The parasite multiplies by longitudinal fission within the endothelial and tissue cells of its host. With virulent strains these cells rupture early, releasing the parasites which then invade fresh cells, thus enabling the parasite to multiply extremely rapidly; though, in the light of present knowledge, with doubtful benefit to itself, since it may result in an overwhelming and rapidly fatal infection of its host. With less virulent strains the cells often remain intact, allowing reproduction to continue until they become greatly distended by 80 or more parasites;

their nuclei are then extruded, and the hypertrophied, cyst-like structures that remain, packed with parasites, are known as pseudocysts. Within them the parasites seem to be in a resting or inactive stage, causing little tissue damage or cellular reaction, the cyst wall probably affording protection from any circulating antibodies, thereby enabling a chronic infection to become established.

*T. gondii* can be cultivated in the laboratory if living tissue cells are used. It propagates most readily on the chorio-allantoic membrane of the developing chick embryo at 35° to 37° C. if protected from bacterial contamination and dehydration. The embryo usually dies between the seventh and tenth days.

**Epidemiology.**—*Toxoplasma gondii* has been found in many species of mammals and birds, and also in certain reptiles. The first authenticated report of human infection was made in 1923, since when human infections have been recorded in many European countries, including Great Britain; in the Middle East; Ceylon; North, Central and South America; Australia and Hawaii. The incidence of toxoplasmosis in man is not known yet, but subclinical infections are probably much more frequent than it is generally realised. Recent surveys using serological tests have shown that positive reactions, suggesting a past infection, may be given by from 10 to 50 per cent. of the adult population in many areas. Such figures should, however, be treated with caution, since doubt has been cast on the validity of some of the tests used, it having been found that they are not specific for *T. gondii*.

Very little is known about the transmission of the parasite to humans or of the source whence it originates, though it is thought to be conveyed from animal reservoirs by some means still awaiting discovery. Rodents and dogs in particular are thought to be a possible source of infection.

Neonatal infections appear to be conveyed transplacentally to the foetus from an infected mother, who almost invariably remains free from any symptoms of the disease herself. If the infection is acquired early in pregnancy by the mother, abortion will probably result, or if the pregnancy continues the foetus will be so extensively damaged that it will be stillborn. Infection late in pregnancy may result in the infant being free from any signs of the disease at birth, and several weeks or even 2 or 3 months may elapse before signs and symptoms appear. Later offspring from such mothers, with one possible exception, have never yet been born with toxoplasmosis. It seems probable that if the mother became infected during the puerperium the disease could be transmitted to the infant if it was breast-fed, as lactating laboratory mice have conveyed the parasite to their offspring in the milk.

Laboratory workers handling *Toxoplasma* have several times acquired very severe or fatal infections, though by what means remains unknown.

Direct case to case infection seems improbable, since laboratory animals have hardly ever been known to infect their cage-mates even in experimental conditions planned to achieve it. In the adult form of the disease with a diffuse pneumonitis, the parasites are often plentiful in the secretions in the small bronchioles, and in such cases droplet infection would seem a possibility.

Nearly all warm-blooded species of animals can be infected experimentally and the parasite has been transmitted in the laboratory:

- (i) by feeding to animals, either tissues containing it or food contaminated with faeces in which it is present;
- (ii) by inoculation by almost any of the usual routes, intranasal, intravenous, intraperitoneal, intracerebral or subcutaneous;
- (iii) by direct penetration of closely shaved skin by the parasite;
- (iv) by penetration of the mucous membrane of the vagina and the conjunctiva.

Infection of animals by the alimentary route is not always easy as the gastric juice tends to kill the vegetative forms of *Toxoplasma*. The pseudocysts are more resistant and the feeding of tissues containing them has proved to be the easiest way of achieving

it. Neither is it always easy to reproduce the disease in animals, and it has been found that if dogs are inoculated with the parasite, even with highly virulent strains, only the younger pups develop the acute form of the disease, the older dogs remaining quite free from all signs of infection. Recently dogs have been suggested as a probable source of human infection, as not only has acute toxoplasmosis occurred in the owners of dogs harbouring *T. gondii* but neutralising antibodies have been demonstrated in the blood of more than one-third of the owners of dogs from whom the parasite has been recovered. Whatever significance may be attached to such findings, it should be remembered that as there is usually a very close association between dogs and their owners, it is equally probable that both could have been infected simultaneously, from the same source.

Until the life cycle of *T. gondii* is known, it seems unlikely that the many problems concerning the epidemiology of toxoplasmosis will be solved. Of the many prevailing surmises on the mode of entry of the parasite into the human body, the majority of those who have studied the disease consider the three following routes the most probable:

- (i) the gastro-intestinal tract, following the ingestion of infected food;
- (ii) the respiratory tract, by inhalation of droplets containing the parasite;
- (iii) the skin and blood-stream, following the bite of an infected arthropod.

It is not yet known whether the vegetative forms of *Toxoplasma* are as vulnerable to human gastric juice as they are to that of experimental animals; nor is it known how resistant the pseudocysts are to storage, desiccation, cold or heat. Since they occur quite frequently in the muscles of animals used as food, the eating of raw or insufficiently cooked meat would seem a likely source of infection. The pseudocysts have also been found in the ovaries of hens; it is therefore possible that eggs could convey the infection. Recently toxoplasmosis has been recognised in cattle and the disease has been transmitted to calves, both congenitally and in the milk. In nearly all rural areas in Great Britain unpasteurised milk is the only form available, and this could well provide another source of infection should the disease become common in cattle.

It has already been mentioned that *Toxoplasma* are present in the bronchioles and probably in the sputum of human cases of toxoplasmosis with pneumonitis, and this is true of domestic animals with clinical evidence of the disease. Moreover, respiratory symptoms are a much more prominent feature of the disease in most animals than they are in man, and thus those looking after such sick animals might well become infected by the inhalation of infected droplets, and also possibly through the conjunctiva, since animals have been infected by this route.

Apart from the bites of infected insects, infection *via* the skin is also possible through the handling of infected tissues as it is known that *Toxoplasma* can penetrate closely shaved skin and it is therefore not improbable that some human infections may be caused by the parasite entering through cracks and small abrasions in the skin. This would certainly explain the increased proportion of positive serological reactions that has already been observed, in veterinary surgeons, slaughterhouse workers and in particular in those handling rabbits.

**Pathology.**—Following infection, the parasites are distributed throughout the body by the blood-stream and become established in the cells of the reticulo-endothelial system, and also in the parenchymal cells. Localisation occurs in many organs, more often in the brain, lung, liver or spleen, parasites often being found also in the kidney, suprarenal glands, bone marrow and lymph nodes. Muscle fibres are also invaded, in particular those of the heart, as well as the skeletal muscles. They may also be found within phagocytic cells and living free in the intracellular fluids of the affected organs.

The typical lesions are small focal areas of necrosis surrounded by a zone of

inflammation containing lymphocytes, mononuclear and plasma cells. Hypertrophied cells distended with parasites, the so-called pseudocysts, are often seen. Serous exudates are commonly found in the various body cavities.

In congenital cases lesions predominate in the brain, spinal cord, retina and choroid. Inflammation often extends to the ependyma, causing ventricular block and hydrocephalus. As well as the typical necrotic foci, minute granulomata are also found in the brain, which calcify if the affected infant survives long enough. The lesions in the central nervous system are not very marked, and often sections must be searched with the greatest diligence before they are seen.

In the acquired adult infections, which usually pass unnoticed, the lesions are often found accidentally. Rarely there is a widespread dissemination of the parasite with lesions throughout the body, though more often the predominant feature is an interstitial pneumonitis with thickening of the alveolar walls, and infiltrations of giant and plasma cells. There may also be scattered areas of purulent bronchiolitis. Inflammatory and necrotic areas are also quite frequently found in the liver, spleen and heart muscle, and encephalitis has occurred in several adult cases, though it is seldom as predominant a feature as in congenital infections, or in the acquired infections of children.

**Clinical Features.**—As knowledge of toxoplasmosis increases, and as more clinical reports become available, so does it appear that the sharply demarcated clinical syndromes that were described in the earlier accounts of the disease, do not in reality exist; apart from the fairly clear-cut distinction between congenital and acquired infections.

Whilst it is still true that there is a preponderance of certain clinical features in children suffering from toxoplasmosis, with others appearing with greater frequency in adults, there no longer seem to be any clinical manifestations of acquired toxoplasmosis that are sufficiently exclusive to one or other age group, to justify the old subdivision into acquired infections—in children; and acquired infections in adults.

### 1. CONGENITAL TOXOPLASMOSIS

Acute infections with widespread dissemination of the parasites and necrotic lesions in many organs, in particular the lungs, the heart, liver, spleen, kidney, supra-renal glands and lymphatic glands have been described, but occur very infrequently in congenital toxoplasmosis. Subacute infection is the common form, with predominating neurological symptoms which may be noted at birth or shortly afterwards. If the foetus is infected very early in pregnancy, the disease will reach an advanced stage *in utero*, and cases have been recorded where the pregnancy having continued to term was followed by an obstructed labour owing to the development of hydrocephalus in the foetus.

In the typical subacute congenital infection, the symptoms and signs may be subdivided into:

- (i) those due to the presence of parasites within the body; these may be called primary symptoms and signs;
- (ii) those secondary to the principal lesions caused by the parasite, namely encephalomyelitis and choroidoretinitis.

The common primary signs are fever, with a fluctuating temperature which may at times be subnormal; jaundice, which has been described in about one-third of all congenital cases; purpura, which occurs infrequently, and a maculo-papular rash, which is extremely rare. Anæmia and leucocytosis, with an absolute increase in monocytes and lymphocytes, are found in about one-half of all cases, and the liver and spleen are not infrequently enlarged.

The signs secondary to encephalomyelitis most frequently found are muscular twitchings and convulsions; stiffness of the neck, paraplegia, respiratory weakness and cyanosis, which at times may be due to an interstitial pneumonitis; vomiting and diarrhoea. Hydrocephalus develops in the majority of infected infants and rapid enlargement of the head may occur. At times when there is early and extensive cerebral damage microcephaly may be found. The cerebral lesions become calcified if the infant survives long enough and may later give rise to Jacksonian convulsions, and the majority of infants who survive for a number of years are nearly always mentally deficient.

The ocular findings most frequently include microphthalmia, the small eyes being in striking contrast to the enlarged head; nystagmus, which may result either from poor fixation due to choroidoretinitis or from the lesions in the central nervous system; vitreous opacities and choroidoretinitis. The lesions are nearly always bilateral and cause blindness or very severe impairment of vision in those infants who survive. The majority of infants, however, die within the first few weeks of life.

## 2. ACQUIRED TOXOPLASMOSIS

(i) *Cerebrospinal*.—In the earlier accounts of toxoplasmosis this form of the disease was usually considered to be not only the invariable manifestation of infection in children, but also to be confined solely to them. Meningo-encephalitis has, in recent years, been reported many times in adults with the disease, but it is seldom the initial feature of the attack, usually occurring as a complication of the exanthematous form towards the end of the first or second week of the illness, not infrequently after the acute stage has subsided and recovery appears to have commenced.

The cerebrospinal form is probably still found more frequently in children, in whom it tends to be the predominant feature of the illness. The onset is marked by fever, very severe headache, vomiting and delirium. Convulsions often occur a day or two later and the picture presented may suggest a brain tumour. Deafness is often found, and very occasionally choroidoretinitis has been recorded, but it is not a constant feature as in the congenital infections. The attacks are frequently severe and often rapidly fatal, with death following within a few days of the onset. Some infections run a more chronic course, but not necessarily with a more favourable outcome, since death may occur several weeks after the commencement of the illness. Complete recovery is, however, by no means uncommon, without the development of any sequelæ, even when the attack has been exceedingly severe.

(ii) *Lymphatic*.—Some of the earlier accounts of toxoplasmosis mentioned that a generalised enlargement of lymphatic glands was occasionally observed, but it is only in recent years that the lymphatic form has been recognised as a clinical type that occurs without any of the other manifestations of the disease. It has been stated quite recently that probably the commonest manifestation of acquired toxoplasmosis in man yet known is a lymphadenitis resembling glandular fever. The total number of cases of this form of infection reported to date does not yet seem large enough to confirm the above statement. Although the lymphatic form is not usually described as occurring predominantly in children, nearly all the recorded cases have been found between the ages of 5 and 15 years.

As with most infectious illnesses, there is a fairly wide range in the severity of the attack and there seems to be no practical advantage in adopting the classification which divides this form into three main clinical groups since they do not appear to differ except in severity.

A proportion of these cases have a sudden febrile onset, often with a rigor, and fatigue is a common premonitory symptom which precedes the onset by several days. The fever usually rises rapidly to about 104° F. and is frequently accompanied by catarrhal symptoms, cough, headache and pain in the back. At times the throat is

sore and there may be abdominal discomfort and diarrhœa. These symptoms and the fever nearly always precede the glandular enlargement and it may be a week or more before the enlarged glands are first observed. The fever usually last for 2 to 3 weeks, occasionally for a few days only whilst it has at times, in adult infections, been prolonged for 6 to 7 weeks, with a high initial fever of about 105° F., slowly subsiding to about 102° F. some ten days from the onset, after which it may fluctuate between 100° F. and 101° F. for 2 to 3 weeks before slowly returning to normal. Although there are no complications, and recovery invariably follows, the febrile cases often require a prolonged convalescence, fatigue being a very prominent feature for 3 or 4 months following an attack.

A large number of cases are afebrile and free from any symptoms apart from, at times, some initial tenderness in the region of the enlarged glands; the general health remains unaffected by the infection. Others remain unaware even of the enlarged glands which are found during some routine examination.

The characteristic feature of this form of toxoplasmosis whatever degree of severity it may assume, is enlargement of one or more groups of lymphatic glands. Those most frequently affected are the cervical, suboccipital, axillary and inguinal groups. A radiograph of the chest may also reveal enlargement of the hilar glands. Enlargement of the cervical glands is fairly constant and they are nearly always the first glands to become affected, other groups becoming enlarged after an interval of several days or even 1 to 2 weeks. The glands are usually firm, discrete and vary in size from that of a hazelnut to that of a walnut. They are usually painless, though there may be some initial tenderness during the first week or two of the illness. There is no inflammation of the skin overlying the glands and suppuration does not occur.

Another very characteristic feature of all cases whether febrile or afebrile is the persistence of the glandular enlargement; enlarged lymph nodes usually can be found 6 to 9 months after the onset of the attack.

(iii) *Exanthematous*.—Although many clinical forms have been described in adults, the most typical is an acute febrile illness of sudden onset, sometimes marked by rigors, soon followed by the appearance of a generalised maculo-papular rash which is absent from the palms of the hands and the soles of the feet, and which closely resembles the rash of typhus or Rocky Mountain spotted fever. There may be a disseminated myositis giving rise to severe aching pain in the muscles, or at times to myocarditis when the heart muscle is involved. The outstanding feature, however, is a diffuse, interstitial pneumonitis resembling an atypical virus pneumonia, which frequently runs a rapid course with severe dyspnœa, cyanosis and respiratory failure. Enlargement of the liver and spleen will be found in a few cases and encephalitis has recently been a feature of several acute cases in adults.

**Diagnosis.**—*Clinical Diagnosis*.—Even presumptive evidence of *Toxoplasma* infection is rarely obtainable on clinical findings alone, except in infants. A combination of convulsions, hydrocephalus or microcephaly, choroidoretinitis and calcified areas in the brain, seen in a radiograph, strongly suggests toxoplasmosis when found in infancy, and in older children a similar picture, together with blindness or serious impairment of vision and mental deficiency makes a similar diagnosis equally probable. In adults clinical diagnosis is extremely difficult and it is more likely to be considered under the differential diagnosis of an unidentified infection than as a probable diagnosis by itself.

**Laboratory findings.**—The usual routine laboratory investigations give little help in toxoplasmosis. (i) *Blood*.—Anæmia of moderate degree is usual, particularly in infants, though the hæmoglobin is seldom less than 12.3 g. or the red cell count below 4 million. The leucocytes are usually slightly increased in numbers, from 9000 to 12,000 being a common finding with a considerable increase in lymphocytes and monocytes in many cases, the increase in monocytes being of lesser degree but

much more constant. In several proved cases eosinophils have been raised to from 14 to 20 per cent. of the differential count.

(ii) *Cerebrospinal fluid*.—This is often xanthochromic in cases with encephalomyelitis. Protein: usually considerably increased, the increase being relatively greater than that of the cells; Sugar: normal in amount or slightly decreased; Cells: leucocytes are often present in large numbers, with a very considerable range, an average or usual figure being around 500 per c.mm., though counts of 60 and 1600 are often recorded; erythrocytes are usually present but in lesser numbers.

*Definitive Diagnosis*.—The definitive diagnosis of toxoplasmosis by the direct isolation of *T. gondii* from the patient, is frequently not possible and therefore indirect methods are also employed, and provided that a full range of investigations is carried out, with consistent findings, a diagnosis of toxoplasmosis may still be established with reasonable certainty.

(i) *Morphological Identification of Toxoplasma*.—During the acute stage of the infection the parasite may sometimes be found in stained smears of bone marrow, in material obtained by splenic puncture or in the centrifuged deposits of exudates, cerebrospinal and ventricular fluids. Fresh cover-slip preparations should also be examined. Smears should likewise be made from a portion of any tissues removed at biopsy or autopsy, and these should be stained with Giemsa; the other portions should be fixed, and thin sections made, which should be stained with hæmatoxylin and eosin, and then very carefully examined with an oil immersion lens. The parasites in the pseudocyst form are those most easily recognised after a little experience.

(ii) *Biological Identification of Toxoplasma*.—Material obtained from a suspected case of toxoplasmosis should be inoculated into laboratory animals, which must be free from naturally occurring infection in themselves. Mice, hamsters and guinea pigs are the most satisfactory animals, and at least six mice and two guinea pigs must be used before any reliance can be placed on the test. Similar material to that used for making stained smears should be injected intracerebrally into the mice and intraperitoneally into the guinea pigs. The animals should be watched for signs of illness; if after a month all have remained well, passage to another group of animals should be undertaken by the inoculation of tissues from one-half of the first group. Where illness develops, exudates should be carefully examined, and if *Toxoplasma* are not found, part of these fluids should be inoculated into other animals. Smears should be made, and carefully examined, from the brain, lung, liver, spleen and the peritoneal lining of any animals that die. The parasite may be found after the primary inoculation and it is frequently isolated after the first passage. For practical purposes not more than three passages should be performed since it is quite exceptional for the parasite to be recovered if the first three passages have proved to be fruitless.

Direct demonstration of the parasites has only been possible in about one-half of the total number of human cases so far described.

*Indirect Methods of Diagnosis*.—(i) *Complement-Fixation Test*.—An antigen derived from chick-embryo cultures should be employed and the test serum should be examined within 24 hours of taking the blood, as complement-fixing activity may develop spontaneously after a longer period. Complement-fixing antibodies develop 3 to 4 weeks after infection occurs and may persist for several years in fairly high titre, although they often disappear during convalescence. Some 10 per cent. of healthy adults give a positive result with this test but a titre of over 1:8 suggests a recent infection.

(ii) *Neutralising-Antibody Test*.—Infection with *T. gondii* leads to the formation of antibodies in the blood which may persist for many years after recovery. They may be demonstrated by their ability to prevent infection of the chick-embryo with *Toxoplasma*, or the development of skin reactions in the rabbit. Although all human

sera produce an erythema with œdema of the rabbit's skin within 24 hours of injection, this usually fades after 4 days. If, however, any *Toxoplasma* are present and are not neutralised by antibody, a typical lesion will develop around the site of the injection after 3 or 4 days, becoming fully developed about the eighth day. The test is performed by injecting intracutaneously mixtures of the patient's serum with living *Toxoplasma*, obtained from cultures, in a shaved area on the back of a rabbit. Several dilutions of the *Toxoplasma* suspension are made in order to obtain the neutralising titre of the serum. This test is not very reliable and it should not be used unless other tests are also performed.

(iii) *Toxoplasmin Skin Test*.—The toxoplasmin is prepared from a special strain of *Toxoplasma* which are killed by irradiation from a germicidal electric lamp. Intradermal injections of suitable dilutions of toxoplasmin and a control antigen are made in the skin of the patient, and the area is observed after 48 and 72 hours. A positive reaction, indicating infection by *Toxoplasma*, consists of an area of erythema and induration exceeding 10 mm., present after 48 hours, with an absence of reaction in the area of the control. The test is more reliable than the neutralising antibody test, but, like the former, it does not indicate the state of activity of the disease, positive reactions being given by from 10 to 20 per cent. of apparently healthy people.

(iv) *Methylene Blue Dye Test*.—If films, made from a suspension of parasites and normal serum, are stained with alkaline methylene blue, the parasites will appear as rounded, deeply stained bodies; if, however, the serum contains specific antibodies together with an "accessory factor", some modification takes place in the cytoplasm of the parasite so that they no longer accept the stain. Until quite recently great reliance was placed on this test, but it is now known that it is by no means specific for *Toxoplasma*, a positive result being obtained also with *Sarcocystis*, *Trichomonas vaginalis* and *Trypanosoma lewisi* and probably other parasites. These findings do not necessarily invalidate the dye test, though the interpretation of the test when low titres are obtained is not easy. It is probably wise to insist that for a diagnosis of active toxoplasmosis to be justifiable, not only must the dye test and the complement fixation tests be positive, but their respective titres should be not less than 1:128 and 1:8. In practice it will be found that the complement fixation test is nearly always positive with a dye test titre of 1:128.

*Differential Diagnosis*.—(i) In infants. When jaundice is present and the liver and spleen are enlarged, it must be distinguished from erythroblastosis foetalis. Birth injury, bacterial meningitis, foetal infection with many viral diseases may also present somewhat similar features.

(ii) In older children, with neurological abnormalities present it must be distinguished from tuberculous sclerosis; cerebral angiomas; also from brain tumours.

(iii) In adults with acute infections, typhus, Rocky Mountain spotted fever and atypical pneumonia are the most likely causes of confusion. Toxoplasmosis should also be considered when myocardial disease is found where the cause remains unexplained. Pseudocysts occur frequently in the skeletal muscles and have at times been mistaken for sarcosporidia.

(iv) The lymphatic form will almost certainly be mistaken for glandular fever in the majority of cases, and it seems highly probable that if this form of toxoplasmosis is much more common than is generally realised, many of the "clinical diagnoses" of glandular fever where the blood picture is atypical and the Paul-Bunnell test negative, may in fact be toxoplasmosis, since of the total number of such cases in any year, a very small proportion indeed will even arouse a suspicion of toxoplasmosis. It is certainly true that in many an outbreak of fever accompanied by glandular enlargement, giving a clinical picture that suggests glandular fever, laboratory confirmation may be obtained for only some 10 to 20 per cent. Enlarged glands may frequently be present in such cases 5 to 6 months later.



The persistence of the glandular enlargement may also at times arouse suspicion of Hodgkin's disease.

**Prognosis.**—The lymphatic form of toxoplasmosis runs a benign course, recovery being apparently invariable, and the prognosis is therefore excellent. Of the other forms of toxoplasmosis the great majority of recorded cases have ended fatally to date, but until the true incidence of the disease is known with accuracy, the case mortality will probably continue to be disproportionately high, since the majority of diagnoses will be amongst the most severe infections, with a large number obtained after post-mortem examination. Until a few years ago, recovery was the exception, but an increasing proportion of recoveries from the clinical forms of toxoplasmosis have more recently been recorded.

The congenitally acquired infections usually have a fatal termination either within the first few months of life, or in early childhood with the few years of survival marred by greatly impaired vision or blindness, and retarded mental development. Acute toxoplasmosis in children, marked by involvement of the central nervous system have usually had a fatal termination, though there have been several reports of complete recovery, no sequelæ being apparent. In adults a greater number of recoveries have been recorded, the outlook being more favourable when the respiratory symptoms predominate, even though the mortality with this form remains high. Encephalitis was considered unusual in adults a few years ago; during the last 5 years it has been a feature of a considerable proportion of the diagnosed infections in adults, with a fatal termination in about one-half. Laboratory infections have not been numerous but they have been exceptionally severe, nearly all of them being fatal.

In recent years evidence based on serological tests has been accumulating, though the findings cannot be accepted without reserve, since, apart from many technical difficulties making the tests often unreliable, the dye test, which was considered the most satisfactory, has recently been shown to give positive reactions with a number of other protozoa. Despite these objections, it appears that in the latent or sub-clinical form toxoplasmosis is common, and that the clinically recognisable infections are extremely rare. Thus it is probably true to say that whilst the case mortality from the disease toxoplasmosis remains very high, the mortality following infection by *Toxoplasma* is extremely low.

**Treatment.**—It will be apparent from the remarks made under prognosis that no effective treatment has been available for toxoplasmosis in the past. Animal experiments have been made in which a very wide range of drugs have been tested, and whilst a number have had some effect, very few have encouraged clinical trials in human infections.

Laboratory experiments have shown that several of the sulphonamide compounds are curative if the infection is not a heavy one and the drug is administered soon after infection. By far the most active of these compounds is sulphapyrazine, which also possesses some antimalarial activity, and even when the dose is reduced to half that of the other sulphonamide compounds it is still much more effective. It may, however, have some toxic properties as it has not yet been made available commercially.

Most of the broad-spectrum antibiotics have given somewhat similar results. Of the newer ones, puromycin and tetracycline (Achromycin—Lederle) have been extensively tested in the laboratory but neither of them are considered sufficiently effective for any further trials. Further recent trials with chlortetracycline (Aureomycin) have shown that it will cure heavy infections in laboratory animals if very large doses are used, but it is doubtful if such high dosage would be tolerated in human infections.

Pyrimethamine (Daraprim), an antimalarial drug found to be suppressive in very small doses as well as an effective therapeutic agent, has very recently been reported to be curative in human toxoplasmosis. Published information is still

limited to a few reports, but it appears to be the most effective remedy at present available, particularly when combined with sulphadiazine. The effect of this combination appears to be synergistic since it has been found to be six times greater than would be expected if it was purely additive. The best results are given by a combination of 22 per cent. pyrimethamine to 78 per cent. sulphadiazine. The most effective doses of pyrimethamine are considerably higher than those normally used in practice, the lower dosage being adopted on account of the risk of toxic effects. Treatment is usually commenced with a small dose of 25 mg. daily which is increased after 3 or 4 days to 50 mg. daily. Treatment is usually continued for 10 to 14 days, the total dosage of pyrimethamine being from 500 to 700 mg. In one series of 13 cases receiving this treatment, one patient was left with a psychosis, the cause being unknown; complete recovery was recorded for the remainder. Pyrimethamine has also been tried in cases of uveitis where serological tests suggested toxoplasmosis to be a possible cause. The results so far have been rather indecisive but further trials are still in progress.

# INDEX

- Abdomen**, in acute peritonitis, 713.  
in chronic dysentery, 115.  
in celiac disease, 619.  
in lead colic, 367.  
in ulcerative colitis, 635.  
retracted, in cerebrospinal fever, 56.
- Abdominal abscess**, in peritonitis, 712, 713, 714, 719.  
allergic attacks, 710, 711.  
cramps in hyperparathyroidism, 502.  
discomfort in nervous dyspepsia, 568.  
distension in acute gastritis, 571.  
in acute intestinal obstruction, 652.  
in acute necrosis of pancreas, 703.  
in ascites, 721, 722.  
in bacillary dysentery, 114.  
in colitis, 633.  
in congenital diaphragmatic hernia, 1097.  
in congenital syphilis, 226.  
in megacolon, 647, 648.  
in pneumococcal peritonitis, 714.  
in pseudocystitis, 567.  
in rickets, 406.  
in tuberculous peritonitis, 719.  
in typhoid, 100, 102.
- migraine**, 711.
- rigidity** in acute peritonitis, 713.  
in appendicitis, 655.  
in Henoch's purpura, 775.  
in pyelitis, 1134.
- tenderness** in acute peritonitis, 713, 714.  
in appendicitis, 654.  
in diverticulitis, 644.  
in gastric ulcer, 577.  
in leptospirosis icterohæmorrhagica, 239.  
in trench fever, 301.
- Abortifacient uses of lead**, 365.
- Abortion** in cholera, 135.  
in malaria, 254.  
in measles, 149.  
in scarlet fever, 41.  
in small-pox, 159.  
in typhoid, 102.  
in undulant fever, 126.  
syphilis as cause of, 225.
- Abortus fever**, 125.
- Abscess**, actinomycotic, 194, 195.  
amœbic, 280.  
appendicular, 656, 657.  
cerebral, 1405.  
chronic, mediastinal, 1091.  
cold, 1019.  
filarial, 327.  
hæmatogenous, 1405.  
in scarlet fever, 40.  
in typhoid fever, 104.  
ischio-rectal, in pulmonary tuberculosis, 1026.  
metaspneumonic, 1002.  
metastatic, 1405.
- Abscess of brain**, 1405.  
of lung, 1002.  
perinephric, 1137.  
peritonsillar, 534.  
retro-pharyngeal, 75, 539.
- Abscesses**, as cause of acute peritonitis 712.  
in glanders, 132.  
in pyæmia, metastatic, 32.  
in suppurative pyelphlebitis, 688.  
in typhoid, 99, 104.  
miliary amœbic, 276.
- Acanthocheilonema perstans**, 326.
- Acanthosis nigricans**, 1307.
- Acarus**, parasite in scabies, 1250.
- Accessory-sinus suppuration**, 940.
- Accommodation**, paralysis of, in diphtheria, 1591.
- Acetarsol** in syphilis, 216.  
toxic effects of, 233.
- Acetylarsan** in syphilis, 216.  
in tropical eosinophilia, 315.  
toxic effects of, 233.
- Acetyl-choline** in relation to myasthenia gravis, 1604.
- Achalasia of the cardia**, 543.  
of Oddi's sphincter, 698.  
of the pharyngo-œsophageal sphincter, 541.
- Achlorhydria**, 554, 555.  
as cause of diarrhœa, 554, 610.  
associated with gastric flatulence, 566.  
effect on central nervous system, 554.  
on hæmatopoiesis, 554.  
in atrophic gastritis, 574.  
in cancer of stomach, 591.  
in cholecystitis and gall-stones, 690.  
in chronic alcoholism, 355.  
in diarrhœa of phthisis, 639.  
in health, 554.  
in idiopathic hypochromic anæmia, 732.  
in pellagra, 473.  
in pernicious anæmia, 554, 736.  
in relation to bacterial activity, 557.  
in sprue, 624.  
in subacute combined degeneration, 1552.  
in syphilis of stomach, 589.
- Acholia**, 618.
- Acholic jaundice**, 741.
- Achondroplasia**, 1182.
- Achromia parasitica**, 1204.
- Achyilia gastrica** in pernicious anæmia, 734.
- Acidæmia**, 418, 419.
- Acid-base balance**, function of kidneys in, 1108.
- Acidosis** in methanol poisoning, 357.  
in uræmia, 1110.  
infantile renal, 618.  
renal, in blackwater fever, 261.
- Acid-sodium urate** in urine, 1098.

- Acidotic breathing**, 1110.  
**Ackee poisoning**, 350.  
**Acne**, *agminata*, 1245, 1285.  
     *bromides* in relation to, 1238.  
     *conglobata*, 1282.  
     *excoriée des jeunes filles*, 1284.  
     in infancy, 1284.  
     in poisoning by chlorinated naphthalenes, 395.  
     *keloid*, 1282.  
     *keloidalis nuchæ*, 1311.  
     *necrotica*, 1285.  
     *papular*, 1282.  
     *punctata*, 1282.  
     *pustular*, 1282.  
     *rosacea*, 1207.  
     *scrofulosorum*, 1245.  
     *sycosis*, 1282.  
     *urticata*, 1255.  
     *varioliformis*, 1285.  
     *vulgaris*, 1282.  
     *white*, 1282.  
**Acnitis**, 1285.  
**Acrocephaly**, 1181.  
**Acrocyanosis**, 925, 1205.  
**Acrodermatitis chronica atrophicans**, 1295.  
     *pustulosa continua*, 1273.  
**Acrodynia**, infantile, 308.  
**Acromegaly**, 484.  
**Acropachy**, 1171.  
**Acroparæsthesia**, 1581.  
**Acrosclerosis**, 935.  
**A.C.T.H.** See *Corticotrophin*.  
**Actinic rays**, dermatitis from, 1210.  
**Actinomyces bovis**, 194.  
     *griseus*, extraction of streptomycin from, 10.  
     *israeli*, 193, 194.  
     sensitivity to penicillin, 7.  
**Actinomycosis**, 193.  
     of brain, 195.  
     of intestines, 194.  
     of jaw, 194.  
     of lungs, 195, 1038.  
     of pleura, 195, 1085.  
     of skin, 195, 1240.  
**Acupuncture** in heart failure, 816.  
**Adamantinoma** of *sella turcica*, 1383.  
**Adamsite**, 376.  
**Addison's anæmia**, 734.  
     disease, 507.  
     neurasthenia accompanying, 1644.  
     suprarenal cortex in relation to, 508.  
     tuberculosis in relation to, 507, 509, 1026.  
**Adenitis** in chancroid, 143.  
     in glandular fever, 305.  
     in lymphopathia venereum, 191.  
     in rubella, 156, 157.  
     in scarlet fever, 40, 42, 47.  
     in trypanosomiasis, 271.  
     in *tsutsugamushi* disease, 290.  
     tuberculous, 1092.  
**Adenoids**, 536, 941.  
**Adenoma**, chromophobe, 1383.  
     *dumb-bell*, 973.  
     *fetal*, 500.  
     *neutrophil*, 1383.  
     *Adenoma* of bronchus, 972.  
     of kidney, 1144.  
     of parathyroids, 501.  
     of pituitary, 484, 1383.  
     of suprarenal glands, 512.  
     *sebaceum*, 1486.  
     (*Pringle*), 1308.  
     *toxic*, 495.  
**Adhesions**, pericardial, 883.  
     peritoneal, 718.  
**Adiposis dolorosa**, 1166.  
     mental symptoms of, 1644.  
**Adiposity**, 449.  
**Adolescence**, affective disorders in relation to, 1646.  
**Adrenal cortical insufficiency**, 507.  
**Adrenaline**, 506.  
     for toxic symptoms due to *arsphenamine*, 230.  
     hypersecretion of, in *phæochromocytoma*, 518.  
     in allergic conditions, 711.  
     in asthma, 980.  
     in complete heart block, 832.  
     in Stokes-Adams syndrome, 832.  
**Adrenals**. See *Suprarenal glands*.  
**Adreno-genital syndrome**, 511.  
**Adult rickets**, 1176.  
**Aedes ægypti**, 184, 189.  
     *albopictus*, 189.  
     *scutellaris*, 189.  
**Aerobacter cloacæ**, in causation of respiratory illness, 1016.  
**Aerocele**, 957.  
**Aerodontalgia**, 397.  
**Aeroembolism** of aviators, 395.  
**Ærogastric bloqué**, 549, 566.  
**Aero-otitis media**, 397.  
**Aerophagy**, 528, 530, 566, 630.  
     cause of intestinal flatulence, 566.  
     *hysterical*, 566.  
     in chronic œsophageal ulcer, 549.  
     mechanism of, 566.  
**Aerosporin** in whooping-cough, 142.  
**Affective disorder**, 1645.  
     alterations of metabolism in, 1648.  
     drug abuse causing, 1647.  
     suicide, risk of, 1650.  
     toxæmia as cause of, 1647.  
     types of, 1645.  
**Albinogenæmia**, congenital, 767.  
**"After-damp,"** 358.  
**Agglutination test** for diagnosis of cerebrospinal fever, 55.  
     of glandular fever, 306.  
     of leptospirosis *icterohæmorrhagica*, 239.  
     of paratyphoid fever, 112.  
     of tularemia, 131.  
     of typhoid, 105.  
     of typhus, 287, 291.  
     of undulant fever, 126.  
**Agglutinin**, 3.  
**Agglutinins** and agglutinogens in relation to blood grouping, 727, 728.  
**Agnosia**, 1376, 1377.  
**Agonadism**, 520.  
**Agranulocytic angina**, 756.  
**Agranulocytosis**, 756.

- Agranulocytosis** as a factor in infection, 2.  
in chloramphenicol therapy, 13.  
in sulphonamide therapy, 26.
- Agaphia**, pure, 1369.
- Ague**, 245.
- Ague-cake spleen**, 249, 254.
- Air embolism**, 854, 1446.
- Air swallowing**, 528, 530, 566, 630.
- Alar collapse** of nostrils in adenoids, 942.
- Alastrim**, 163.
- Albers-Schönberg disease**, 748.
- Albinism**, 1203.  
of the lung, 998.
- Albright's syndrome**, 502.
- Albuminuria**, 1102.  
due to arsphenamine therapy, 230.  
due to bismuth therapy, 218.  
in diabetic glomerulosclerosis, 1125.  
in diphtheria, 73.  
in erysipelas, 35.  
in nephritis, 1116, 1121.  
in polycystic disease of the kidneys, 1146.  
in pyelonephritis, 1137.  
in tuberculosis, 87.  
in yellow fever, 186.
- Albumosuria**, 1103.
- Alcohol** as a cause of gastritis, 571.  
in blood and urine during intoxication, 353.  
in relation to cirrhosis of liver, 674, 675.  
to gout, 445.  
in treatment of ackee poisoning, 351.  
of summer diarrhoea, 616.  
injections in peripheral facial spasm, 1351.  
in trigeminal neuralgia, 1348.  
susceptibility to, 1637.
- Alcoholic coma**, 354.  
delirium, acute, 1638.  
drinks in relation to gout, 355, 445.  
epilepsy, 1639.  
excess, in relation to necrosis of liver, 670.  
hallucinosis, acute, 1638.  
hepatosis, 672.  
mental disorders, 1637.  
neuritis, 1589.  
paranoia, 1639.  
poisoning, acute, 353, 354.  
effect of, on liver, 355.  
pseudo-paresis, 356.  
pseudo-tabes, 356.  
psychosis, Korsakoff's, 1590.
- Alcoholism**, 353.  
acute, 353.  
as a cause of oesophagitis, 548.  
chronic, 355, 1637.  
deleterious effects of, 355.  
delusional states in, 1638.  
demoralisation in, 1637.  
in relation to insanity, 1637.  
pellagra, 472.  
pneumonia, 356.  
pulmonary tuberculosis, 355, 1029.  
tuberculosis, 356.  
typhoid, 102.  
medico-legal aspect of diagnosis of, 353.  
predisposing to lead poisoning, 364.  
prophylaxis of, 1639.  
symptoms of, 353, 354, 355.  
treatment of, 353, 355, 356.
- Aldehyde test**, Napier's, for kala-azar, 267.
- Aleppo sore**, 268.
- Aleukæmic leukæmia**, 761, 763.
- Alimentary symptoms** of pulmonary tuberculosis, 1024.
- Alkalæmia**, 418, 419.
- Alkali reserve**, 419.
- Alkaline tide** in urine, 1098.
- Alkalis** in chronic gastric and duodenal ulcer, 582, 583.
- Alkaptonuria**, 1105.
- Allergy**, 5, 939.  
bacterial, 5.  
gastro-intestinal, 710.  
manifestations of, 939.  
seasonal, 940.  
to inanimate foreign material, 5.
- Almonds, bitter**, oil of, 389.
- Alopecia**, androgenic, 1318.  
areata, 1317.  
cicatricial, 1319.  
congenital, 1317.  
diffusa, 1318.  
non-cicatricial, 1317.  
totalis, 1317.  
universalis, 1317.
- Alphatocopherol**, 456.
- Altitude sickness**, 400.  
high, polycythæmia at, 750.
- Aluminosis**, 1015.
- Alveolar-ectasis**, 997.
- Alzheimer's disease**, 1630.
- Amaas**, 163.
- Amanita muscaria**, a poisonous fungus, 346.  
phalloides, a poisonous fungus, 346.
- Amaurosis fugax**, 1339.  
in cerebrospinal fever, 59.
- Amaurotic familial idiocy**, 1482.
- Amblyomma americanum**, 293, 294.  
cayennense, 293, 294.
- Amblyopia** after trypanamide, 233.  
in quinine therapy, 256.  
malarial, 254.
- Amenorrhœa** in anorexia nervosa, 564.  
in Cushing's syndrome, 517.  
in Graves's disease, 493.  
in kala-azar, 266.  
in pulmonary tuberculosis, 1024.  
in Simmonds's disease, 487.  
in virilism, 511, 512.
- Amentia in Schülder's disease**, 1413.
- Amimia**, 1371.
- Amino-aciduria**, 1107.
- Aminophylline** in asthma, 980.  
in pulmonary œdema, 989.
- Ammonia excretion** in urine, 1099.
- Ammonium chloride** to accelerate elimination of lead, 370.
- Amnesia**, verbal, 1370.
- Amnesic syndromes**, 1627.
- Amœbiasis**, 275-283.  
intestinal, 275.
- Amœbic abscess**, 280.  
dysentery, 275.  
complications of, 277.  
in relation to hepatitis and abscess, 279, 282.  
hepatitis, 276, 279, 280.
- Amœbomas**, colonic, 276.

- Amphetamine** in diabetes mellitus, 427.  
in narcolepsy, 1503.  
in obesity, 451.
- Amyl nitrite** in anginal attacks, 840.  
in glottic spasm, 954.  
in laryngismus stridulus, 947.
- Amyloid kidney**, 1131.  
substance, 1131.
- Amyloidosis**, 1300.
- Amyotonia congenita**, 1599.  
Werdnig-Hoffmann paralysis and, 1599.
- Amyotrophic lateral sclerosis**, 1554.
- Amyotrophy**, syphilitic, 1470.
- Anæmia**, 729-749.  
Addison's, 734.  
aplastic, 738.  
after arsphenamine therapy, 232.  
aregenerative, 738.  
Cooley's, 743.  
dys hæmopoietic, 731.  
erythroblastic, of Cooley, 743.  
febrile, 747.  
fish tapeworm, 735.  
hæmolytic, acute, of Lederer, 747.  
chronic (type Marchiafava-Micheli), 744.  
congenital (type Chauffard-Minkowski), 741.  
idiopathic acquired, 747.  
type Hayem-Widal, 747.  
with recurrent hæmoglobinuria, 744.  
hypochromic, familial, 743.  
idiopathic, 732.  
dysphagia in, 543.  
in acholuric jaundice, 741.  
in acute endocarditis, 887.  
in acute nephritis, 1118.  
in amebic dysentery, 276.  
in anilism, 392.  
in ankylostomiasis, 332.  
in arseniuretted hydrogen poisoning, 375, 730.  
in benzene poisoning, 388.  
in blackwater fever, 261.  
in cancer of colon, 641.  
in cancer of stomach, 590.  
in chloramphenicol therapy, 13.  
in chronic arsenical poisoning, 374.  
in chronic mercurial poisoning, 382.  
in celiac disease, 619.  
in coliform bacillus infections, 96.  
in Hodgkin's disease, 730, 790.  
in hook-worm infection, 332.  
in idiopathic steatorrhœa, 620.  
in infective granulomata, 730.  
in intestinal stenosis, 735.  
in kala-azar, 266, 730.  
in kwashiorkor, 481.  
in lead-poisoning, 367, 368, 730.  
in malaria, 251.  
in malignant disease, 730.  
in methyl chloride poisoning, 393.  
in multiple myeloma, 1185.  
in myxœdema, 497.  
in nephritis, 730.  
in nitrobenzene poisoning, 390.  
in Oroys fever, 144.  
in pellagra, 473.  
in pemphigus vulgaris, 1288.
- Anæmia** in Plummer-Vinson syndrome, 542.  
in polyarteritis nodosa, 932.  
in pregnancy, 749.  
in radiation sickness, 411, 412, 414.  
in rheumatic fever, 49, 730.  
in rheumatoid arthritis, 730, 1151.  
in rickets, 466.  
in scurvy, 462.  
in septicæmia, 31.  
in sprue, 621.  
in steatorrhœa, 735.  
in Still's disease, 1164.  
in subacute bacterial endocarditis, 887.  
in subacute combined degeneration, 1551, 1552.  
in sulphonamide therapy, 26, 730.  
in syphilis, 207, 730.  
in temporal arteritis, 933.  
in trinitrotoluene poisoning, 390.  
in typhoid, 103, 730.  
in undulant fever, 125.  
in uræmia, 1110.  
in X-ray workers, 410.  
iron deficiency of adults, 732.  
of infants, 731.  
leuco-erythroblastic, 747.  
macrocytic, nutritional, 475, 749.  
Mediterranean, 743.  
megaloblastic of infancy, 735.  
microcytic, familial, 743.  
myelophthisic, 730, 747.  
nutritional macrocytic, 475, 749.  
in pregnancy, 749.  
hæmolytic, 476.  
of infants, nutritional, 731.  
of the new-born, 745.  
of pregnancy, physiological, 749.  
of prematurity, 731.  
osteosclerotic, 747.  
papilledema in, 1386.  
pernicious, 734.  
schlorhydria in, 554, 736.  
associated with subacute combined degeneration of spinal cord, 1550, 1551, 1552, 1554.  
mental disorders in, 1643.  
of pregnancy, 475, 749.  
physiological, of pregnancy, 749.  
pseudo-leukæmic infantum, 748.  
radiotoxic, 412.  
refractory, 738.  
secondary hypochromic, 729.  
sickle-celled, 743.  
splenic, 781.  
target-cell, 743.  
tropical hæmolytic, 476.  
megaloeytic, 475.  
non-hæmolytic, 476.
- Anæmias**, deficiency dys hæmopoietic, 731.  
hæmolytic, 740.  
acquired, 744.  
hereditary, 740.  
hyperchromic, 729.  
hypochromic, 729.  
macrocytic, 729.  
megalocytic, 729.  
microcytic, 729.

- Anæmias, normocytic, 729.**  
   orthochromic, 729.  
   secondary hypochromic, 729.  
   symptomatic, 729.
- Anæsthesia in hysteria, 1671.**  
   in leprosy, 91.  
   in syringomyelia, 1546.  
   "sleeved jacket," 1546.
- Anakhre, 236.**
- Anal ulcers, 607.**
- Anamnestic reaction in typhoid, 105.**
- Anaphylactic condition in animals infested with warble larvæ, 338.**
- shock, leucocytes in, 755.**
- Anaphylactoid symptoms in arsphenamine therapy, 230.**  
   in dracontiasis, 330.
- Anaphylaxis, 4, 5.**  
   after diphtheria antitoxin, 78.  
   definition of, 4.  
   desensitisation for, 4, 5.  
   following insect bites and stings, 337.  
   in relation to asthma, 978.  
   treatment of, 5.
- Anastomatic ulcer, 671.**
- "Anchovy sauce" pus in amœbic abscess, 280, 281, 282.**
- Aneurine (vitamin B<sub>1</sub>), 457.**  
   in beriberi, 471.
- Aneurysm, 929.**  
   aortic, 859.  
     syphilis in relation to, 859.  
     treatment of, 862.  
   arterial, 929.  
   arterio-venous, 929.  
   atheroma and, 930.  
   berry, 929, 1447.  
   causes of, 929, 930.  
   cerebral, 1447.  
   cirsoid, 929.  
   congenital, 929.  
   false, 1435.  
   in relation to cerebral thrombosis and hæmorrhage, 1435.  
   in tuberculous cavities, 1019.  
   intracranial, 1447.  
   mycotic, 886, 929.  
   of abdominal aorta and branches, 859.  
   of aorta, dissecting, 930.  
     fusiform, 859, 930.  
   of heart, 345.  
   of internal carotid, 1447.  
   pressure symptoms of, 859, 860.  
   racemose, 1447.  
   rupture of, 859, 860.  
   syphilis and, 859, 929.  
   traumatic, 929.
- Angina, agranulocytic, 756.**  
   cruris, 919.  
   Heberden's, 837.  
   Ludwig's, 538.  
   membranous, 74.  
   monocytic, 305.  
   of effort, 837.  
   pectoris, 837.  
     aneurysm causing, 859.  
     diagnosis of, 839.  
     from atheroma of coronary arteries, 839.
- Angina pectoris, in aortic incompetence, 875.**  
   in aortic stenosis, 873.  
   in hypochromic idiopathic anæmia, 732.  
   in hypothyroidism, 902.  
   in myocarditis, 890.  
   in pernicious anæmia, 736.  
   in phæochromocytoma, 518.  
   in syphilitic aortitis, 859.  
   pain of, 838.  
     sites of, 837.  
   prevention of attacks, 840.  
   redux, 78.  
   syphilis in relation to, 859.  
   treatment of, 840.
- Vincent's, 537.**
- Angiocardiography, 805.**  
   in syphilitic aortitis, 860.
- Angiography, cerebral, 1390.**  
   in peripheral vascular disease, 919.
- Angiokeratoma, 1315.**
- Angioma, cerebral, 1448.**  
   serpiginosum (Hutchinson), 1260.
- Angiomyomata, 1313.**
- Angio-neurotic œdema, affecting larynx, 944.**
- Aniline derivatives causing enterogenous cyanosis, 751.**  
   poisoning, 392.
- Anilism, 392.**
- Anisocytosis, 727.**  
   in leukæmia, 759.  
   in malaria, 249.  
   in pernicious anæmia, 736.
- Ankylosing spondylitis, 1160.**
- Ankylosis of joints, fibrous, in hæmophilia 768.**  
   of the spine, 768, 1160.
- Ankylostoma braziliense, 332, 1334.**  
   caninum, 332.  
   duodenale, 332.  
   malayanum, 332.
- Ankylostomiasis, 332.**
- Anonychia, 1323.**
- Anopheline mosquitoes, 245, 247, 248.**
- Anorexia, 563.**  
   in acute catarrhal gastritis, 571.  
   in cancer of stomach, 590.  
   in digitalis overdosage, 815.  
   in pulmonary tuberculosis, 1021, 1024.  
   see *Simmonds's disease*, 487.
- nerve, 564.**  
   in hysteria, 1671.  
   pituitary disorders in, 1644.
- Anosmia, 1338, 1358, 1364.**  
   in cadmium poisoning, 387.
- Anoxæmia, 399.**  
   anoxic, 400.  
   arterial, 399.  
   mental effects of, 400.  
   passive, 400.  
   stagnant, 400.  
   tolerance to, 400.
- Antabuse in the treatment of alcoholism, 1640.**
- Anthrax, 79.**
- Antibiosis, definition of, 6.**
- Antibiotics, 6-16.**

- Antibiotics**, bacterial resistance to, acquired, 15, 16.  
in combination, 15.  
sensitivity of principal pathogens to 12.
- Antibodies** in bacterial infection, 3.
- Anticoagulant therapy** in cardiac infarction, 847.  
in cor pulmonale, 834.  
in thrombosis, 926.
- Antiformin** in the detection of tubercle bacilli, 88.
- Antihistamine drugs** in acute coryza, 149.  
in allergic rhinitis, 940.  
in infantile eczema, 1222.  
in travel sickness, 403.  
in urticaria, 1256, 1257.
- Antimony** in American dermal leishmaniasis, 268.  
in filariasis 328.  
in kala-azar, 267, 268.  
tartrate in schistosomiasis, 321.
- Antisera** of therapeutic value, 3, 4.
- Antispasmodics** in asthma, 980.  
in chronic gastric and duodenal ulcer, 582.
- Antitetanus serum**, 82, 83, 84.
- Antitoxin**, diphtheria, dosage of, 77.  
in botulism, 124.  
production of, in body 4.  
tetanus, 83, 84.
- Antitoxins**, 4  
and active immunisation, 4.  
methods of preparation, 4.
- Antivenene** against scorpion stings, 340.  
in snake poisoning, 342.
- Antrum**, maxillary, suppuration in, 940.
- Anuria**, causes of, 1102.  
in arsenuretted hydrogen poisoning, 375.  
in bacillary dysentery, 114.  
in blackwater fever, 261, 262.  
in leptospirosis icterohæmorrhagica, 240.  
in renal calculus, 1141.  
in sulphonamide therapy, 26.  
in yellow fever, 187.  
traumatic, 1128.
- Anus**, pruritus of, 1191.  
in enterobiasis, 335.
- Anxiety** in cardiac neurosis, 904.  
states, 1651, 1677.  
sexual factors in causation of, 1647.  
visceral symptoms of, 568.
- Aorta**, abdominal, and its branches, aneurysm of 859.  
ascending arch of, aneurysm of, 859.  
coarctation of, 895.  
descending arch of, aneurysm of, 860.  
dissecting aneurysm of, 930.  
over-riding, in Eisenmenger's complex, 900.  
in Fallot's tetralogy, 897.  
radiography in diseases of, 804.  
syphilis of, 858.  
transposition of, 899.  
transverse arch of, aneurysm of, 859.
- Aortic aneurysm**, 859.  
incompetence, 874.  
in coarctation of aorta, 895.  
in syphilitic aortitis, 859.  
murmur in, 875.  
stenosis, 872.
- Aortic stenosis**, calcific, heart block in, 830.  
congenital, 872, 895.  
murmur in, 873.  
pulse of, 873.  
with incompetence, 876.  
valves, bicuspid, 894.  
valvulitis, 889.
- Aortitis**, syphilitic, 858.  
radiography in, 860.
- Aperients**, abuse of, effects of, 609, 631.  
in constipation, 608.
- Aphasia**, 1367.  
anatomical considerations, 1368.  
estimation of testamentary capacity in, 1372.  
in encephalitis lethargica, 1417.  
in lesions of temporal lobes, 1360.  
jargon, 1360, 1369, 1370.  
method of examination in, 1370.  
motor, 1369, 1376.  
physiological considerations, 1369.  
pure, 1368.  
verbal, 1376.
- Aphasic attacks** in migraine, 1509.
- Aphonia**, functional, 952.  
hysterical, 1672.  
in beriberi, 469, 470.  
in laryngeal tuberculosis, 1020.  
in ordematous laryngitis, 944.
- Aptha epizootica**, 182.
- Apthous stomatitis**, 526.  
after bismuth therapy, 217.  
ulcers in sprue, 624.
- Apical infection**, 529.
- Aplastic anæmia**, 738.
- Apneumatosis**, 992.
- Apocrine epitheliomata**, 1309.
- Apoplectic chorea**, 1362, 1519.  
syndrome, the, 1449.
- Apoplexy**, causes of, 1435.  
cerebellar, 1440.  
determination of side of lesion in, 1438, 1439.  
differential diagnosis of, 1441.  
hæmorrhage as cause of, 1436, 1437.  
pontine, 1438.  
pulmonary, 989, 990.  
thrombosis as cause of, 1436, 1437.
- Appendicitis**, 653.  
acute, 654.  
catarrhal, 654.  
recurrent subacute, 658.  
tendency to recurrence in, 657.
- Appendicular concretion**, 654.
- Appendix**, abscess formation in, 654, 656, 657.  
infections of, in relation to peritoneum, 654, 656.  
perforation of, 654, 656.  
situation of, as affecting symptoms of appendicitis, 655.
- Appetite**, voracious, in exophthalmic goitre, 492.
- Apple-jelly nodules** of lupus, 1241.  
of sarcoidosis, 1246.
- Apraxia**, 1376.
- Arachnoiditis**, 1537.
- Aran-Duchenne type** of paralysis, 1594.
- Argemone poisoning**, 348.



- Argyll Robertson pupil, 1343.  
in tabes, 1462, 1464.
- Ariboflavinosis, 458
- Arrhythmia, cardiac, 819.  
sinus, 821
- Arsenic acid, uses of, 373.  
in food, 373.  
lethal dose of, 374.
- Arsenical neuritis, 374, 1590.  
poisoning, 372.  
acute, 374.  
chronic, 374.  
preparations in treatment of disseminated sclerosis, 1477.  
in pinta, 1334.  
in syphilis, 212.  
in tropical eosinophilia, 315.  
pentavalent, in treatment of syphilis, 215.  
trivalent in treatment of syphilis, 213.  
in treatment of yaws, 235.
- Arsenious sulphide, 373.
- Arseniuretted hydrogen, 373.  
poisoning by, 375.
- Arsine poisoning, 376.
- Arsphenamine preparations, 213.  
administration of, 214.  
contra-indications to, 215.  
dosage of, 214.  
effect of, on liver, 231, 232.  
in rat-bite fever, 245.  
in relapsing fever, 244.  
in syphilis, 213.  
jaundice following use of, 231, 232.  
precautions necessary in use of, 215.  
toxic effects of, 229.
- Arterial blood-pressure, 907.  
degeneration, 906.  
*degenerations allied to atheroma*, 919.  
disease, classification of, 906.  
high blood-pressure in, 909.  
embolism, 925.  
spasm in electrical injuries, 404.  
thrombosis, 925, 1435, 1443.  
cerebral syphilitic, 1435.
- Arteries, diseases of the, 906.  
pipe stem in atheroma, 836.  
pulmonary. *See* Pulmonary artery.  
silver-wire, 910.
- Arteriolar resistance, 1109.
- Arteriosclerosis, peripheral, 919.
- Arterio-venous aneurysm, 929.
- Arteritis of aorta, syphilitic, 858.  
temporal, 932.
- Artery of hæmorrhage, the, 1437.
- Arthritis (and pseudo-arthritis), 1150-1165.  
acute suppurative, 1155.  
atrophic, 1150.  
deformans, 1157.  
dysenteric, 1156.  
from focal sepsis, 1150, 1153.  
gonococcal, 67, 1154.  
differentiated from rheumatic fever, 52.  
gouty, 444.  
hypertrophic, 1157.  
in abacterial urethritis, 311.  
in acute specific fevers, 1155.  
in bacillary dysentery, 116.
- Arthritis (and pseudo-arthritis) in burns, 1155.  
in cerebrospinal fever, 59, 64.  
in dengue, 190.  
in furunculosis, 1155.  
in gonorrhœa, 67.  
in hæmophilia, 768.  
in infected varicosities, 1155.  
in measles, 152.  
in meningitis, 1155.  
in mumps, 176.  
in osteomyelitis, 1155.  
in pneumonia, 1053, 1155.  
in purpura, 774.  
in pyelitis, 1155.  
in rheumatic fever, 48.  
in children, 51.  
in scarlet fever, 43, 1155.  
in septic endocarditis, 1155.  
in small-pox, 164.  
in tonsillitis, 1155.  
in typhoid and paratyphoid fevers, 105, 1155.  
in ulcerative colitis, 1156.  
in undulant fever, 1156.  
infective, 1154.  
meningococcal, 1155.  
menopausal, 1159, 1166.  
"mixed," 1150.  
of the spine, 1160.  
pneumococcal, 1155.  
pseudo-, 1165.  
rheumatoid, 1150.  
blood sedimentation rate in, 1151.  
diet in, 1152.  
focal sepsis in, 1150, 1153.  
in children, 1163.  
order of infection of joints in, 1151.  
pregnancy in relation to, 1151.  
suppurative, acute, 1155.  
tuberculous, 1156.  
types of, 1150.  
vertebral, 1160.
- Arthroplasty in osteo-arthritis, 1160.
- Arthropods, injurious, diseases due to, 336-340.
- Artificial respiration in carbon monoxide poisoning, 360.  
in electrical injuries, 406.  
respirators, 1432, 1433.
- Asbestos bodies, 1012.
- Asbestosis, 1012.
- Ascariasis, 334.
- Ascaris lumbricoides, 334.
- Ascending paralysis, acute, 1594.
- Aschoff's nodes in rheumatic fever, 48.
- Ascites, 721.  
causes of, 723.  
chylous, 686, 787, 928.  
in cancer of liver, 686.  
in cirrhosis of liver, 677.  
in cancer of gall-bladder, 699.  
in cancer of liver, 685, 686.  
in chronic peritonitis, 717, 882.  
in cirrhosis of liver, 677.  
in congestion of liver, 666.  
in heart failure, 811.  
in malignant peritonitis, 721.

Ascites in myeloid leukaemia, 759.  
in portal thrombosis, 688.  
in tuberculous peritonitis, 719.  
Ascorbic acid (Vitamin C), 461  
in corliac disease, 620.  
in scurvy, 463, 464.  
in Vincent's angina, 538.  
Ashkabad sore, 268.  
Aspergillosis, 196.  
pulmonary, 1039.  
Aspergillus fumigatus, 196, 1039.  
nidulans, 1039.  
Aspirin, idiosyncrasy to, 569.  
Assmann's focus, 1018.  
Astereognosis in lesions of parietal lobe, 1359.  
in subacute combined degeneration, 1552.  
Asthenia, neurocirculatory, 904.  
Asthenic habitus in schizophrenia, 1657.  
Asthma, 977-982.  
adenoids in relation to, 977.  
after influenza, 180.  
allergic, 978.  
anaphylaxis in relation to, 972.  
aura in, 978.  
bronchial, 979.  
in polyarteritis nodosa, 931.  
cardiac, 979.  
in mitral stenosis, 866.  
coal miners', 1012.  
cotton card room, 1015.  
emphysema in relation to, 980.  
grinders', 1015.  
hay, 979.  
-hay fever-prurigo syndrome, 1195.  
ovarian disturbance in, 978.  
pseudo, in hypoparathyroidism, 504.  
renal, 979, 1111.  
strippers', 1015.  
tropical eosinophilic, 313.  
uræmic, 979.  
week-end, 978.  
Asthmatic aura, 978.  
paroxysm, 978  
Astrocytoma, 1381.  
Ataxia, cerebellar, 1363.  
congenital cerebellar, 1488.  
Friedreich's, 1479.  
hereditary, 1479.  
in barbiturate poisoning, 360.  
in carbon monoxide poisoning, 359.  
in cerebellar apoplexy, 1440.  
in cerebral diplegia, 1488.  
in diphtheritic neuritis, 1591.  
in methyl mercury poisoning, 383.  
in tabes, 1462, 1463.  
treatment of, 1467.  
intrapsychic, 1659.  
locomotor, 1461.  
sensory, 1591.  
spastic, in cerebrospinal fever, 59.  
Ataxic dysarthria, 1373.  
Atelectasis, 992.  
Atheroma, 919.  
generalised cerebral, 1443.  
in diabetes mellitus, 902.  
in relation to cerebral thrombosis and hæmorrhage, 1435.

Atheroma of coronary arteries, 834, 835.  
Atheromatous plaques, 909.  
Athetosis, congenital bilateral, 1488.  
in lesion of optic thalamus, 1361.  
in pellagra, 474.  
Athlete's foot, 1236.  
Atmospheric pressure, effects of increased, 396.  
Atomic warfare, injuries due to, 413.  
Atrial septal defect, 896.  
Atrophoderma neuriticum, 1295.  
reticulatum, 1295.  
Atrophy, insulin fat, 431.  
muscular, in leprosy, 91.  
of cerebellum, delayed, 1481.  
of liver, acute yellow, 671.  
of skin, 1295.  
peroneal, muscular, 1563.  
progressive muscular, 1554.  
progressive spinal muscular, of children, 1565.  
tonic, in progressive muscular atrophy, 1557.  
Atropine as antidote in insecticide poisoning, 380.  
in ergotism, 345.  
in gastric hypersecretion, 582.  
poisoning, 352.  
Auchmeromyia luteola, 339.  
Auditory and vestibular nerves, affections of, 1351.  
Auditory nerve tumours, 1382.  
word centre, 1367.  
Aura, asthmatic, 978.  
hallucinations associated with, 1498.  
sensory, of migraine, 1510.  
the epileptic, 1495, 1498.  
Aureomycin. See Chlortetracycline.  
Auricles, radiographic appearances in diseases of the, 804.  
Auricular fibrillation, 826.  
electrocardiogram of, 827.  
in Graves's disease, 492.  
in mitral stenosis, 868.  
in thyrotoxic conditions, 901.  
value of digitalis in, 827, 828.  
flutter, 825.  
electrocardiogram of, 825.  
jugular pulse in, 825.  
value of digitalis in, 826.  
Auricular paroxysmal tachycardia, 823.  
septal defect, 896.  
bundle branch block in, 833.  
Auriculo-ventricular block, 829.  
dissociation, complete, 830.  
node, 793.  
Aurothioglucose in relapsing fever, 244.  
Auscultation in heart disease, technique of, 796.  
Austin Flint murmur, 859, 876.  
Automatism, post-epileptic, 1500.  
Avellis, syndrome of, 951.  
Aviators, decompression sickness of, 396.  
Axonmesis, 1567.  
Ayerza's disease, 750.  
Babinski-Frölich's syndrome, 488.  
Bacillary dysentery, 112.

- Bacille Calmette-Guérin (B.C.-G.),** 89.  
     *in tuberculosis,* 1031.  
**Bacilluria, coliform,** 96.  
     *typhoid,* 99, 104.  
**Bacillus abortus,** 125, 126.  
**acidophilus in chronic colitis,** 634.  
     *in diarrhoea,* 614.  
**aertrycke,** 120.  
**anthracis,** 79.  
     *meningitis due to,* 1393.  
     *sensitivity to penicillin,* 7.  
**bottle,** 1216.  
**Boyd's,** 113.  
**brevis,** 6.  
**coli.** *See Bacterium coli.*  
**dysenteriae, in bacillary dysentery,** 113.  
     *types of,* 113.  
**Flexner's,** 112.  
**of Friedländer in acute tracheitis,** 954.  
     *in bronchitis,* 963.  
**Hofmann's,** 69.  
**influenzae.** *See Haemophilus influenzae.*  
**Klebs-Löffler,** 67, 68.  
     *in measles,* 152.  
**Morgan's,** 113.  
**of smegma, distinguished from tubercle bacillus,** 88.  
**Pfeiffer's,** 179, 963.  
     *in acute tracheitis,* 954.  
     *in relation to influenza,* 179.  
     *meningitis due to,* 1393.  
**proteus,** 1133.  
     *relationship of rickettsias to,* 285, 287.  
**pseudo-diphtheria,** 69.  
**Shiga's,** 112, 113.  
**Sonne's,** 113.  
**tuberculosis.** *See Mycobacterium tuberculosis.*  
**Bacitracin,** 15.  
**Backache in dengue,** 190.  
     *in small-pox,* 160, 167.  
     *in trench fever,* 301.  
     *in typhus,* 296.  
     *toxic,* 30.  
**Bacteria, action of penicillin on,** 6.  
     *contaminating food,* 119, 120.  
     *non-pathogenic,* 1.  
     *pathogenic,* 1.  
     *role of leucocytes in destruction of,* 752.  
     *saprophytic,* 1.  
     *susceptibility to penicillin,* 7.  
**Bacteræmia,** 3, 30.  
**Bacterial activity, effects of, 1, 2, 3.**  
     *food-poisoning,* 119.  
     *infection,* 1, 2.  
**Bacteriolysin,** 3.  
**Bacterium coli group of organisms,** 94.  
     *in acute intestinal obstruction,* 651.  
     *in acute necrosis of pancreas,* 702.  
     *in appendicitis,* 95, 654.  
     *in the bladder,* 95.  
     *in the bowel,* 94.  
     *in bronchial tract,* 97.  
     *in cholecystitis,* 95, 689, 693.  
     *in cholelithiasis,* 95.  
     *in colitis,* 94.  
     *in cystitis,* 95.  
     *in diverticulitis,* 95.  
**Bacterium coli in gall-bladder sepsis,** 95.  
     *in intestinal intoxication,* 94.  
     *in lung abscess,* 1002.  
     *in middle ear,* 97.  
     *in pericolic suppuration,* 95.  
     *in peritonitis,* 95, 712.  
     *in pleura,* 97.  
     *in puerperal sepsis,* 96.  
     *in pyelitis,* 1133.  
     *in sinus thrombosis,* 1452.  
     *in urine,* 95.  
     *infection of urinary tract,* 95.  
         *of uterus and tubes,* 96.  
     *infections,* 94.  
         *treatment,* 97.  
     *modes of infection by,* 94.  
     *resistance to penicillin,* 7, 8.  
     *septicæmia,* 97.  
     *tularensis.* *See Brucella tularensis.*  
**Bacteriuria,** 1134.  
**Bagassosis,** 1016.  
**Baghdad button,** 268.  
**BAL.** *See Dimercaprol.*  
**Balanitis circinata,** 312.  
**Balantidium coli,** 283.  
**Baldness,** 1317.  
**Bamberger-Marie's disease,** 1171.  
**Bands, adventitious, in intestinal obstruction,** 649.  
**Banti's syndrome,** 781.  
**Barany's caloric test for vestibular lesions,** 1352.  
**Barber's rash,** 1227.  
**Barbers,** 468.  
**Barbitone, addiction to,** 1641.  
**Barbiturate poisoning,** 360.  
**Barbiturates, addiction to,** 1641.  
     *idiosyncrasy to,* 362.  
     *in affective disorder,* 1655.  
**Baritosis,** 1014.  
**Barium pneumoconiosis,** 1014.  
**Barlow's disease,** 463.  
**Barraquer-Simmons' disease,** 451.  
**Barrel chest,** 999.  
**Bartholinitis in gonorrhoea,** 67.  
**Bartonella bacilliformis,** 144, 145.  
**Bartonellosis,** 144.  
     *generalised,* 144.  
     *localised,* 145.  
**Basal ganglia in encephalitis lethargica,** 1416.  
     *localisation of lesions of,* 1361.  
     *metabolism,* 415.  
**Basedow's disease,** 491.  
**Basophilia,** 755.  
     *diffuse,* 729.  
     *punctate,* 729.  
**Bats as transmitters of rabies,** 1421.  
**Bazin's disease,** 1244, 1261.  
**B.C.-G. vaccine,** 89, 1031.  
**Beau's lines,** 1323.  
**Bee-stings,** 337.  
**Beef worm, the,** 338.  
**Beet tongue in pellagra,** 473.  
**Behcet's syndrome,** 1326.  
**Bejel,** 233.  
**Bell's palsy,** 1349.  
**Bence Jones proteinuria,** 1103, 1185.  
**"Bends," the, in caisson disease,** 397.

- Benedikt's syndrome, 1342, 1362.  
 Benethamine in syphilis, 219.  
 Benzene poisoning, 388.  
 Benzhexol in paralysis agitans, 1514.  
   in travel sickness, 403.  
 Benzidine test for occult blood, 604.  
 Benzyl benzoate in pediculosis, 1253, 1254.  
   in scabies, 1252.  
   penicillin in syphilis, 218.  
 Beryberi, 468.  
   acute fulminating, 469.  
   associated deficiency diseases, 470.  
   chronic, 470.  
   heart in, 470, 903.  
   infantile, 470.  
   larval or ambulatory, 469.  
   pellagrous, 470.  
   secondary, 470.  
   ship's, 470.  
   subacute, 469.  
   wet and dry forms of, 468, 469, 470.  
 Bernheim's syndrome, 810, 874.  
 Bertiella satyri, 322.  
 Beryllium, poisoning by, 385.  
 Besnier's prurigo, 1195.  
 Betanaphthol in distomiasis, 317, 318.  
 Bête rouge, 336.  
 Bile, method of obtaining, for analysis, 692.  
 Bile-duct, common, obstruction of, results of, 661, 702.  
 Bile-ducts, cancer of the, 700.  
   congenital obliteration of the, 699.  
   diseases of, 689.  
   obstruction of, in relation to jaundice, 661, 662.  
 Bile-pigment stones, 695.  
 Bile-pigments in blood, 661.  
   in urine, 1104, 1105.  
 Bilharzia hæmatobia, 319.  
 Bilharziasis, 319.  
 Biliary calculi, 694.  
   cirrhosis, 679.  
   colic, 698.  
   without gall-stones, 698.  
   crises, 698.  
   dyskinesia, 698.  
   stasis in relation to gall-stones, 694.  
 Bilious attacks, 1508.  
   remittent fever, 242, 251.  
 Bilirubin in blood, Van den Bergh test for, 659.  
   in urine, 662.  
 Bilirubinuria, 1104.  
 Binet and Simon tests of intelligence, 1686.  
 Biotin, 459.  
 Biotropism, 1255.  
 Birth injuries and idiocy, 1683, 1684.  
 Biskra button, 268.  
 Bismuth preparations in treatment of syphilis, 217.  
   choice of, 218.  
   combined with arsphenamine, 217.  
   in treatment of yaws, 235.  
   toxic effects of, 217.  
 Black death, 127.  
   fever, 264.  
   vomit in yellow fever, 185, 187.  
 Blackheads, 1282.  
 Blackwater fever, 260.  
   quinine in relation to, 256, 257, 261.  
 Bladder, disturbances of, and spinal cord lesions, 1531.  
   lesions in schistosomiasis, 319.  
   symptoms in appendicitis, 655.  
   in diverticulitis, 644.  
   in tabes, 1462.  
   treatment of, 1468.  
 Blanching test in scarlet fever, 38, 44.  
 Blastomyces brasiliensis, 199.  
   dermatitidis, 198.  
   infecting lungs, 1039.  
 Blastomycosis, 1039, 1239.  
   European, 197.  
   North American, 198.  
   South American, 199.  
 Bleeding tendencies, hereditary, 767.  
 Blepharospasm in hysteria, 1672.  
 Blighia sapida, 350.  
 Blindness after small-pox, 164.  
   and retrobulbar neuritis, 1339.  
   hystenical, 1672.  
   in congenital syphilis, 226.  
   in hydrocephalus in children, 1402.  
   in hypoparathyroidism, 504.  
   in intracranial tumour, 1388, 1390.  
   in leprosy, 91.  
   in neuromyelitis optica, 1478.  
   in onchocerciasis, 329.  
   in post-basic meningitis of infants, 59.  
   in Schilder's disease, 1412.  
   in Tay-Sachs disease, 1483.  
 Blood alcohol in alcoholic intoxication, 353, 354.  
   cells, immaturity of, in the leukæmias, 758.  
   red, 726.  
   formation and development of, 729.  
   fragility of, 661, 741.  
   nomenclature of, 729.  
   nucleated, in leukæmia, 759.  
   number of, 726.  
   stippling of, in plumbism, 366, 367.  
   substances necessary for development of, 731.  
   white, 752.  
 coagulation, 765.  
   disturbances of, 767.  
 constituent elements of the, 725, 726, 752-755.  
 diseases of the, 725-776.  
   classification of, 729.  
   dyscrasias after arsphenamine, 230, 232.  
   effects of radium on, 412.  
   factor, Christmas, 766, 767.  
   factors V and VII, 765, 766.  
   groups, 727, 728, 729.  
   Landsteiner classification of, 727.  
   hydrogen-ion concentration of, 418, 419, 420.  
   in anæmia pseudo-leukæmica infantum, 748.  
   in alcoholic jaundice, 741.  
   in acute anterior poliomyelitis, 1426.  
   in acute leukæmia, 763.  
   in agranulocytosis, 756.  
   in ankylostomiasis, 332.  
   in splastic anæmia, 739.

- Blood in arseniuretted hydrogen poisoning,** 375.  
 in Banti's syndrome, 782.  
 in benzene poisoning, 389.  
 in blackwater fever, 261, 262.  
 in cancer of stomach, 590.  
 in carbon monoxide poisoning, 358.  
 in carbon tetrachloride poisoning, 394.  
 in cerebrospinal fever, 57.  
 in cholera, 134.  
 in chronic lymphatic leukaemia, 761.  
 in chronic myeloid leukaemia, 759.  
 in diphtheria, 72.  
 in erythroblastosis foetalis, 746.  
 in essential thrombocytopenia, 772.  
 in glandular fever, 306.  
 in gout, 445.  
 in Hodgkin's disease, 790.  
 in hyperparathyroidism, 502.  
 in hypochromic anaemia, 733.  
 in idiopathic steatorrhoea, 621.  
 thrombocytopenic purpura, 772.  
 in jaundice, 662.  
 in kala-azar, 266.  
 in lead poisoning, 366, 367.  
 in leukaemia, 759, 761, 763.  
 in lobar pneumonia, 1051.  
 in malaria, 248, 254.  
 in measles, 151.  
 in Mediterranean anaemia, 743.  
 in myxoedema, 497.  
 in nitrobenzene poisoning, 390.  
 in nutritional macrocytic anaemia, 476.  
 in Oroya fever, 145, 744.  
 in pellagra, 473.  
 in perinephritis, 1138.  
 in pernicious anaemia, 736.  
 in pleurisy, 1073.  
 in polycythemia, 750.  
 in pulmonary tuberculosis, 1023.  
 in relapsing fever, 242, 243.  
 in rheumatic fever, 49.  
 in rickets, 466.  
 in Rocky Mountain tick typhus, 294.  
 in rubella, 157.  
 in scarlet fever, 40.  
 in septicemia, 31.  
 in sickle-celled anaemia, 743.  
 in sleeping sickness, 272.  
 in small-pox, 160.  
 in subacute combined degeneration, 1551, 1552.  
 in tropical eosinophilia, 314, 315.  
 in tropical sprue, 624.  
 in typhoid, 102.  
 in undulant fever, 126.  
 in urine, 1104.  
 in virus pneumonia, 1057.  
 in whooping-cough, 139.  
 in yellow fever, 186.  
 occult, recognition of, in stools, 603.  
 plasma, 725.  
 platelets, 765.  
 in acute leukaemia, 763.  
 in essential thrombocytopenia, 772.  
 in purpura, 770.  
**Blood pressure, arterial,** 907.  
 in Addison's disease, 508.  
**Blood pressure, in aortic stenosis,** 873.  
 in cholera, 135.  
 in coarctation of aorta, 895.  
 in diphtheria, 71, 72.  
 in hypotension, 916, 917.  
 in intracranial tumour, 1388.  
 in malignant hypertension, 915.  
 in mitral stenosis, 864.  
 in paratyphoid fever, 111.  
 in pulmonary tuberculosis, 1023, 1030.  
 in relation to cerebral thrombosis and hæmorrhage, 1436.  
 to treatment of apoplexy, 1442.  
 in typhoid, 103.  
 in yellow fever, 186.  
**high,** in angina pectoris, 838.  
 in myxoedema, 496.  
 in nephritis, 1116, 1121.  
 in relation to epistaxis, 938.  
**low,** during epileptic attack, 1495, 1499.  
 in Addison's disease, 508.  
 in blackwater fever, 262.  
 in diabetic coma, 440.  
 in kala-azar, 266.  
 in typhus, 291, 298.  
**normal,** 794, 907.  
 physiological variations in, 907.  
**Blood sedimentation rate in diarrhoea,** 613.  
 in disseminated lupus erythematosus, 934.  
 in leprosy, 92.  
 in rheumatoid arthritis, 1151.  
 in spondylitis, 1161.  
 in tuberculosis, 1027, 1031.  
**Blood-storage, function of spleen in,** 778.  
**-sugar, in diabetes mellitus,** 423, 424, 425, 426.  
 in hyperinsulinism, 443.  
 lag or steep curves, 426.  
 normal limits, 424.  
**-urea clearance test of renal capacity,** 1100.  
**-vessels, cerebral tumours of,** 1382.  
 diseases of, 906-930.  
 radiography in, 803.  
**Blood, viscosity of, in cholera,** 134.  
 in polycythemia, 751.  
**Blood-volume,** 725.  
**Blue line after bismuth therapy,** 217.  
 on gums in lead poisoning, 363, 368.  
 in mercurial poisoning, 382.  
**Bockhart's impetigo,** 1229.  
**Boeck's sarcoidosis,** 1246.  
**Boils,** 1229.  
 in diabetes, 1229.  
 in small-pox, 164.  
 in typhoid, 104.  
 treatment of, 1230.  
**Bone, aneurysmal pressure on,** 859.  
 carcinomatosis of, as cause of leucoerythroblastic anaemia, 748.  
 diseases of, 1171-1184.  
 echinococcosis of, 324.  
 excrescences in goundou, 236.  
 necrosis of, in scarlet fever, 42.  
 sarcoidosis of, 1246.  
**Bone lesions in acromegaly,** 484.  
 in congenital syphilis, 226.

- Bone lesions in cretinism**, 498.  
in Cushing's syndrome, 517.  
in erythroblastic anaemia of Cooley, 743.  
in goundou, 236.  
in gout, 446.  
in Graves's disease, 493.  
in hyperparathyroidism, 501, 502.  
in idiopathic steatorrhoea, 621.  
in infantile scurvy, 463, 464.  
in leprosy, 91.  
in rickets, 465, 466.  
in sarcoidosis, 1246.  
in scurvy, 462.  
in syphilis, 203, 209.  
in typhoid, 104.  
in uraemia, 1111.  
in yaws, 234.
- Bone-marrow, aplasia of**, 738.  
degeneration of, in chloramphenicol therapy, 13.  
in pernicious anaemia, 734.  
diseases of, 1184.
- hyperplasia of**, in acholuric jaundice, 741.  
in haemorrhage, 730.  
in agranulocytosis, 756.  
in benzene poisoning, 389.  
in chronic myeloid leukaemia, 758.  
in essential thrombocytopenia, 772.  
in Gaucher's disease, 785.  
in hyperparathyroidism, 501.  
in kala-azar, 265.  
in leukaemia, 758, 764.  
in malaria, 249.  
in Niemann-Pick's disease, 785.  
in nutritional macrocytic anaemia, 475.  
in pernicious anaemia, 735.  
in polycythaemia, 750.  
in relation to red blood cell formation, 729.  
lesions of, in relation to anaemia, 730.  
necrosis of, in small-pox, 160.  
poisons acting on, 738.  
typhoid bacilli in, 105.
- Bones, action of radium on**, 412.  
disease of the, 1171-1187.
- Borborogmi, cause of**, 630.
- Bordet and Gengou, bacillus vaccine in**  
whooping-cough, 142.
- Bornholm disease**, 193, 1166.
- Bosch yaws**, 268.
- Bottle bacillus**, 1216.
- Botulism**, 123.
- Bouton diaphragmatique of Guéneau de**  
Mussy, 1066.
- Bouton d'Orient**, 268.
- Bovine tuberculosis**, 85, 1017.
- Bowen's disease**, 1306.
- Bow-leg in rickets**, 466.
- Box head in rickets**, 466.
- Brachial neuritis**, 1166, 1577.  
plexus, anatomy and physiology of, 1568.  
birth injury to, 1585.  
lesions of, 1568.  
paralysis, 1568.
- Bracht-Wächter bodies**, 885.
- Bradycardia in dengue**, 190.  
in diphtheria, 73.  
in heart block, 831.  
in myxoedema, 496, 902.
- Bradycardia in overdosage of digitalis**, 815.  
in phlebotomus fever, 189.  
in Stokes-Adams syndrome, 831.  
in yellow fever, 186.  
sinus, 820.
- Brain, abscess of**, 1405.  
actinomycosis of, 195.  
cysts of, 1383.  
disease, degenerative and hereditary, 1627.  
gumma of, 1460.  
hydatid cysts of, 1384.  
in chronic alcoholism, 355.  
signs of local lesions of, 1357-1366.
- Brain-stones**, 1384.  
tumours of, 1380-1391.
- Braunia jassyensis**, 322.
- Break-bone fever**, 189.
- Bright's disease**, 1114.
- Brill's disease**, 296.
- Brissaud's syndrome**, 485.
- Broca's centre and speech**, 1367.
- Bromethol (Avertin) poisoning**, delayed,  
causing hepatic necrosis, 670.
- Bromide intoxication**, 1641.
- Bromidrosis**, 1198.
- Bromsulphthalein test of liver function**, 660.
- Bronchi, adenoma of**, 972.  
cicatrical stenosis of the, 976.  
diseases of the, 963-986.  
foreign bodies in the, 974.  
gummata of, 973.  
infective granulomata of the, 973.  
injuries to, 986.  
leprosy of the, 973.  
obstruction of, by external causes, 977.  
syphilis of the, 973.  
tuberculosis of the, 973.  
tumours of the, 972.
- Bronchial casts**, 968.
- catarrh**, 963.  
in rickets, 466.  
spasm in relation to asthma, 978.  
stenosis and obstruction, 974.
- Bronchiectasis**, 982.  
aneurysm formation in, 983.  
cerebral abscess in, 985.  
congenital, 983.  
cylindrical, 983.  
following bronchial stenosis, 974, 976.  
in pulmonary fibrosis, 1007.  
saccular, 983.
- Bronchiolectasis**, 983.
- Bronchiolitis fibrosa obliterans**, 967.  
in influenza, 179.  
in measles, 152.  
in typhus, 298.
- Bronchitis**, 963-972.  
acute catarrhal, 963.  
fibrinous, 967.  
plastic, 967.  
purulent, 965.  
suppurative, 965.  
adenoids in relation to, 942.  
bacteriology of, 963, 965, 966.  
capillary, 965, 1059.  
in whooping-cough, 140.  
chronic, 969.  
catarrhal, 969.

- Bronchitis, chronic, fibrinous, 972.**  
     secondary, 972.  
     suppurative, 971.  
     classification of, 963.  
     fetid, 971.  
     from mechanical and chemical agencies, 967, 972.  
     hæmoptoic, 1023.  
     in beryllium poisoning, 386.  
     in measles, 152.  
     in neoplasms of the lung, 1042.  
     in paratyphoid fever, 111.  
     in small-pox, 164.  
     in typhoid, 103.  
     in whooping-cough, 139, 140.  
     secondary, 967.
- Bronchiolitis as cause of bronchial obstruction, 974.**
- Bronchophony in pulmonary tuberculosis, 1025.**
- Broncho-pneumonia, 1059.**  
     aspiration, in scarlet fever, 43.  
     in diphtheria, 70, 71, 74.  
     in measles, 150, 152.  
     in paratyphoid fever, 111.  
     in plague, 128.  
     in rickets, 466.  
     in scarlet fever, 43.  
     in small-pox, 164.  
     in typhus, 298.  
     in undulant fever, 126.  
     in whooping-cough, 140.  
     inhalation and deglutition, 1061.  
     pneumococcus in relation to, 1059.  
     primary, 1058.  
     secondary, 1059.
- Bronzed diabetes, 680.**
- Brooke's disease, 1309.**
- Brown-Séquard syndrome, 1529.**
- Brucella abortus, 125, 126.**  
     as cause of undulant fever, 125, 126.  
     melitensis, 125.  
     resistance to penicillin, 7.  
     sensitivity to streptomycin, 10.  
     tularensis, 130.
- Brucellosis, 125.**
- Bruit d'airain, in pneumothorax, 1082.**  
     in tuberculous cavity, 1025.
- de cornage in suppurative mediastinitis, 1090.**
- de drapeau, 968.**
- de grelottement, 960.**
- de pot fêté, 1025.**
- systolic, in intracranial aneurysm, 1448.**
- Brushburn, electrical, 404, 405.**
- Bubas, 233.**  
     braziliانا, 268.
- Bubo, climatic, 191.**  
     indolent, 204.  
     of chancroid, 143.  
     of plague, the, 127, 128.  
     syphilitic, 204.  
     tropical, 191.
- Bubonic plague, 128.**
- Buerger's disease, 921.**
- Bulbar paralysis, dysphagia in, 542.**  
     in encephalitis lethargica, 1416  
     progressive, 1554.
- Bulldog facies in congenital syphilis, 227.**  
     jaw in congenital syphilis, 227.
- Bull-neck in diphtheria, 70.**
- Bundle branch block, 833.**
- Burnet's intradermal test for undulant fever, 126.**
- Burns, acute nephritis in relation to, 1115.**  
     arthritis following, 1155.  
     in lightning stroke, 404, 405, 406.  
     scarlet fever following, 41.
- Bursæ, syphilitic affections of, 207.**
- Bursitis, 1167.**
- Byssinosis, 1015.**
- Cachexia in Addison's disease, 508.**  
     in cancer of stomach, 591.  
     in chronic mercurial poisoning, 382.  
     in kala-azar, 266.  
     in Simmonds's disease, 487.  
     in subacute bacterial endocarditis, 887.  
     in tropical eosinophilia, 314.  
     light-headedness due to, 1642.  
     malarial, 253.  
     pituitary, 487.
- Cadmium, poisoning by, 387.**
- Cæcum, hyperplastic tuberculosis of, 639.**
- Caisson disease, 395.**
- Calabar swellings in loa loa, 329.**
- Calciferol (vitamin D<sub>2</sub>), 455.**  
     in treatment of lupus, 1242.  
     of osteitis deformans, 1174.  
     of osteomalacia, 1178.  
     of sarcoidosis, 1246.  
     of tetany, 505.
- Calcification, faulty in rickets, 465.**  
     of mesenteric glands, 719.
- Calcinosis cutis, 1300.**
- renal, 618.**
- Calcium balance, negative, in Graves's disease, 493.**  
     caseinate in osteitis deformans, 1174.  
     content of bone in rickets, 465.  
     deposits in hyperparathyroidism, 501.  
     gluconate in acute tetany, 505.  
     in carbon tetrachloride poisoning, 394.  
     in spider bites, 339.  
     in perniosis, 1206.  
     in relation to blood coagulation, 765.  
     to lead poisoning, 365, 370.  
     in sprue, 622.
- lactate in osteitis deformans, 1174.**  
     in oxalic acid poisoning, 363.
- metabolism in idiopathic steatorrhœa, 620.**  
     in relation to fatty and soap diarrhœa, 613  
     parathyroids in relation to, 502.
- oxalate crystals in urine, 1099.**
- of serum deficient in hypoparathyroidism, 504.**  
     salts, in relation to tetany, 503, 505.  
     in treatment of lead colic, 364.
- versenate in acute lead poisoning, 364**  
     to accelerate elimination of lead, 371
- Calculi, biliary, 694.**  
     pancreatic, 704, 707.  
     pulmonary, 1021.  
     renal, 1140.
- California disease, 200.**
- Callosities, 1297.**

- Calomel, 381.  
 Camp fever, 295.  
 Campbell de Morgan spots, 1315.  
 Cancer as cause of intestinal obstruction, 641, 649.  
   as a cause of jaundice, 662.  
   as a sequel of gall-stones, 697.  
   as a sequel of schistosomiasis, 320.  
   en cuirasse, 1305.  
   intestinal, sites of, 640.  
   lupus, in relation to, 1241.  
   of bile-ducts, 700.  
   of brain, secondary, 1382.  
   of colon, 640.  
   of gall-bladder, 699.  
   of liver, 685.  
   of lung, 1041.  
   of mediastinum, 1094.  
   of œsophagus, 551.  
   of pancreas, 708.  
   of peritoneum, 720.  
   of stomach, 589.  
     hæmatemesis in, 569, 591.  
     resulting from X-ray injury, 410.  
     treatment of, 411.  
 Cancerum oris, 527.  
   in kala-azar, 266.  
 Candida albicans, 527.  
   not affected by antibiotics, 16.  
 Canites, 1317.  
   unguim, 1323.  
 Capillaries, fragility of, 776.  
   toxic effects of arspenamine remedies on, 229.  
 Capillaroses, toxic, 1259.  
 Capillary bronchitis, 965, 1059.  
   permeability in scurvy, 462.  
   pulsation in Graves's disease, 492.  
   toxicosis, hæmorrhagic, 774.  
 Capsular hæmorrhages, 1437.  
 Capsulitis, proliferative, 1116.  
 Carate, 1333.  
 Carapata fever, 243.  
 Carbarson in amœbic dysentery, 278.  
 Carbohydrate dyspepsia, intestinal, 629.  
   causing spastic constipation, 605.  
   digestive ferments in relation to, 629.  
   enterococci in, 630.  
   in idiopathic steatorrhœa, 620.  
   excess in relation to spontaneous hypo-  
     glycemia, 443.  
   metabolism, in pancreatic disease, 702.  
 Carbomycin, 14.  
 Carbon dioxide, accumulation of, in in-  
   testine, 630.  
   as respiratory stimulant, 360.  
   snow in Bowen's disease, 1306.  
   in chronic discoid lupus erythematosus,  
     1263.  
   in warts, 1302.  
 disulphide poisoning, delirium in, 1642.  
 monoxide, 357.  
   action of, 358.  
   poisoning, 357.  
     mental disorder in, 1642.  
 tetrachloride as liver poison, 670.  
   in ankylostomiasis, 333.  
   in ascariasis, 334.  
 Carbon tetrachloride in distomiasis, 316,  
   317, 318.  
   in hook-worm infection, 333.  
   in tæniasis, 323.  
   poisoning, 394.  
 Carbuncle, 1229.  
   in plague, 128.  
   treatment of, 1230.  
 Carcinoma. *See under* Cancer.  
   basal cell, 1303.  
   erysipelatoides, 1305.  
   squamous cell, 1305.  
 Cardia, achalasia of, 543.  
 Cardiac. *See also under* Heart.  
   arrhythmia, 819.  
   asthma, 809.  
   catheterisation, 806.  
   cells in hyperæmia and œdema of lungs,  
     988.  
   cirrhosis, 811.  
   cycle, the, 793.  
   failure, 807.  
   infarction, 836, 842.  
     electrocardiographic appearances in, 802.  
   irregularity, 796.  
   kidney, 1108.  
   murmurs, 796, 797.  
   neurosis, 904.  
   output, 793, 806.  
   pain, 794.  
   tamponade, 879.  
 Cardiacos negros, 750.  
 Cardioliplip in complement fixation tests for  
   syphilis, 205.  
 Cardiomegaly, familial, 892.  
 Cardiospasm, 543.  
 Cardio-vascular system, diseases of the,  
   793-937.  
   examination of, 795.  
 Caries, dental, 528.  
   spinal, tuberculous, 1538.  
 Caronamide, prolongation of action of peni-  
   cillin by, 9.  
 Carotene and vitamin A, 454.  
 Carotid artery, internal, aneurysms of, 1447.  
   sinus, massage of, 824.  
   sinus syndrome, 818.  
 Carpal tunnel syndrome, 1572.  
 Carphology, 1497.  
 Carpo-pedal spasm, 504.  
   in idiopathic steatorrhœa, 621.  
 Carriers, amœbic dysentery, 275.  
   bacillary dysentery, 112, 117.  
   bacterial, 1.  
   as cause of food poisoning, 120, 122.  
   cerebrospinal fever, 54, 63.  
   cholera, 134.  
   diphtheria, 68, 77.  
   meningococcus, 54, 55.  
   paratyphoid, 111.  
   pneumonia, 1049.  
   scarlet fever, 36, 46.  
   small-pox, 159.  
   typhoid, 98, 99, 108.  
   typhus, 295.  
   undulant fever, 125.  
   whooping-cough, 138.  
 Carrion's disease, 144.



- Caseation of pulmonary tubercles**, 1018.  
**Casoni's intradermal test for hydatid disease**, 685, 1047, 1085.  
**Castle's extrinsic factor**, 460.  
     intrinsic factor, 734.  
**Castration, mental effects of**, 1645.  
**Casts in acute fibrinous bronchitis**, 968.  
     in acute nephritis, 1121.  
     in lardaceous disease of kidney, 1132.  
**Cataplexy**, 1507.  
**Cataract following lightning-stroke**, 405.  
     in diabetes mellitus, 441.  
     in dystrophia myotonica, 1602.  
**Catarrh, bronchial**, 963.  
     in bacterial infection, 3.  
     mucous of stomach, 615.  
     suffocative, 965.  
**Catatonias**, 1658.  
**Catatonic stupor**, 1663, 1668.  
**Catheterisation, cardiac**, 806.  
**Causalgia**, 1571.  
**Cavernous sinus, syndromes of**, 1366.  
     thrombosis of, 1366, 1453.  
**Cavitation process in pulmonary tuberculosis**, 1019.  
     signs of, 1024.  
**Cellulitis, cervical, in diphtheria**, 70.  
     in scarlet fever, 40.  
     orbital, in erysipelas, 35.  
**Centipedes, diseases due to**, 340.  
**Centurus exlicauda**, 340.  
**Cephalin cholesterol flocculation test, in liver function**, 660.  
**Cerebellar abscess in scarlet fever**, 42.  
     localisation of, 1408, 1409.  
     apoplexy, 1440.  
     ataxy, 1363, 1488.  
     atrophies, 1481.  
         delayed, 1481.  
     gait, 1364.  
     thrombosis, 1440.  
**Cerebellum, localisation of lesions of**, 1363.  
**Cerebral abscess, 1405-1411.**  
     differentiated from meningitis, 1409, 1410.  
     in accessory-sinus suppuration, 941.  
     in bronchiectasis, 985.  
     in empyema, 1074.  
     in gangrene of the lung, 1006.  
     mental symptoms in, 1407, 1635.  
     aneurysm, 1447.  
     angiography, 1390.  
     arterial disease and hypertension,  
         mental disorders associated with,  
         1630.  
     thrombosis and hæmorrhage, 1435.  
     aneurysm in relation to, 1435.  
     differential diagnosis of, 1441.  
     syphilis in relation to, 1435.  
     arteries, aneurysm of, 1447.  
     syphilitic disease of, 1435.  
     thrombosis of, 1435.  
     artery, anterior, syndrome of, 1358.  
     atheroma, 1443, 1630.  
     diplegia, 1487.  
     and deafness, 1488.  
     birth abnormalities associated with, 1487.  
     epilepsy in, 1489.  
     paresis and rigidity in, 1488.  
**Cerebral diplegia, perverse movements in**  
     1489.  
     embolism, 1445.  
     in aneurysm, 1441.  
     in septic endocarditis, 885, 886.  
     hæmorrhage in encephalitis lethargica,  
         1415.  
     in essential thrombocytopenia, 773.  
     hemispheres, signs of local lesions of,  
         1357.  
     localisation, 1336.  
     meningo-vascular syphilis, 1459.  
     softening after thrombosis, 1436.  
     syphilis, 1459.  
     thrombosis as cause of apoplexy, 1436,  
         1437.  
         and hæmorrhage, 1435-1443.  
         atheroma in relation to, 1435.  
         syphilitic, 1435.  
     trauma, mental disorders in, 1635.  
     tuberculoma, 1384.  
     tumour, 1380.  
     mental disorders in, 1635.  
     vascular lesions, 1435.  
         in relation to insanity, 1630.  
**Cerebro-macular degeneration**, 1482.  
**Cerebrospinal fever**, 54.  
     acute or ordinary type of, 55.  
     age in relation to prognosis of, 63.  
     and influenza, 57, 61.  
     arthritis in, 64.  
     carriers of, 54, 55, 63.  
     cerebrospinal fluid in, 59, 60.  
     chronic stage of, 56.  
     complications of, 58.  
     diet in, 64.  
     differential diagnosis of, 62.  
     epidemics of, 54, 63.  
     fulminating type of, 57.  
     incubation period of, 55.  
     lumbar puncture in, 57, 59.  
         repetition of, 64.  
     malignant type of, 57.  
     mild, confused with influenza, 57.  
     mild types of, 57.  
     mortality in, 63.  
     prophylaxis of, 29.  
     supercute type of, 37.  
**fluid, 1377-1380.**  
     appearance of, 1379.  
     cell count, 1379, 1380.  
     circulation of, 1377.  
     cytology of, 1378.  
     in acute poliomyelitis, 1426.  
     in acute syphilitic meningitis, 1398, 1461.  
     in apoplexy, 1436, 1437.  
     in cerebral abscess, 1409.  
     in cerebral syphilis, 1461.  
     in cerebral thrombosis and hæmorrhage,  
         1436.  
     in cerebrospinal fever, 59, 60.  
     in compression of spinal cord, 1535.  
     in diphtheria, 70.  
     in disseminated sclerosis, 1475.  
     in encephalitis, 1411.  
     in encephalitis lethargica, 1415.  
     in general paralysis, 1457.  
     in hydrocephalus, 1399, 1403.

- Cerebrospinal fluid**, in hydrophobia, 1422.  
 in intracranial tumours, 1389, 1390.  
 in intramedullary tumours, 1534.  
 in Landry's paralysis, 1594.  
 in lead encephalopathy, 368.  
 in meningococcus meningitis, 59.  
 in mumps, 176.  
 in pneumococcal meningitis, 1392.  
 in spinal cord tumours, 1534.  
 in syphilis of nervous system, 1455.  
 in tabes, 1457.  
 in trypanosomiasis, 272.  
 in tuberculosis, 88.  
 in tuberculous meningitis, 1396.  
 in typhoid, 101.  
 in typhus fever, 297.  
 in yellow fever, 186.  
 increased pressure of, in intracranial tumours, 1389, 1390.  
 pressure of, 1378.  
 spirochaetes in, 242, 243.  
 turbidity of, 1379.  
 Wassermann reaction in, 1380.  
 syphilis, 1459.
- Cervical glands**, enlargement of, in diphtheria, 70.  
 in measles, 150.  
 in scarlet fever, 39, 40, 42.  
 in small-pox, 164.  
 in trypanosome fever, 271.  
 tuberculosis of, 788.  
 opisthotonos of infants, 58.  
 ribs, 1579.  
 sympathetic paralysis, 1345.  
 in syringomyelia, 1547.
- Cervico-brachial syndromes**, 1167.  
 -occipital neuritis, 1577.
- Cestodes**, diseases due to, 322-325.
- Ceylon sore mouth**, 623.
- Chagas' disease**, 274.
- Chancre**, hard, 204.  
 herpeticiform in lymphogranuloma inguinale, 191.  
 primary, 203.  
 soft, 143.
- Chancroid**, 143, 144, 210.  
 prophylaxis with sulphonamides, 28.
- Chaps**, 1206.
- Charcot's dissociated sensory loss**, 1545.  
 joint disease, 1157.  
 in syringomyelia, 1547.  
 in tabes, 1462, 1465.  
 treatment of, 1469.  
 triad of symptoms in disseminated sclerosis, 1476.
- Charcot-Leyden crystals** in acute fibrinous bronchitis, 968.  
 in asthmatic sputum, 979.  
 in amebic dysentery, 277.
- Charcot-Marie-Tooth type** of muscular atrophy, 1563.
- Chauffard-Minkowski type** of hæmolytic anæmia, 741.
- Chaulmoogra oil** in leprosy, 92.
- Cheilitis**, commissural exfoliativa, 1218, 1324.  
 glandularis, 1324.
- Chemical irritants**, dermatitis from, 1212.
- Chenopodium**, oil of, as parasiticide, 323, 333, 334, 335.
- Cherry-red spot** in retina in amaurotic family idiocy, 1483.
- Chest**, deformities of, in adenoids, 942.  
 in emphysema, 999.  
 in relation to bronchitis, 963.  
 pain, causes of, 839, 1064.  
 in pulmonary tuberculosis, 1001.  
 radiography of the, 1026.
- Cheyne-Stokes respiration**, in acute hepatic necrosis, 671.  
 in apoplexy, 1438.  
 in cardiac failure, 810.  
 in intracranial tumours, 1388.  
 in tuberculous meningitis, 1396.
- Chicago disease**, 198.
- Chicken-pox**, 171.  
 and herpes zoster, 173.  
 complications of, 173.  
 differentiation from small-pox, 165, 166, 173, 1249.  
 rash of, 1248, 1249.
- Chilblains**, 1205.
- Child-bearing**, mental disorders associated with, 1644, 1646.
- Chilomastix mesnili**, 284.
- Chiniofon** in amebic dysentery, 278.
- Chloasma uterinum**, 1202.
- Chloral**, addiction to, 1642.
- Chloramphenicol**, 11.  
 in acute laryngo-tracheo bronchitis, 946.  
 in chancroid, 144.  
 in enteritis, acute infective, 121.  
 in flea typhus, 287.  
 in folliculitis barbæ, 1128.  
 in gonorrhœa, 66.  
 in granuloma venereum, 1250.  
 in impetigo vulgaris, 1226.  
 in lymphogranuloma inguinale, 192.  
 venereum, 1250.  
 in lung abscess, 1004.  
 in nummular eczema, 1219.  
 in pneumonia, atypical, 1057.  
 in psittacosis, 1058.  
 in "Q" fever, 304.  
 in rickettsial diseases, 287, 292, 295.  
 in Rocky Mountain tick typhus, 295.  
 in tropical ulcer, 1332.  
 in tsutsugamushi disease, 292.  
 in typhoid fever, 109.  
 in typhus fever, 12, 13, 300.  
 in ulcerating granuloma, 1335.  
 in virus pneumonia, 1057.  
 in whooping-cough, 142.  
 in yaws, 235.  
 indications for use of, 12, 13.  
 toxic effects of, 13.
- Chlorcyclizine** in travel sickness, 403.
- Chloride content** of cerebrospinal fluid, 1378, 1380.
- excretion** in urine, 1099.  
 in pneumonia, 1051.  
 increased in Addison's disease, 1099.
- Chlorinated naphthalenes**, poisoning by, 395.
- Chlorine** in relation to bronchitis, 967.
- Chloroform** contra-indicated in diabetes, 437.

- Chloroform poisoning**, in relation to  
necrosis of liver, 670.
- Chloroma**, 763.
- Chlorophyll** in treatment of halitosis, 530.
- Chloroquine diphosphate** in amœbic abscess,  
282.  
in blackwater fever, 263, 264.  
in malaria, 255, 257, 258.
- Chlorosis**, 732.
- Chlortetracycline**, 13, 14.  
in abacterial urethritis, 312.  
in amœbic dysentery, 279.  
in chancreoid, 144.  
in flea typhus, 287.  
in folliculitis barbæ, 1228  
in furunculosis, 1230.  
in gonorrhœa, 66.  
in impetigo vulgaris, 1226.  
in leptospirosis icterohæmorrhagica, 241.  
in lung abscess, 1004.  
in lymphogranuloma inguinale, 192.  
venereum, 1250.  
in nummular eczema, 1219.  
in psittacosis, 184.  
in "Q" fever, 304.  
in rat-bite fever, 245.  
in relapsing fever, 244.  
in Rocky Mountain tick typhus, 295.  
in tropical eosinophilia, 315.  
in tropical ulcer, 1332.  
in tsutsugamushi disease, 292.  
in tularemia, 131.  
in typhus fever, 300.  
in ulcerating granuloma, 1335.  
in ulcerative colitis, 637.  
in undulant fever, 127.  
in virus pneumonia, 1057.  
in whooping-cough, 142.  
in yaws, 235.  
indications for use of, 14.  
toxic effects of, 14.
- Chlorovinyl dichlorarsine**, poisoning by,  
376.
- Choix fever**, 293.
- "Chokes," the**, in caisson disease, 397.
- Cholangioma**, 685.
- Cholangitis**, in gall-stones, 696.  
suppurative, in cancer, 686, 699.  
in hydatid disease, 684  
in portal pyelephlebitis, 689.
- Cholecystitis**, 689.  
achlorhydria, in, 690, 693.  
acute, 690.  
bacteriology of, 689.  
chronic, 691.  
and gall-stones, 694.  
gangrenous, 690.  
suppurative, 690.
- Cholecystography**, 692, 697.
- Cholelithiasis**, 694.
- Cholera**, 133.  
ambulatory, 134.  
carriers of, 134.  
complications and sequelæ of, 135.  
gravis, 134.  
infantum, 614.  
mortality in, 136.  
nostras, 135.
- Cholera**, prophylaxis of, 136.  
siccæ, 134.  
types of, 134.
- Choleraic diarrhœa**, 134.
- Cholerine**, 134.
- Cholesteatoma of brain**, 1383.
- Cholesterin** in pseudo-chylous pleural effusion, 1080.
- Cholesterol**, activation of, by ultra-violet rays, 455.  
excess of, in blood and bile, 694.  
histiocytoses, 1298.  
in blood in jaundice, 662.  
in corpus luteum of pregnancy, 694.  
in pancreatic cysts, 708.  
in relation to atherosclerosis, 835, 919.  
gall-stones, 694.  
stones, 694.  
-free diet, 693.
- Cholesterolæmia**, 694.
- Cholesterolosis**, 694.
- Choline**, 460.
- Chondrodysplasia**, hereditary deforming,  
1183.  
unilateral, 1184.
- Chondrodystrophia fœtalis**, 1182.
- Chondromata**, multiple, 1183.
- Chorea**, 1515.  
apoplectic, 1362, 1519.  
congenital, 1488.  
gravidarum, 1515.  
gravis, 1518.  
heart disease in relation to, 1517.  
hereditary, of adults, 1519.  
Huntington's, 1519.  
in pregnancy, 1515.  
in scarlet fever, 43.  
involuntary movements in, 1516.  
limp, 1517.  
mental disorders in, 1517.  
mollis, 1517.  
psychical disturbances in, 1517.  
recurrences in, 1518.  
relation of, to rheumatism, 1515.  
rheumatic, 1515.  
manifestations in, 1517.  
senile, 1519.  
Sydenham's, 1515.  
mental changes in, 1634.  
tetanoid, 1484.
- Chorio-meningitis**, 1397.
- Choroiditis** in congenital syphilis, 226.  
in onchocerciasis, 329.
- Christmas factor** in blood coagulation, 766,  
767.
- Chromaffin cells**, 506.
- Chrome hole**, 384.
- Chromidrosis**, 1198.
- Chromium**, poisoning by, 384.
- Chvostek's sign** in hypoparathyroidism, 504.  
in sprue, 621, 624.
- Chyliform effusion into pleura** 1080.
- Chylorhœax**, 1079.
- Chylous ascites**, 686, 787.  
effusions, 787, 1079.
- Chyluria**, 787, 1107.  
in filariasis, 327.
- Chyme**, 599.

- Cigarette-smoking** in relation to chronic tracheitis, 956.  
to emphysema, 997.  
lung cancer, 1041.
- Circulatory failure**, 806.  
in diphtheria, 72.  
system, diseases of the, 793-937.
- Circumcision**, preputial diphtheria after, 72.
- Cirrhosis**, biliary, 679.  
Lænnec's, 674.  
multilobular, 674.  
of the liver, 673.  
in splenic anemia, 781.  
of the lung, 1006.  
pericellular, 681.  
pigmentary, 680.  
pleurogenous, 1006.  
portal, 674.  
primary hypertrophic biliary, 679.  
secondary obstructive biliary, 680.
- Citrovorum factor**, 460.
- Cladorchis watsoni**, 316.
- Cladosporium mansonii**, 1333.
- Claudication**, intermittent, 919.  
in thrombo-angiitis obliterans, 921.
- Claustrophobia**, 1679.
- Claviceps purpurea**, the ergot fungus, 345.
- Clavus**, 234, 1297.  
in hysteria, 1671.
- Claw-hand** in leprosy, 91.  
in ulnar paralysis, 1572.
- Climacteric**, 522.  
affective disorders at, 1645, 1647.
- Climatic bubo**, 191.
- Clonorchiasis**, 317.
- Clonorchis sinensis**, 317.
- Clostridia**, sensitivity of, to penicillin, 7.
- Clostridium**, botulinum, 123.  
toxin of, 123.  
diphtheria, sensitivity of, to penicillin, 7.  
tetani, 81.  
welchii, 33.  
in food poisoning, 124.  
sensitivity of, to penicillin, 7.
- Clubbing of fingers**, causes of, 1171.  
in asbestosis, 1012.  
in bronchiectasis, 984.  
in chronic bronchitis, 970.  
in congenital cystic disease of lung, 1044.  
in emphysema, 999.  
in empyema, 1073.  
in fibrosis of pancreas, 706.  
in hypertrophic osteo-arthritis, 1171.  
in idiopathic steatorrhœa, 621.  
in lung abscess, 1003.  
in morbus cœruleus, 897.  
in pulmonary emphysema, 998.  
in pulmonary fibrosis, 1007.  
in pulmonary tuberculosis, 1026.  
in regional ileitis, 632.  
in subacute bacterial endocarditis, 887.  
in ulcerative colitis, 635.
- Clutton's joints**, 227.
- Coagulation of blood**, 767.
- Coal** in relation to pneumoconiosis, 1008.  
-gas, poisoning by, 357.  
-tar derivatives, account of, 388.  
poisoning by, 388.
- Coal miners' asthma**, 1011.  
pneumoconiosis, 1011.
- Coastal erysipelas**, 329.
- Cocainism**, 352, 1641.
- Coccidioides** affecting lung, 1039.  
immitis, 200.
- Coccidioidomycosis**, 200.
- Coccidioidosis**, 200.
- Cochliomyia americana**, 337, 338.  
macellaria, 338.
- Coco**, 233.
- Cod-liver oil** in rickets, 467.  
vitamin value of, 455.
- Cœliac disease**, 618.  
adult, 620.  
macrocytic anemia in, 621.
- Cœnurus cerebralis**, 324.
- Coffee-ground vomiting** in cancer of stomach, 591.  
in yellow fever, 187.
- Colchicum**, specific for acute gout, 448.
- Cold**, common, 147.  
sensitivity to, in myxœdema, 497.
- Colic**, appendicular, 654.  
biliary, 695.  
without gall-stones, 698, 705.  
due to flatulence, 630.  
in acholic jaundice, 741.  
in acute infective enteritis, 121.  
in acute intestinal obstruction, 651.  
in bacillary dysentery, 112, 114.  
in cancer of the colon, 641.  
in chronic pancreatitis, 705.  
in diarrhœa, 611.  
in diverticulitis, 644.  
in Henoch's purpura, 774.  
in intussusception, 646.  
in toxic Salmonella enteritis, 122.  
in regional ileitis, 632.  
in tuberculous peritonitis, 719.  
lead, 363, 364, 367, 371.  
muco-membranous, 627.  
renal, 1141.
- Coliform bacillus infections**, 94-97  
modes of infection in, 94.  
of gastro-intestinal system, 94.  
of urinary tract, 95.  
treatment of, 97.
- Colitis**, 633.  
acute catarrhal, 633.  
as cause of diarrhœa, 611, 633.  
as result of mercurial treatment, 233.  
chronic catarrhal, 633.  
enteritis in relation to, 633.  
in chronic mercurial poisoning, 382.  
localisation of, 633.  
mucous, 633.  
tuberculous, 638.  
ulcerative, 634.  
in mercurial poisoning, 381.
- Collagen diseases**, 930-937.
- Collar of Venus** in syphilis, 205.
- Colloid milium**, 1312.
- Colon**, absorption in, 600.  
cancer of, 640.  
dilatation of, in idiopathic steatorrhœa, 621.  
distal, 599.  
diverticula of, 644.

- Colon, dyspepsia, 41.**  
 in bacillary dysentery, 112, 113, 115, 116.  
 irritable, 627.  
 movements of, 600.  
 neurosis, 627.  
 polyp of, 639.  
 proximal, 599.  
 size, shape and position of, 601.  
 spasm of, 627.  
 stricture of, in ulcerative colitis, 635.  
 ulceration of, in amœbic dysentery, 276, 277.  
 X-ray examination of, 602.  
**Colonic spasm, 605.**  
 stomach, 599.  
**Colour index of blood, 726.**  
 in hæmolytic anæmias, 740  
 in pernicious anæmia, 736.  
 in polycythæmia, 750.  
**Coma after arsenamine, 230.**  
 diabetic, 439.  
 differential diagnosis of, 1441.  
 in acute alcoholism, 354.  
 in acute necrosis of liver, 671.  
 in barbiturate poisoning, 360.  
 in Bright's disease, 1116.  
 in carbon monoxide poisoning, 359.  
 in cerebral thrombosis and apoplexy, 1441.  
 in cerebrospinal fever, 56.  
 in encephalitis lethargica, 1407.  
 in heat hyperpyrexia, 408.  
 in intracranial tumour, 1390.  
 in plague, 128.  
 in tuberculous meningitis, 1395.  
 uræmic, 1111.  
 vigil in typhus, 277.  
**Comedones, 1282.**  
**Compensation neurosis, 1616, 1636.**  
**Compensatory circulation in cirrhosis of liver, 675.**  
**Complement fixation reactions in virus diseases, 147.**  
 in amœbic dysentery, 277.  
 in psittacosis, 184.  
 test for hydatids, 325.  
 for schistosomiasis, 320.  
**Compound F. See Hydrocortisone.**  
**Compressed air illness, 395.**  
**Concato's disease, 717.**  
**Concussion, mental symptoms following, 1635.**  
**Condylomata, scuminata, 1301.**  
 broad, 205.  
 lata, 205, 225.  
**Confusional state, 1626.**  
**Congenital heart disease, 893.**  
 hydrops, 745.  
 spastic paralysis, 1487.  
 syphilis, 225, 1471.  
 of nervous system, 1471.  
**Congo floor maggot, 339.**  
**Conjugate deviation of eyes in apoplexy, 1438.**  
 in encephalitis lethargica, 1418.  
 in epilepsy, 1500.  
 in lesions of motor area, 1359.  
**Conjunctivæ in leptospirosis icterohæmorrhagica, 239, 240.**  
 in phlebotomus fever, 188.  
 in rubella, 157.  
 in trench fever, 301.  
 in yellow fever, 186.  
**Conjunctival diphtheria, 71, 72.**  
**Conjunctivitis in abacterial urethritis, 312.**  
 in allergic rhinitis, 939.  
 in beryllium poisoning, 386.  
 in chromium poisoning, 384.  
 in chronic arsenical poisoning, 375.  
 in measles, 152, 155.  
 in onchocerciasis, 329.  
 in Reiter's syndrome, 1156.  
 in rosacea, 1207.  
 in small-pox, 162, 164.  
 in South American trypanosomiasis, 274.  
 metastatic, in gonorrhœa, 67.  
 phlyctenular, with adenoids, 942.  
**Connective tissue, diseases of, 930**  
**Consciousness, 1613.**  
 loss of, in epileptic attacks, 1438.  
 in Stokes-Adams syndrome, 831.  
**Consolidation of lung, physical signs of, 1024.**  
**Constipation, 605.**  
 colonic, 605.  
 in acute appendicitis, 655.  
 in acute intestinal obstruction, 651.  
 in chronic duodenal ulcer, 578.  
 in colon neurosis, 628.  
 in diverticulitis, 644.  
 in encephalitis lethargica, 1415, 1419  
 in hypertrophic pyloric stenosis, 596.  
 in megacolon, 647.  
 in peritonitis, 713.  
 in tuberculous meningitis, 1395, 1396.  
 spastic, 605.  
**Consumption, 1017.**  
**Contracture, Dupuytren's, 1167.**  
**Contractures in cerebral diplegia, 1489, 1490.**  
 hysterical, 1672.  
 in Friedreich's ataxia, 1480.  
 in peroneal muscular atrophy, 1564.  
 in syringomyelia, 1546.  
 muscular, after poliomyelitis, 1428, 1430.  
**Convalescent serum in glandular fever, 307.**  
 in measles, 154.  
 in mumps, 177.  
 in whooping-cough, 142.  
 in yellow fever, 187.  
**Conversion mechanism of hysteria, 1671.**  
 symptoms, hysterical, 1614.  
**Convulsion therapy in mental disorders, 1621, 1654.**  
 in schizophrenia, 1667.  
**Convulsions in acute necrosis of liver, 671.**  
 in ascariasis, 334.  
 in cerebral diplegia, 1489.  
 in cerebrospinal fever, 55, 58.  
 in chicken-pox, 172, 173.  
 in congenital syphilis, 1471.  
 in heat hyperpyrexia, 408.  
 in hydrocephalus in children, 1401.  
 in infantile hemiplegia, 1490.  
 in intracranial tumours, 1388.  
 in measles, 152.  
 in pneumonia in children, 1052.  
 in rickets, 466.  
 in scarlet fever, 38, 41, 43.

- Convulsions** in tuberculous meningitis, 1396.  
 in typhoid, 104.  
 in uræmia, 1111, 1118.  
 in whooping-cough, 140, 141.
- Cooley's anæmia**, 743.
- Copper arsenite**, uses of, 373.  
 colloidal in coccidioidosis, 201.  
 traces of, essential for blood, 731.
- Coproporphyrinuria**, 368.
- Cor pulmonale**, 851, 852.
- Cordylobia anthropophaga**, 338.
- Cornea**, sloughing of, in cholera, 135.  
 in diphtheria, 72.
- Corneal lesions**, due to vitamin A deficiency, 455.  
 ulceration in congenital syphilis, 226.  
 in leprosy, 91.  
 in measles, 152, 155.  
 in small-pox, 164.
- Corns**, 1297.
- Corona veneris**, 206.
- Coronary arteries**, atheroma of, 834, 835, 836, 902.  
 diseases of the, 834.  
 in aortic incompetence, 875.  
 insufficiency, acute, 849.
- occlusion**, 836, 842, 843.  
 angina pectoris in relation to, 843.  
 atheroma as cause of, 836.  
 hypertension in relation to, 843.  
 in diabetes mellitus, 902.  
 with infarction of heart, 836.
- thrombosis**, 836, 842.  
 electrocardiogram in, 844.
- Corpora quadrigemina**, localisation of lesions of, 1362.
- Corpus luteum**, a source of cholesterol, 694.  
 striatum, localisation of lesions of, 1362.
- Corrigan's sign**, 874, 875.
- Corrosive poisons**, 362.  
 sublimate, poisoning by, 381.
- Corticotrophin (A.C.T.H.)**, 483.  
 in acute gout, 448.  
 in acute leukaemia, 764.  
 in ankylosing spondylitis, 1161, 1162.  
 in arthritis, 312.  
 in asthma, 981.  
 in dermatomyositis, 937, 1294.  
 in erythema multiforme, 1258.  
 in erythroderma, 1269.  
 in generalised scleroderma, 936.  
 in gout, 448.  
 in idiopathic acquired hæmolytic anæmia, 747.  
 thrombocytopenic purpura, 773.  
 in lichen planus, 1279.  
 in lupus erythematosus, disseminated, 935.  
 systematised, 1265.  
 in pemphigoid, 1289.  
 in pemphigus, benign, 1290.  
 erythematodes, 1289.  
 foliaceus, 1289.  
 vulgaris, 1288.  
 in polyarteritis nodosa, 932.  
 in rheumatoid arthritis, 1153, 1154.  
 in Stevens-Johnson syndrome, 1258.  
 in Still's disease, 1164.  
 in ulcerative colitis, 637.
- Cortisone**, in acute leukaemia, 764.  
 in Addison's disease, 510, 511.  
 in adrenal surgery, 517.  
 in ankylosing spondylitis, 1161, 1162.  
 in arthritis, 312.  
 in asthma, 981, 982.  
 in dermatomyositis, 937, 1294.  
 in disseminated lupus erythematosus, 935.  
 in erythroderma, 1270.  
 in generalised scleroderma, 936.  
 in hirsutism, 513.  
 in idiopathic acquired hæmolytic anæmia, 747.  
 thrombocytopenic purpura, 773.  
 in interstitial keratitis, 229.  
 in lupus erythematosus, disseminated, 935.  
 systematised, 1265.  
 in pemphigoid, 1289.  
 in pemphigus, benign, 1290.  
 erythematodes, 1289.  
 foliaceus, 1289.  
 vulgaris, 1288.  
 in polyarteritis nodosa, 932.  
 in pseudohermaphroditism, 516.  
 in rheumatoid arthritis, 1153, 1154.  
 in Simmonds's disease, 488.  
 in Still's disease, 1164.  
 in temporal arteritis, 933.  
 in ulcerative colitis, 637.  
 in virilism, 513.  
 therapy, pulmonary oedema in, 988.
- Corynebacterium diphtheriæ**, 67.
- Coryza**, acute, 147.
- Cotton card room asthma**, 1015.  
 cold, 1015.
- Cough**, brassy, in acute suppurative mediastinitis, 1090.  
 in tracheal tumours, 958.  
 gander, 958.  
 in acute bronchitis, 964.  
 in acute pleurisy, 1064.  
 in amœbic abscess, 280.  
 in aortic aneurysm, 860.  
 in asthma, 979.  
 in beryllium poisoning, 386.  
 in bronchial obstruction, 973, 975, 976.  
 in bronchiectasis, 984.  
 in broncho-pneumonia, 1058, 1060.  
 in chronic bronchitis, 969.  
 in diphtheria, 71, 75.  
 in emphysema, 999.  
 in enlarged mediastinal glands, 1092.  
 in heart failure, 809.  
 in hyperæmia of lungs, 988.  
 in influenza, 179, 180.  
 in lung abscess, 1003.  
 in measles, 150.  
 in pleurisy, 1064.  
 in pneumococcal pneumonia, 1050.  
 in pneumoconiosis, 1009, 1011.  
 in psittacosis, 184.  
 in pulmonary collapse, 993.  
 in pulmonary emphysema, 998.  
 in pulmonary tuberculosis, 1021, 1022, 1030.  
 in tracheal obstruction, 960.  
 in tracheitis, 955, 956.  
 in tropical eosinophilia, 313.  
 in tsutsugamushi disease, 290.

- Cough in virus pneumonia, 1057.  
 in whooping-cough, 138, 139.  
 tea-factory, 1040.  
 tea-taster's, 1040.  
 weavers', 1015.
- Coumarin in cardiac infarction, 848.
- Courvoisier's law, 696.
- Cow-pox, 168.
- Crab yaws, 234.
- Crabs in relation to paragonimiasis, 317.
- Crachats perlés, 970.
- Cracked-pot sound in hydrocephalus, 1401, 1404.  
 in tubercular cavity, 1025.
- Craft palsy, 1525.
- Cramp, occupational, 1526.  
 writer's, 1526.
- Cramps, heat, 407.  
 in arsenical poisoning, 230, 374.  
 in cholera, 134.  
 in manganese poisoning, 385.  
 in progressive muscular atrophy, 1556.
- Cranial abnormalities in cerebral diplegia, 1489.  
 enlargement in hydrocephalus, 1400, 1401.  
 nerve palsies in intracranial tumour, 1366, 1388.  
 in encephalitis lethargica, 1416.  
 in relapsing fever, 243.  
 in syphilitic meningitis, 1399.
- nerves, affections of the, 1338.  
 syphilitic paralysis of, 1399.  
 tabetic affections of, 1464.
- Cranio-pharyngioma in Fröhlich's syndrome, 489.
- Cranio-scleriosis, 1175.  
 -tabes in rickets, 465.
- Craniostenosis, 1181.
- Craw-craw, 1329.
- Creatinine clearance test of renal function, 1101.  
 excretion in urine, 1098.
- Creeping eruption, 1334.
- Cretinism, 498.
- Crises, Dietl's, 1148.  
 gastric, 1462, 1465, 1468.  
 hypertensive, 1444.  
 hyperthermic, 488.  
 in exophthalmic goitre, 493.  
 tabetic, 1462, 1465.
- Crohn's disease, 631.
- Crossed paralysis in lesions of pons and medulla, 1363.
- Croup, 945.
- Crush syndrome, 1128.
- Cry, hydrocephalic, 1395.  
 of syphilitic infant, 226.
- Cryptococcosis, 197.
- Cryptococcus neoformans, 197.
- Crystals in urine, 1099.
- "Cuffing" of cerebral vessels in lethargic encephalitis, 1415.  
 in syphilitic disease, 1435, 1455.
- Cuneus, lesions of, 1359.
- Curare, in hydrophobic spasms, 1423.
- Curschmann's spirals in acute fibrinous bronchitis, 968.
- Curschmann's spirals in asthma, 979.
- Cushing's syndrome, 516.  
 mental disorders in, 1644.
- Cutis hyperelastica, 1296.  
 laxa, 1298.  
 rhomboidalis nuchæ, 1295.
- Cyanocobalamin (vitamin B<sub>12</sub>), 460, 734, 735.  
 as extrinsic factor, 734.  
 in the treatment of pernicious anæmia, 737, 738.  
 of subacute combined degeneration, 1554.
- Cyanose tardive, 895.
- Cyanosis, enterogenous, 751, 752.
- Cyanosis, central, in congenital heart disease, 893.  
 heliotrope, 180.  
 in acute suppurative bronchitis, 966.  
 in anilism, 392, 393.  
 in cor pulmonale, 853.  
 in emphysema, 998, 999.  
 heart disease, 856.  
 in Fallot's tetralogy, 898.  
 in heart disease, 809, 811.  
 in laryngismus stridulus, 947.  
 in morbus cœruleus, 897.  
 in passive hyperæmia of the lungs, 988.  
 in phenylenediamine poisoning, 393.  
 in pneumothorax, 1082.  
 in polycythæmia vera, 750.  
 in pulmonary infarction, 991.  
 edema, 989.
- Cyclical vomiting, ketosis in, 1105, 1106.  
 of children, 561.
- Cyclops as intermediate host of guinea-worm, 330.  
 leuckarti in relation to tæniasis, 323.
- Cylindromata, 1309.
- Cysticercosis of brain, 324.
- Cysticercus bovis stage of tape-worm, 322.  
 cellulose stage of tape-worm, 322, 1384.
- Cystine calculi, 1107, 1141.
- Cystinuria, 1107.
- Cystitis, bacillus coli, 95.  
 in paratyphoid fever, 111.  
 in schistosomiasis, 320.  
 in typhoid, 104, 110.
- Cysts, dermoid, 1303.  
 echinococcus, 324, 1147.  
 epidermal, 1303.  
 hydatid, 324, 684.  
 implantation, 1303.  
 in compression of spinal cord, 1537.  
 in paragonimiasis, 317, 1043.  
 in tæniasis, somatic, 324, 325.  
 myxomatous degeneration, 1312.  
 of brain, 324, 1383.  
 of kidneys, 1146.  
 of lung, 1044.  
 of spleen, 779.  
 pancreatic, 708.  
 pleuro-pericardial, 1094.  
 sebaceous, 1303.  
 synovial, 1312.  
 tracheal, 957.
- Da Costa's syndrome 904,

- Dactylitis** in congenital syphilis, 226  
in yaws, 234.  
syphilitic, 209.
- Damoiseau's line** in pleural effusion, 1068.
- Dandruff**, 1217.
- Dandy fever**, 189.
- Dapsone** in dermatitis herpetiformis, 1287.
- Darier-Roussy** subcutaneous sarcoid, 1261.
- Darier's disease**, 1277.
- Day-dreaming**, in schizoid personality, 1657.
- D.D.T.** in pediculosis, 1253, 1254.  
in prophylaxis of Oroya fever, 145.  
in prophylaxis of plague, 129.
- Deaf-mutes**, mental deficiency in, 1683.
- Deafness**, after cerebrospinal fever, 57, 59.  
after small-pox, 164.  
hysterical, 1672.  
in congenital syphilis, 226.  
in disseminated sclerosis, 1475.  
in measles, 152.  
in mumps, 176.  
in osteitis deformans, 1173.  
in osteogenesis imperfecta, 1180.  
in quinine therapy, 256.  
in scarlet fever, 42.  
in Schilder's disease, 1413.  
in streptomycin therapy, 11.  
in typhoid, 104.  
in typhus, 297.  
meningitic, in cerebrospinal fever, 59.
- nerve**, 1351.  
as complication of mumps, 176.  
in Ménière's disease, 1353.  
in tsutsugamushi disease, 291.
- Debré phenomenon** in measles, 154.
- Decompression sickness**, 395.
- Deer-fly fever**, 130.
- Defecation**, 600.  
directions as to in constipation, 607.  
reflex, training of, 600, 606.
- Deficiency**, conditioned, 734.  
diseases, 454-482.
- Defluvium capillorum**, 1319.
- Degeneration**, cerebro-macular, 1482.  
hepato-lenticular, 1484.  
progressive lenticular, 1484.  
stigmata of, 1684.  
subacute combined, 1550.  
in pellagra, 473.  
in pernicious anemia, 736.
- Degenerative and hereditary brain disease**, 1627.
- Deglutition**, normal, mechanism of, 541.  
painful, in acute oesophagitis, 547.
- Dehydration**, 416, 417.  
for relief of intracranial pressure, 1391.  
in acute infective enteritis, 121.  
in acute laryngo-tracheo bronchitis, 946.  
in bacillary dysentery, 114.  
in diarrhoea, 611.  
in summer diarrhoea, 615.  
in uræmia, 1110.  
sodium, 416.  
water, 417.
- Dejerine and Roussy**, "thalamic syndrome" of, 1361.
- Delhi boil**, 268.
- Delirium**, 1625.  
hallucinations in, 1625, 1626.  
in acute hepatic necrosis, 671.  
toxæmic, 30, 1642.  
tremens, 1638.
- Deltoid bursitis**, 1167.
- Defusional states**, chronic, 1639.
- Delusions** in anxiety states, 1651.  
in general paralysis, 1456, 1633.  
in mental depression, 1649.  
in schizophrenia, 1660.
- Dementia**, 1626.  
after typhus, 298.  
in pellagra, 1643.  
paralytica, 1455.  
paranoides, 1664.  
phantastica, 1664.  
Pick's, 1629.  
præcox, 1656.  
secondary, after cerebrospinal fever, 58.  
senile and præsenile, 1628.  
simplex, 1664.
- Demoralisation** in chronic alcoholism, 1637.
- Demyelination** in Schilder's disease, 1412.  
in subacute combined degeneration, 1550.
- Dengue**, 189.  
peri-arthritis in, 1156.
- Dental caries**, 528, 529.  
and actinomycosis, 194.  
in relation to adenoids, 942.  
in relation to mercurial stomatitis, 383.  
vitamins in relation to, 529.
- hygiene**, 529.  
treatment, importance of, in relation to oral sepsis, 529.
- Dentition**, delayed, in rickets, 465.  
in congenital syphilis, 227.
- Depersonalisation** in anxiety states, 1651.
- Depression**, mental, in obsessional disorders, 1679.  
symptoms of, 1649.
- De Quervain's disease**, 1167.
- Dercum's disease**, 1166.
- Dermacentor andersoni**, 293, 294, 336.  
rickettsi, 294.  
variabilis, 293, 294.  
venustus, 336.
- Dermacentroxenus rickettsi**, 293.
- Dermatitis**, arsenical, 231.  
after arsenamine preparations, 231.  
ankylostome, 332.  
artifactual, 1211.  
atopic, 1195.  
bullosa striata pratensis, 1210.  
congelationis, 1210.  
contact, 1214.  
contagious pustular, of sheep, 1250.  
cutisformis, 308.  
due to actinic rays, 1210.  
to cold, 1209.  
to chemical substances, 1212.  
to fungi, 1232.  
to heat, 1209.  
to mechanical causes, 1211.  
to radioactivity, 1210.
- exfoliative**, 1263.  
after arsenamine preparations, 231.  
after intravenous penicillin, 219.



- Dermatitis, exfoliative**, after sulphonamide preparations, 27.  
**neonatorum** (Ritter), 1226.  
**herpetiformis**, 1286.  
**senile**, 1289.  
 in beryllium poisoning, 386.  
 in chronic mercurial poisoning, 382.  
 in dinitro-ortho-cresol poisoning, 392.  
 in pellagra, 473.  
 in phenylenediamine poisoning, 393.  
 in trinitrotoluene poisoning, 390.  
**infective**, 1216.  
**medicamentosa**, 1265.  
 of erysipelas, the, 34.  
 radium, 412.  
 red mite, 336.  
**seborrhœic**, 1200, 1216.  
**vegetans**, 1231.  
 X-ray, 410.
- Dermatofibroma**, 1312.
- Dermatofibrosarcoma protuberans**, 1312.
- Dermatobia hominis**, 338.
- Dermatographism**, 1255, 1256.
- Dermatomyositis**, 936, 1293.
- Dermatoses, acneiform**, 1281-1286.  
 after arsphenamine therapy, 230, 231.  
 lichenoid, 1277-1281.  
 squamous, 1270-1277.
- Dermatosis, pigmentary** (Gougerot and Blum), 1260.  
 progressive pigmentary (Schamberg), 1260.
- Dermis, tumours of the**, 1310-1316.
- Dermographism**, 1255.
- Dermoid cyst of brain**, 324, 1383.  
 of skin, 1303.
- Desensitisation in asthma**, 981.
- Desert sore**, 1329.
- Deoxycortone acetate in Addison's disease**, 510.
- d'Espine's sign in enlarged mediastinal glands**, 1093.
- Desquamation, in measles**, 151.  
 in rubella, 157.  
 in scarlet fever, 39.  
 in small-pox, 162.
- De Toni-Fanconi syndrome**, 1179.
- Devic's disease**, 1478.
- Devil's grip**, 193.
- Dextrocardia**, 894.
- Dhobie itch**, 1333.
- Diabetes, bronzed**, 680.  
**insipidus**, 489.  
 in Hand-Schüller-Christian's disease, 489, 784.  
 in cerebral syphilis, 1460.
- mellitus**, 422-443.  
 acute infections in, 431.  
 adiposity in relation to, 449.  
 ætiology of, 422.  
 complications of, 438.  
 diagnosis of, 425.  
 dietetic treatment of, 427, 431.  
 heart disease in, 902.  
 in acromegaly, 484.  
 in Cushing's syndrome, 517.  
 in hæmochromatosis, 680.  
 in relation to arterial degeneration, 439.  
 in relation to pancreatitis, 705.
- Diabetes mellitus in relation to tubercu-  
 losis**, 438.  
 incidence of, 422, 423.  
 insulin treatment of, 427-437.  
 mental disorders in, 1643.  
 pathology of, 423.  
 pregnancy in, 438.  
 renal lesions in, 1125.  
 surgical operations in, 437.  
 symptoms of, 424.  
 treatment of, 426.  
 xanthoma in, 1298.  
 tenuifluus, 490.
- Diabetic coma**, 439.  
 gangrene, 439.  
 glomerulosclerosis, 1125.  
 neuritis, 425, 1592.
- Diabetic acid in urine**, 1105.  
 test for, 1106.
- Diachylon as an abortifacient**, 365.
- Diamidines in kala-azar**, 268.
- Diaphragm, clonic spasm of**, 1087.  
 diseases of, 1087.  
 displacement of, in ascites, 719, 732.  
 effects of megacolon on, 647.  
 epidemic spasm of, 193.  
 eventration of, 647.  
 hysterical spasm of, 1088.  
 paralysis of, 1088, 1432.  
 spasm of the, 567, 1087.  
 tonic spasm of, 1088.
- Diaphragmatic acute dry pleurisy**, 1065.
- hernia**, 1096.
- spasm, epidemic**, 325.
- Diaphyses, cupping of, in rickets**, 466.
- Diaphysal aclasis**, 1183.
- Diarrhœa**, 609-614.  
 achlorhydria causing, 554, 610.  
 acute, treatment of, 613.  
 chronic, 609, 614.  
 Cochin-China, 623.  
 epidemic, in children, 614  
 fatty, 612, 613, 664-701.  
 false, in dyschezia, 611.  
 fermentative, 609, 612.  
 flagellate, 284.  
 gastrogenous, 610.  
 hull, 626.  
 in bacillary dysentery, 114.  
 in children, epidemic, 614.  
 in cholera, 134.  
 in colitis, 633, 634.  
 in dyschezia, 611.  
 in epidemic dropsy, 348, 349.  
 in food poisoning, 121, 122, 124.  
 in idiopathic steatorrhœa, 621.  
 in intestinal carbohydrate dyspepsia, 630.  
 in intestinal lipodystrophy, 632.  
 in kala-azar, 266.  
 in measles, 150.  
 in polyposis, 640.  
 in plague, 128.  
 in rickets, 466.  
 in tropical sprue, 624.  
 in regional ileitis, 632.  
 in tuberculous enteritis, 639.  
 infective or infectious, 614.  
 nervous, 610.

- Diarrhœa**, nervous, treatment of, 614.  
 nocturnal in diabetes mellitus, 442  
 post-prandial, 610.  
 putrefactive, 609.  
 soap, 613.  
 summer, 614.  
 tropical, 610.
- Diaschisis**, 1337, 1371.
- Diastase** in urine, 701, 1100.
- Diastatic index** in mumps, raised, 176  
 in acute pancreatitis, 1100.
- Diazo reaction** in measles, 151.  
 in small-pox, 162.  
 in typhus, 297.
- Dick test** in scarlet fever, 37, 44.
- Dientamoeba fragilis**, 275.
- Diet**, cholesterol-free, 693.  
 in celiac disease, 619.  
 in diabetes, 431-435.  
 in epidemic diarrhœa, 617.  
 in gastric and duodenal ulcer, 581.  
 in gastritis, 572, 574.  
 in gout, 448.  
 in hæmatemesis, 570.  
 in heart failure, 813.  
 in hypoparathyroidism, 506.  
 in idiopathic steatorrhœa, 622.  
 in ketosis, 435, 437.  
 in obesity, 450, 451.  
 in tropical sprue, 625, 626.  
 low calcium, to accelerate elimination of  
 lead, 370.  
 reducing, 450, 451.  
 salt-free, in ascites, 724.
- Dietl's crises** in movable kidney, 1148.  
 treatment of, 1149.
- Digestion**, 599.  
 rôle of stomach in, 556.
- Digestive disorders** and neurasthenic states,  
 1645.  
 in dental caries, 528.  
 in rickets, 466.  
 system, diseases of the, 525-724.  
 in typhoid fever, 102.
- Digitalis**, action of, 814.  
 as cause of bradycardia, 815.  
 of extra-systoles, 815.  
 of heart block, 831.  
 of sino-auricular block, 821.  
 dosage of, 814.  
 effect of, as shown by electrocardiograph, 815.  
 forms of, in use, 814.  
 in auricular fibrillation, 827, 828, 870.  
 in auricular flutter, 826.  
 in heart failure, 813.  
 in hypertensive heart failure, 851.  
 in paroxysmal tachycardia, 824.  
 overdosage of, symptoms of, 815.
- Digitalisation**, 814.
- Digoxin**, 814, 824.
- Dihydrostreptomycin**, 11.
- Dihydrotachysterol** (A.T. 10) in treatment  
 of tetany, 505.
- Dilatation of the heart**, 892.  
 of the œsophagus in cancer, 551.  
 of the stomach, acute, 597.  
 in pyloric obstruction, 595, 596.
- Dimenhydrinate** in travel sickness, 403.
- Dimercaprol** in acute mercurial poisoning,  
 381.  
 in arsenical dermatitis, 231.  
 in arsenical encephalopathy, 232.  
 poisoning, acute, 374.  
 in arsine poisoning, 376.  
 in bismuth poisoning, 218.  
 in erythroderma, 1269.  
 in gold poisoning, 1153.  
 in hepato-lenticular degeneration, 1485.  
 in mercurial stomatitis, 233.
- Dimethylarsine**, 373.  
 poisoning by, 376.
- Dimethylphthalate** in prophylaxis of insect  
 bites, 337.
- Dinitrobenzene poisoning**, 390.
- Dinitro-ortho-cresol**, poisoning by, 391.
- Dinitrophenol poisoning**, 391.
- Diorchitrema pseudocirrata**, 318.
- Dipetalonema streptocerca**, 326.
- Diphenhydramine** in travel sickness, 403.
- Diphtheria**, 67-79.  
 ætiology of, 67.  
 age-incidence of, 67.  
 antitoxin, 77, 78.  
 bacteriology of, 68.  
 blood in, 72.  
 carriers, 68, 77.  
 complications of, 72.  
 conjunctival, 71, 72.  
 contacts, immunisation of, 76, 77  
 cutaneous, 72, 1232, 1330.  
 diagnosis of, 74.  
 faucial, 70.  
 hæmorrhagic, 72, 76.  
 incubation period of, 70.  
 infections of the skin, 72, 1232, 1330.  
 intubation in, 78.  
 laryngeal, 71, 75, 78.  
 malignant, 70, 75, 76, 77.  
 mortality in, 75.  
 myocarditis in, 890, 891.  
 nasal, 71.  
 of eye, 71, 72.  
 paralysis in, 73, 78, 1591.  
 pathology of, 69.  
 pharyngeal paralysis in, 1355, 1591  
 post-scarlatinal, 44.  
 preputial, 72.  
 prognosis in, 75.  
 prophylactic treatment of, 76.  
 quarantine for, 76.  
 Schick test of susceptibility to, 76.  
 seasonal prevalence, 67.  
 septic, 72, 76.  
 rashes in, 72.  
 symptoms of, 70.  
 toxin in immune therapy, 3.  
 toxins of, 69.  
 treatment of, 76.  
 umbilical, 72.  
 vaginal, 72.  
 vulval, 72.  
 wound, 72.
- Diphtheritic sores**, 1330.
- Diphylobothrium cordatum**, 322.  
 houghtoni, 322.  
 latum, 322.

- Diphyllobothrium mansonii**, 323.  
**parvum**, 322.  
**Diplegia, cerebral**, 1487.  
**Diplogonoporus grandis**, 322.  
**Diplopia**, as symptom of increased intra-cranial pressure, 1387.  
 crossed, 1341.  
 diagnostic indications of, 1341.  
 in acute alcoholism, 353.  
 in barbiturate poisoning, 360.  
 in botulism, 123.  
 in cerebral abscess, 1387.  
 in disseminated sclerosis, 1474.  
 in encephalitis lethargica, 1416.  
 in fourth-nerve paralysis, 1341.  
 in intracranial tumour, 1387.  
 in migraine, 1510.  
 in myasthenia gravis, 1604.  
**Dipsomania**, 355.  
**Dipylidium caninum**, 322.  
**Displacement murmur** in pleurisy with effusion, 1069.  
**Disseminated sclerosis**, 1472.  
**Dissociation**, in hysteria, 1673.  
**Distoma crassum**, 316.  
 hepaticum, 316.  
 heterophyes, 318.  
 ringeri, 317.  
 sinense, 317.  
 westermani, 317.  
**Distomatosis, pulmonary**, 317.  
**Distomiasis**, 316-321.  
**Dithranol** in psoriasis, 1273.  
**Dittrich's plugs**, 1200.  
 in bronchiectasis, 984.  
 in chronic suppurative bronchitis, 971.  
**Diuretics** in ascites, 724.  
 in chronic nephritis, 1123.  
 in heart failure, 815.  
**Divers' paralysis**, 395.  
**Diverticula** as cause of acute intestinal obstruction, 649.  
 of stomach and small intestine, 598.  
 of the colon, 644.  
 of pharynx and œsophagus, 546.  
 traction, 546.  
**Diverticulitis**, 644.  
 causing peritonitis, 712.  
 in relation to cancer, 645.  
 indications for operation in, 645.  
**Diverticulosis**, 644.  
**Diving**, conditions entailed by, 395.  
**Dog nose**, 236.  
**Dog's disease**, 188.  
**Dolichocolon**, 646.  
**Dracontiasis**, 330.  
**Dracunculus medinensis**, 330.  
**Drainage**, postural, 1004.  
 in abscess of the lung, 1005.  
 in bronchiectasis, 986.  
 in collapse of the lungs, 993.  
**Dreamy state** as precursor of epileptic attack, 1499.  
**Drepanocytosis**, hereditary, 740, 743.  
**Dreyer's agglutination test** for typhoid, 105.  
**Drop foot**, 1574, 1589.  
 wrist, 1569, 1589.  
**Droplet infection** in acute poliomyelitis, 1424.  
 in the common cold, 148.  
 in plague, 127.  
 in scarlet fever, 36.  
 in tuberculosis, 85.  
**Dropsy, epidemic**, 348.  
 in cancer of liver, 686.  
 in cardiac failure, treatment of, 809.  
 pleural, 1076.  
 renal, 1113, 1116, 1121.  
 theories of causation of, 1113.  
**Drug addiction**, 1637-1642.  
 eruptions, 27, 1265.  
**Drugs**, as a cause of skin eruptions, 1265-1268.  
 effect of, on colour of urine, 1106.  
 in the treatment of insanity, 1620.  
**Drunkenness**, 353.  
**Dubini's disease** (electric chorea), 1414.  
**Ducrey's infection**, 143.  
**Duct, thoracic**, diseases of, 787.  
**Ductus arteriosus**, patent, 896, 897.  
**Duguet's ulcerations** in typhoid, 102.  
**Duhring's disease**, 1286.  
**Duodenal bulb**, irregularity in, significance of, 579.  
 contents, pancreatic ferments in, 701.  
 drainage for obtaining bile, 692.  
 feeding, 587.  
 ileus, 597.  
 ulcer, chronic, 578-587.  
 hyperchlorhydria in, 579.  
 intermissions in, 578.  
 not liable to malignant change, 579.  
 perforation in, 579.  
 pylalism in, 530.  
 smoking in relation to, 576, 579.  
 treatment of, 580-587.  
**Duodenum**, as source of infection in cholecystitis, 690.  
 diverticula of, 598.  
**Dupuytren's contracture**, 1167.  
**Dust** as predisposing to tubercular infection, 1008-1017.  
 consumption, 1009.  
 disease of the lung, 1008.  
 in relation to asthma, 978.  
 to bronchitis, 939.  
 to emphysema, 997.  
 to pneumoconiosis, 1008.  
 to silicosis, 1010.  
**Dwarfism**, 486.  
 in achondroplasia, 1182.  
 in cretins, 499.  
 in Fanconi syndrome, 1179.  
 in Fröhlich's syndrome, 489.  
 in idiopathic steatorrhœa, 621.  
 pituitary in relation to, 486.  
**Dysarthria**, 1367, 1373.  
 ataxic, 1373.  
 flaccid or atrophic, 1373.  
 following heat hyperpyrexia, 408.  
 in barbiturate poisoning, 360.  
 in cerebellar apoplexy, 1440.  
 in cerebral atheroma, 1444.  
 in Friedreich's ataxia, 1480.  
 in hepato-lenticular degeneration, 1484.  
 in methyl mercury poisoning, 333.

- Dysarthria** in progressive muscular atrophy, 1558.  
 spastic, 1373.
- Dyschezia**, 602, 605-609.  
 as cause of false diarrhœa, 611.  
 of infants, 606.
- Dyschondroplasia**, 1183.
- Dysdiadochokinesis** in cerebellar lesions, 1364.
- Dysenteric arthritis**, 1156.
- Dysentery**, amœbic, 275.  
 ascariis, 334.  
 bacillary, 112-119.  
 acute, 113-115.  
 bacteriology of, 113.  
 chronic, 115-119.  
 complications and sequelæ of, 116, 119.  
 epidemics of, 112.  
 incubation period in, 113.  
 prophylactic treatment of, 117.  
 prophylaxis, antisera in, 118.  
 with sulphonamides, 29, 117.  
*rheumatoid arthritis following*, 1156.  
 subacute, 115.  
 sulphonamides in, 117.  
 ulcerative colitis in relation to, 634.
- bilharzial**, 320.  
 ciliate, 283.  
 flagellate, 284.  
*Flexner-Boyd type*, 113.  
*schistosomiasis*, 320.  
*Shiga type*, 113, 114.  
*Sonne type*, 113, 115.
- Dysidrosis**, 1220.
- Dyskeratosis follicularis**, 1277.  
 mucosal, 1326.
- Dysmetria** in cerebellar lesions, 1363.
- Dyspepsia**, chronic cholecystitis as a cause of, 691.  
 gall-bladder, 695, 697.  
 gouty, 447.  
 in pernicious anæmia, 736.  
 in relation to pulmonary tuberculosis, 1024.  
 to rosacea, 1207.  
*intestinal carbohydrate*, 629.  
*nervous*, 567.
- Dysphagia**, 541.  
 hysterical, 542.  
 in acute tonsillitis, 533.  
 in diverticula of pharynx, 546.  
 in œdematous laryngitis, 944.  
 in œsophageal cancer, 551.  
 in œsophagitis, 547.  
 in organic nervous diseases, 542.  
 in pharyngitis, 538.  
 in quinsy, 535.  
 in retro-pharyngeal abscess, 539.  
 in tuberculosis of larynx, 1024.  
 lower œsophageal, 541.  
 mid-œsophageal, 541.  
 pharyngo-œsophageal, 541.  
 upper, with anæmia (*Plummer-Vinson syndrome*), 542.
- Dysphasia**, 1367.
- Dyspnœa**, asthmatic, 979.  
 cardiac, 979.  
 effort, 809.  
 in acute fibrinous bronchitis, 968.
- Dyspnœa** in acute suppurative 'bronchitis, 966, 9.  
 in acute suppurative mediastinitis, 108  
 in asbestosis, 1012.  
 in bagassosis, 1016.  
 in coal miners' pneumoconiosis, 1012.  
 in cor pulmonale, 853.  
 in cystic disease of the lung, 1044.  
 in diaphragmatic hernia, 1097.  
 in disseminated lupus erythematosus, 934.  
 in effort syndrome, 905.  
 in emphysema, 998, 1001, 1002.  
 in epidemic dropsy, 348.  
 in heart disease, 794.  
 in heart failure, 808, 809, 810.  
 in hydrothorax, 1077.  
 in lung abscess, 1003.  
 in massive collapse of lung, 993.  
 in mediastinal tumours, 1094.  
 in mitral stenosis, 866.  
 in nephritis, 1116.  
 in œdematous laryngitis, 944.  
 in passive hyperæmia of the lungs, 988.  
 in pneumothorax, 1082.  
 in pulmonary œdema, 989.  
 in pulmonary fibrosis, 1007.  
 in pulmonary infarction, 991.  
 in pulmonary tuberculosis, 1022.  
 in sero-fibrinous pleurisy, 1067.  
 in silicosis, 1009, 1010.  
 in tracheal obstruction, 960, 961.  
*paroxysmal cardiac*, 809.  
     nocturnal, 873, 914.  
 spasmodic expiratory type, forms of, 979.  
 uræmic, 979.
- Dystonia musculorum deformans**, 1484.
- Dystrophia adiposo-genitalis**, 488.  
*mental symptoms of*, 1644.  
*myotonic*, 1600.
- Dystrophies**, muscular, 1596.
- Dystrophy**, nutritional, 478.
- Dysuria** from coliform infection, 95.  
 in encephalitis lethargica, 1417.  
 in gonorrhœa, 65.  
 in schistosomiasis, 320.
- Ear**, "block", 397.  
 disease, adenoids in relation to, 942.  
 effect of increased atmospheric pressure on, 397.  
 lesions of, in congenital syphilis, 226.  
 middle, coliform infection of, 97.
- Earache** in scarlet fever, 42, 47.
- Ebstein's disease**, 877.
- Ecchondromata**, hereditary multiple ossifying, 1183.
- Ecchymoses**, 770.  
 in scurvy, 462.
- Echinococcosis**, 324.
- Echinococcus** cyst of kidney, 1147.  
 granulosus, 324.  
 multilocularis, 324.
- Echolalia**, 1525.
- Eclampsia**, whooping-cough, 140.
- Ecthyra**, 1227.
- Ectomorph habitus** in schizophrenia, 1657.
- Ectopia cordis**, 894.
- Ectropion** in leprosy, 91.

- Eczema ab solare**, 1210.  
 atopic, 1222.  
 autolytic, 1220.  
 craquelé, 1211.  
 discoid, 1219.  
 endogenous, 1221.  
 hypostatic, 1223.  
 infantile, 1221.  
 nummular, 1219.  
 pruriginous, 1222.  
 facial, 1195.  
 vaccinatum, 1249.
- Eczematide**, 1218, 1220.
- Effort syndrome**, 904.
- Effusion, pericardial**, 879, 880.  
 peritoneal, 721.  
 pleural, 1067.  
*anomalous forms of*, 1072.
- Effusions, serous, causes of**, 1067.
- Ehlers-Danlos syndrome**, 1296.
- Eisenmenger's complex**, 900.
- Elbow, "tennis,"** 1167.
- Electrical convulsant therapy in affective disorder**, 1654.  
 injuries, 403.
- Electrocardiogram, abnormal**, 800.  
 normal, 799, 800.  
 of acute pericarditis, 879, 880.  
 of angina pectoris, 838.  
 of aortic stenosis, 873.  
 of auricular fibrillation, 827.  
 of auricular flutter, 825.  
 of auriculo-ventricular block, 830.  
 of bundle-branch block, 801, 833.  
 of cardiac infarction, 844, 845.  
 of chronic constrictive pericarditis, 882.  
 of congenital heart disease, 896, 898.  
 of coronary insufficiency, acute, 849.  
 of effect of digitalis, 815.  
 of emphysema heart disease, 856.  
 of hypertension, 851.  
 of intra-ventricular block, 801.  
 of left ventricular hypertrophy, 800.  
 of mitral stenosis, 868.  
 of myocardial injury, 801.  
 of paroxysmal tachycardia, 824.  
 of pulmonary heart disease, 853.  
 of right ventricular hypertrophy, 801.  
 of Stokes-Adams syndrome, 831.  
 of syphilitic aortitis, 861.  
 of ventricular tachycardia, 828.  
 of Wolff-Parkinson-White syndrome, 833.
- Electrocardiography**, 798-802.
- Electrocution, judicial**, 403.
- Electro-encephalography**, 1493, 1682.  
 in epilepsy, 1493.  
 in psychopathic personality, 1682.
- Electrolyte control, function of kidneys in**, 1109.
- Electrolytes and water, disturbances of**, 415-422.
- Elementary bodies of Paschen in vaccinal lesions**, 169.
- Elephantiasis**, 928.  
 filarial, 326, 327.  
 from sparganum infection, 323.  
 nostras, 1224.  
 verrucosa, 327.
- Elephantiasis, vulval in lymphogranuloma inguinale**, 192.
- Elliptocytosis**, 740.
- Ellis, curve of, in pleural effusion**, 1068.
- Emboli, gas, in caisson disease**, 396, 397.  
 in auricular fibrillation, 827.  
 in subacute bacterial endocarditis, 886.  
 malignant, from cancer of liver, 685.  
 varieties of, 886.
- Embolic forms of pulmonary infarction**, 990.
- Embolism**, 925.  
 air, 854, 1446.  
 cerebral, 1445.  
 fat, 854, 1446.  
 femoral, 925.  
 in apoplexy, 1446.  
 in diphtheria, 73.  
 in endocarditis, 32, 886.  
 in mitral stenosis, 868.  
 of central artery of retina, 886.  
 paradoxical, 925.  
 parasitic, 243.  
 pulmonary, 852, 990.  
 thrombosis and, 925.
- Emetics, action of**, 562.
- Emetine in amœbic dysentery**, 278.  
 in amœbic hepatitis and abscess, 282.  
 in chronic alcoholism, 1639.  
 in distomiasis, 316, 317, 318.  
 in schistosomiasis, 321.  
 poisoning, 278.
- Emetine-Bismuth-Iodide**, 278.  
 in amœbic dysentery, 278.  
 in amœbic hepatitis, 282.
- Emotional causes of vomiting**, 561.  
 changes in mania, 1648.  
 incongruity in schizophrenia, 1662.  
 instability in progressive muscular atrophy, 1560.
- Emphysema, acute vesicular**, 1002.  
 bullous, 998, 999.  
 compensatory, 1026.  
 in cadmium poisoning, 387.  
 focal, 1011.  
 heart disease, 855.  
 marginal, 998.  
 mediastinal, 1091.  
 pulmonary, 997, 1026.  
 theories of, 998.
- Emphysematous chest**, 999.  
 girdle, the, 999.
- Empirothotonos in tetanus**, 82.
- Empyema**, 1072.  
 actinomycotic, 1038.  
 apical, 1075.  
 bacteriology of, 1072.  
 diaphragmatic, 1076.  
 evacuation of pus in, 1075.  
 fetid, 1073.  
 interlobar, 1076.  
 necessitatis, 1073, 1074.  
 as a cause of pneumothorax, 1081.  
 of accessory sinuses, 940.  
 of antrum, 940.  
 path of infection in, 1072.  
 pointing, 1073.  
 pulsating, 1073.  
 special varieties of, 1075.

- Encephalitis**, 1404.  
 associated with acute specific fevers, 1411.  
**acute**, 1411.  
**epidemic**, 1414.  
**hæmorrhagic**, 1414.  
**lethargica**, 1414.  
   mental state in, 1634.  
   Parkinsonian syndrome in, 1513.  
   sequelæ of, 1417.  
**periaxialis**, 1412.  
**subacute inclusion body**, 1413.  
**suppurative**, 1405.  
**Encephalo-myelitis**, 1411.  
 complicating measles, 152.  
 following vaccination, 170.  
**Encephalopathy, arsenical**, in arsphenamine therapy, 230, 232.  
**Encephalopathy, hypertensive**, 1444.  
 in acute nephritis, 1116, 1119.  
   lead, 368, 371.  
**Enchondromatosis**, 1183.  
**Enteritis**, 931.  
 in generalised scleroderma, 935.  
**Endocarditis**, 884.  
 acute bacterial, 889.  
 atypical verrucous, 889.  
 bacterial, 884.  
 in acute tonsillitis, 533.  
 in measles, 152.  
 in relation to chorea, 1518.  
 in rheumatic fever, 50.  
 in scarlet fever, 43.  
 infective, 884.  
 rheumatic, 49, 51, 889.  
 subacute bacterial, 885.  
   embolism in, 886.  
   murmur in, 886.  
   Osler's nodes in, 886.  
   penicillin in, 888.  
   valvular defects in, 886.  
   vegetations in, 885.  
 verrucous, 933.  
**Endocardium**, diseases of the, 884-890.  
 tuberculosis of, 890.  
**Endochondral ossification**, diseases of, 1182.  
**Endocrine causes of sexual precocity**, 523.  
 glands, diseases of the, 483-524.  
 mental disorders associated with diseases of, 1643.  
**Endodermophyton in tinea imbricata**, 1333.  
**Endolimax nana**, 275.  
**Endometritis in gonorrhœa**, 67.  
**Endothelial lesions**, as cause of hæmorrhagic states, 771.  
**Endothelioma of brain**, 1382.  
   of pleura, 1086.  
**Endothelium in relation to hæmorrhagic tendencies**, 771.  
**Endotoxins**, 3.  
 and exotoxins contrasted, 3.  
**Enema, opaque**, technique of, 602, 603.  
**Enophthalmos**, 1345.  
 in cancer of œsophagus, 552.  
 in mediastinal tumours, 1095.  
**Entamoeba coli**, 275.  
   histolytica, 113, 275, 279, 636.  
**Enteric fever**, 97.  
**Enteric fever, group of organisms**, 98.  
**Enteritis**, 631.  
   acute infective, 119.  
   as a cause of diarrhœa, 610.  
   chronic, 631.  
   toxic Salmonella, 121.  
   tuberculous, 638.  
**Enterobiasis**, 335.  
**Enterobius vermicularis**, 335.  
**Enterococci in carbohydrate dyspepsia**, 630.  
**Enterocolitis**, 152.  
**Enterogastrone**, 587.  
**Enterogenous cyanosis**, 752.  
**Enterokinase**, 599, 701.  
**Enuresis in ascariasis**, 334.  
   nocturnal, adenoids as a cause of, 942.  
**Envelope crystals**, 1099.  
**Eosinophilia**, 753.  
   hereditary, 753.  
   pulmonary tropical, 313.  
   tropical, 313, 753.  
   with splenomegaly, 754.  
**Eosinophilic leucæmia**, 754.  
**Epeira diadema**, 339.  
**Ependymoma**, 1534.  
**Ephedrine in Stokes-Adams syndrome**, 832.  
   in accessory sinus suppuration, 941.  
   in allergic conditions, 711.  
   in asthma, 980.  
   in chronic postural hypotension, 818.  
   in complete heart block, 832.  
   in myasthenia gravis, 1606.  
**Ephelides**, 1202.  
**Epidemic diarrhœa in children**, 614.  
   jaundice, 663.  
**Epidermolysis bullosa**, 1291.  
**Epidermophyton inguinale**, 1333.  
**Epididymitis in coliform infections of urinary tract**, 96.  
   in gonorrhœa, 66.  
   in syphilis, 207.  
**Epididymo-orchitis**, filarial, 327.  
   in mumps, 175.  
**Epiglottitis**, swollen in œdematous laryngitis, 944.  
**Epilepsia partialis continua**, 1502.  
**Epilepsy**, 1492-1507.  
   ætiology of, 1493.  
   alcoholic, 1639.  
   aura in, 1495, 1498.  
   cardiac, 1502.  
   convulsion in, 1495.  
   cursive, 1499.  
   cysticercus, 324, 1504.  
   diagnosis of, 1503.  
   diurnal, 1501.  
   effect of, on intellectual powers, 1500, 1637.  
   electro-encephalogram in, 1493.  
   essential, 1492.  
   exciting causes of, 1494.  
   hereditary in, 1494.  
   idiopathic, 1492.  
   in cerebral abscess, 1407, 1408.  
   in cerebral diplegia, 1489.  
   in infantile hemiplegia, 1491.  
   in somatic tetanias, 324.  
   in tuberosc sclerosis, 1487.  
   Jacksonian, 1492.

- Epilepsy**, major fits of, 1495.  
 marriage and pregnancy in relation to, 1505.  
 mental disorders associated with, 1636.  
   state in, 1500.  
 minor, 1499.  
 myoclonus, 1502, 1520.  
 nocturnal, 1501.  
 periodicity of, 1500.  
 post-convulsive phenomena in, 1500.  
 prodromata, 1495.  
 prognosis of, 1504.  
 psychomotor, 1360.  
   fits of, 1499.  
   reflex, 1502.  
   symptomatic, 1492.  
   symptoms of, 1495.  
   traumatic, 1501.  
   treatment of, 1504.  
   varieties of, 1501.
- Epileptic cry**, 1496.  
 furor, 1636.
- Epileptiform attacks in brain tumours**, 1384.  
   in cerebral syphilis, 1460.  
   in general paralysis of the insane, 1456.  
   in lead poisoning, 368.
- Epiloia**, 1486.
- Epiphyseal changes in congenital syphilis**, 226.  
   in rickets, 465.
- Epiphyses in achondroplasia**, 1182.
- Epiphysitis, syphilitic**, 226.
- Epistaxis**, 938.  
   in cirrhosis of the liver, 677.  
   in hereditary hæmorrhagic telangiectasia, 775.
- Epithelioma adenoides cysticum**, 1309.  
   apocrine, 1309.  
   calcifying (Malherbe), 1310.  
   of œsophagus, 551.
- Epituberculosis**, 1026.
- Erb type of paralysis in birth injury**, 1585.
- Erb's juvenile type of muscular dystrophy**, 1598.  
   myotonic reaction, 1603.  
   palsy, 1568.  
   sign in hypoparathyroidism, 504.  
   syphilitic spastic paraplegia, 1469.
- Erethism**, 382.
- Ergotamine tartrate in migraine**, 1511.
- Ergotism**, 345.
- Eructation, offensive**, in pyloric obstruction, 594.
- Eruption, bullous**, in congenital syphilis, 225.  
   creeping, 1334.
- Erysipelas**, 34.  
   coastal, 329.  
   recurring, 35.
- Erysipeloid**, 1232.
- Erysipelothrix rhusiopathiæ**, 7.
- Erythema after arsenamine remedies**, 231.  
   annulare centrifugum (Darier), 1258.  
   chronicum migrans, 1258.  
   contusiform, 1260.  
   elevatum diutinum, 1299.  
   figuratum perstans, 1259.  
   fixed, 1255.  
   in bacterial food poisoning, 121.  
   in pellagra, 473.
- Erythema in septicæmia**, 31.  
   induratum, 1244, 1261.  
   infantum of Jacquet, 1223.  
   infectious, 305.  
   multiforme, 1257.  
   nodosum, 307, 1260.  
   of the ninth day, 231, 1255.  
   pernio, 1205.  
   rheumatic, 50, 51.  
   simple, 1254.  
   simplex gyratum, 1258.  
   toxic, 1254.
- Erythræmia**, 749, 750.  
   in anoxæmia, 400.
- Erythralgia**, 924.
- Erythroblastosis fœtalis**, 745.
- Erythroblasts**, 729.
- Erythrocyanosis**, 924, 1205.  
   crurum puellarum frigida, 924, 1206.
- Erythrocyte sedimentation rate**, 727.  
   in pregnancy, 727.  
   in rheumatoid arthritis, 1151.  
   in tuberculosis, 1027.
- Erythrocytosis**, 749.  
   in mountain sickness, 400.
- Erythroderma**, 1268.  
   lymphadenopathic, 1268.
- Erythroedema**, 308.
- Erythromelalgia**, 924.  
   in chronic arsenical poisoning, 374.
- Erythromycin**, 14.
- Erythroplasia (Queyrat)**, 1307.
- Esundia**, 268.
- Esthiomene**, 192.
- Ether**, addition to, 1642.
- Eugenics in relation to mental deficiency**, 1867.
- Euglobulin in urine**, 1102.
- Eunuchism**, 520.  
   mental changes due to, 1645.
- Eunuchoid giants**, 485, 521.
- Eunuchoidism**, 520.
- Euphoria**, in disseminated sclerosis, 1475.  
   in general paralysis, 1456.  
   in septicæmia, 31.
- Eurymorph habitus**, 1646.
- Euscorpium italicus**, 340.
- Exercises**, Buerger's, for thrombo-angiitis obliterans, 922.  
   postural, for osteo-arthritis, 1159.
- Exhaustion and inanition**, mental disorders associated with, 1642.
- Exner's centre for written language**, 1367.
- Exophthalmic goitre**, 491.  
   cardio-vascular system in, 492.  
   gastro-intestinal system in, 492.  
   metabolism in, 493.  
   nervous system in, 492.  
   ocular signs in, 493.  
   psychogenic factors in, 1643.  
   thiouracil in, 494.
- Exophthalmic ophthalmoplegia**, 493.
- Exophthalmos in chloroma**, 763.  
   in exophthalmic goitre, 492.  
   in Hand-Schüller-Christian's disease, 784.  
   in lesion of cervical sympathetic, 1345.  
   in rat-bite fever, 245.
- Exostoses**, multiple, 1183.

- Exostosis** in pulmonary new growths, 1042.  
**Exostosis**, subungual, 1322.  
**Exotoxins**, 3.  
     and endotoxins, contrasted, 3.  
**Expectoration** in pulmonary tuberculosis, 1021.  
**Extrasystoles**, 821.  
     auricular, 821.  
     in digitalis overdosage, 815.  
     interpolated, 821.  
     nodal, 822.  
     ventricular, 822.  
**'Extrinsic factor'** in protein food, 556.  
     in relation to anæmias, 734.  
**Eye affections** in acromegaly, 484.  
     in cerebrospinal fever, 59.  
     in diabetes mellitus, 441, 442.  
     in herpes zoster, 1248.  
     in measles, 152, 155.  
     in methanol poisoning, 357.  
     in pemphigus, 1290.  
     in small-pox, 162, 164.  
     in syphilis, 207, 226.  
     in trichlorethylene poisoning, 395.  
     in vitamin A deficiency, 455.  
     complications of sleeping sickness, 272.  
     lesions, filarial, 329.  
**Eyes**, care of the, in small-pox, 168.  
     conjugate deviation of, in apoplexy, 1438.  
     in exophthalmic goitre, 493.  
     in Gaucher's disease, 785.  
     in toxic adenomatous goitre, 495.  
**Facial contracture** after Bell's paralysis, 1350.  
     hemispasm, 1341.  
     paralysis, 1349.  
         from birth injury, 1585.  
         from caries of temporal bone, 1349.  
         from herpes of the geniculate ganglion, 1349.  
         in encephalitis lethargica, 1416.  
     spasm, peripheral, 1351.  
**Facies**, adenoid, 943.  
     choleraic, 135.  
     Hippocratica, 713.  
     in aortic aneurysm, 860.  
     in cerebral atheroma, 1443.  
     in cerebral diplegia, 1489.  
     in cirrhosis of the liver, 676.  
     in congenital syphilis, 227.  
     in cretinism, 499.  
     in Cushing's syndrome, 516.  
     in encephalitis lethargica, 1416.  
     in hepato-lenticular degeneration, 1484.  
     in Horner's syndrome, 1345.  
     in hypochromic idiopathic anæmia, 732.  
     in manganese poisoning, 385.  
     in Mediterranean anæmia, 743.  
     in myxœdema, 496.  
     in myasthenia gravis, 1605.  
     in paralysis agitans, 1512.  
     in peritonitis, 713.  
     in sleeping sickness, 272.  
     in systemic sclerosis, 1292.  
     leprotic, 91.  
     mongoloid, 1685.  
     myopathic, 1599, 1601.  
**Facies**, tabetic, 1465.  
**Facio-scapulo-humeral type** of myopathy, 1598.  
**Factors V and VII** in blood coagulation, 765.  
**Fæcal accumulation** as cause of acute intestinal obstruction, 649.  
     effects of, 607.  
     vomiting in intestinal obstruction, 651.  
**Fæces**, bile-products in, 663.  
     demonstration of tubercle bacilli in, 87.  
     examination of, 603.  
     in jaundice, 663.  
     occult blood in, 603.  
         tests for, 603, 604.  
     pancreatic ferments in, 701.  
     retention of, effects of, 607.  
**Faget's sign** in yellow fever, 186.  
**Fainting** in heart disease, 794, 817.  
     in methæmoglobinæmia, 752.  
**Fallot**, tetralogy of, 897.  
**Falx cerebri**, localisation of lesions about the, 1361.  
**Familial icterus gravis neonatorum**, 745.  
     periodic paralysis, 1607.  
     spastic paralysis, 1482.  
**Famine fever**, 241.  
**Fanconi syndrome**, 468, 1179.  
**Fannia canicularis**, 339.  
**Farcy**, 131, 132.  
     buds, 131, 132.  
     pipes, 131.  
**Farmers' lung**, 1016.  
     skin, 1210.  
**Fasciæ**, fibrositis of, 1166.  
**Fasciola hepatica**, 316.  
**Fascioliasis**, 316.  
**Fasciolopsis buski**, 316.  
**Fat**, affinity of, for nitrogen, 396.  
     digestion defective in sprue, 620, 624.  
     embolism, 854, 1446.  
     excess of, in stools, 612, 619, 663, 705.  
     in stools from deficient pancreatic digestion, 701.  
     in urine, 1107.  
     metabolism in coeliac disease, 618.  
     in idiopathic steatorrhœa, 620.  
     necrosis in acute necrosis of pancreas, 702.  
     -soluble vitamins, 454, 455, 456.  
     subcutaneous, loss of in lypodystrophia, 452.  
**Fatigue** as symptom of rheumatoid arthritis 1151.  
     in relation to lead palsy, 367.  
**Fatty diarrhœa**, 610, 612, 701.  
     in diphtheria, 70.  
**Fauces** in scarlet fever, 38, 40.  
     syphilitic ulcer of, 206.  
**Fausse teigne amiantacée**, 1194.  
**Favus**, 1234, 1235.  
**Febris comatosa**, 1414.  
     flava, 184.  
     recurrens, 241.  
**Feeble-mindedness**, 1684.  
**Felty's syndrome**, 1151.  
**Feminisation**, 513.  
**Femoral thrombosis**, 927.  
     in typhoid, 103.  
     in typhus, 298.



- Fermentation, gastric, in relation to flatulence, 566.**  
 in pyloric obstruction, 594.  
 intestinal, as cause of diarrhoea, 610, 612.  
 in carbohydrate dyspepsia, 629.  
**Ferments in relation to carbohydrate digestion, 629.**  
**Ferric chloride test for ketone bodies in urine, 425.**  
**Festination in paralysis agitans, 1512.**  
**Fever, abortus, 125.**  
 bilious remittent, 242.  
 black, 264.  
 blackwater, 260.  
 break-bone, 189.  
 camp, 295.  
 Carapata, 243.  
 cerebrospinal, 54.  
 Choix, 293.  
 dandy, 189.  
 deer-fly, 130.  
 enteric, 97.  
 famine, 241.  
 five-day, 300.  
 following sulphanilamide administration, 27.  
 gastric, 97.  
 glandular, 305.  
 hæmoglobinuric, 260.  
 icteric, 242.  
 intermittent, 245.  
 jail, 295.  
 Japanese river, 288.  
 jungle, 245.  
 Kendal's, 184.  
 Malta, 125.  
 marsh, 245.  
 Mediterranean, 125.  
 melanuric, 260.  
 meningococcal, 54.  
 Meuse, 300.  
 Monday, 1015.  
 Oroya, 144.  
 Pahvant Valley, 130.  
 papataci, 188.  
 paratyphoid, 110.  
 phlebotomus, 188.  
 pinta, 293.  
 Pym's, 188.  
 "Q," 302.  
 quintan, 300.  
 rat-bite, 244.  
 relapsing, 241.  
 remittent, 245.  
 rheumatic, 48.  
 Rocky Mountain spotted, 293.  
 sand-fly, 188.  
 São Paulo, 293.  
 scarlet, 36.  
 spirillum, 241.  
 splenic, of animals, 79.  
 spotted, of Eastern type, 293.  
 Sumatra mite, 288.  
 swamp, 237.  
 three-day, 188.  
 tick, 243.  
 Tobia, 293.  
 trench, 300.  
 trypanosome, 271.  
**Fever, tsutsugamushi, 288.**  
 typhoid, 97.  
 typhus, 295.  
 undulant, 125.  
 Volhynia, 300.  
 yellow, 184.  
**Fibrillation, auricular, 826.**  
 muscular, clinical instances of, 1559, 1560.  
 in encephalitis lethargica, 1417.  
 in interstitial neuritis, 1576.  
 in peroneal muscular atrophy, 1564.  
 in progressive muscular atrophy, 1559.  
**Fibrin, 765.**  
**Fibrinogen, 765, 767.**  
**Fibrocystic disease, local, 1175.**  
**Fibro-elastosis, 889.**  
**Fibroma colli, 1312.**  
 durum, 1312.  
 en pastille, 1312.  
 molle, 1312.  
 of kidney, 1144.  
**Fibromatosis osteoplastica osseum, 1175.**  
**Fibroplasia, endocardial, 889.**  
**Fibrosis, endocardial, 889.**  
 in pulmonary tuberculosis, 1019, 1020, 1025.  
 insular, 1007.  
 of wasted muscles in peroneal muscular atrophy, 1563, 1564.  
 progressive massive, 1011.  
 reticular, 1007.  
**Fibrositis, 1165.**  
 types of, 1165.  
**Fibrous nodules, 1166, 1169.**  
 tissues, diseases of the, 1150.  
**Fièvre amarilla, 184.**  
**Fiedler's myocarditis, 891.**  
**Fièvre boutonneuse, 286, 293.**  
 jaune, 184.  
**Fifth disease, 305.**  
**Filaria bancrofti, 326, 328.**  
 as cause of chyl thorax, 1079.  
 as cause of chyluria, 1107.  
 as cause of elephantiasis, 326, 327, 328.  
 life cycle of, 326.  
 loa, 326, 328.  
 malayi, 326, 328.  
 ozzardi, 326.  
 perstans, 326.  
**Filariasis, 326.**  
**Filatow-Dukes disease, 304.**  
**Filix mas for tape-worm, 323.**  
**Filtrable viruses, 146, 147.**  
**Fingers, clubbing of, 1171.**  
 "dead," 920.  
 Hippocratic, 1171.  
 in Raynaud's phenomenon, 923.  
 in systemic sclerosis, 1292.  
 sausage-like, in syringomyelia, 1547.  
 webbed, in oxycephaly, 1181.  
**Fish, poisonous, 343.**  
**Fish-liver oils, vitamin value of, 454, 455.**  
**Fistula between gall-bladder and bowel, 696.**  
 gastro-colic, 588, 592.  
 gastro-jejuno-colic, 588.  
 in ano, after ulcerative colitis, 635.  
 in pulmonary tuberculosis, 1026.  
 jejuno-colic, 588.  
 vesico-colic, 645.

- Fits, auditory, 1498.**  
   in frontal lobe tumours, 1358.  
   Jacksonian, 1497.  
   local, 1497.  
   paralytic, 1498.  
   olfactory and gustatory, 1498.  
   psychic, 1499.  
   sensory, 1498, 1499.  
   visual, 1498.
- Five-day fever, 300.**
- Flaccid paralysis in cerebrospinal fever, 58.**  
   paraplegia in subacute combined degeneration, 1552, 1553.
- Flaccidity in progressive spinal muscular atrophy of children, 1566.**
- Flagellate diarrhoea, 284.**
- Flatulence, gastric, 566.**  
   in bacillary dysentery, 115.  
   in cirrhosis of liver, 676.  
   in intestinal carbohydrate dyspepsia, 630.  
   in pulmonary tuberculosis, 1021, 1024.  
   in sprue, 624.  
   intestinal, 630.
- Flea typhus, 286.**
- Fleas in relation to spread of plague, 127, 129.**
- Fleck-typhus, 295.**
- Fleshy hand in syringomyelia, 1547.**
- Flexibilitas cerea in encephalitis lethargica, 1416.**
- Flies as carriers of infection in epidemic diarrhoea, 615.**  
   genera of, causing intestinal myiasis, 337.  
   in relation to bacillary dysentery, 112.  
   in relation to cholera, 134.  
   in relation to typhoid, 93.
- Fluid retention as a factor in infection, 2.**
- Flukes, diseases due to, 316-321.**
- Flush, hectic, in pulmonary tuberculosis, 1012.**  
   malar, in myxoedema, 496.
- Foam cells in xanthoma, 1298.**
- Focal sepsis in relation to arthritis, 1153.**  
   to fibrositis, 1165.  
   to gall-bladder infection, 689.  
   to gout, 445.  
   to Henoch's purpura, 774.  
   to pyæmia, 32.  
   to rheumatic fever, 48.
- Fœtal adenoma, 500.**
- Folic acid, 460, 735.**  
   deficiency in idiopathic steatorrhœa, 620.  
   in nutritional macrocytic anemia, 477.
- Folie à deux, 1669.**
- Folinic acid, 460.**
- Folliculitis barbae, 1227.**  
   profunda, 1227.
- Fontanelle, anterior, in rickets, 466.**
- Food, arsenical contamination of, 373.**  
   as a cause of diarrhoea, 609, 614.  
   highly seasoned, as a cause of cirrhosis of liver, 674.  
   in relation to fibrositis, 1166, 1167.  
   in relation to gout, 444, 448.  
   in relation to urticaria, 1255.  
   lead contamination of, 365.  
   poisoning, 119.  
     by *Clostridium botulinum*, 123.  
     by *Clostridium welchii*, 124.  
     by *Salmonella* organisms, 119, 121.
- Food poisoning, staphylococcal, 122.**  
   toxin, type of, 122.
- Foods, allergic reactions to, 710, 939.**
- Foot-and-mouth disease, 182.**
- Foot deformities in bacterial urethritis, 312.**  
   in acromegaly, 484.  
   in mycetoma, 197.
- Foot-drop, 1574, 1589.**  
   in beriberi, 470.  
   rot, 1218.
- Fordyce condition, 1309.**
- Foreign bodies in appendix, 654.**  
   in bronchi, 974.  
   in nose in relation to diphtheria, 71.  
   in trachea, 959.
- Forest yaws, 268.**
- Formol-gel test in kala-azar, 267.**
- Fortification spectrum of migraine, 1509.**
- Foster Kennedy's syndrome, 1358.**
- Fouadin in filariasis, 328.**  
   in schistosomiasis, 321.
- Fourth disease, 304.**
- Fowler's solution in disseminated sclerosis, 1477.**
- Fox-Fordyce disease, 1281.**
- Fractional test-meal, 559.**
- Fractures in enchondromatosis, 1183.**  
   in focal osteitis fibrosa, 1176.  
   in fragilitas ossium, 1180.  
   in Gaucher's disease, 1186.  
   in hyperparathyroidism, 501.  
   in multiple myeloma, 1185.  
   in osteomalacia, 1177.  
   in the Fanconi syndrome, 1179.  
   spontaneous, in idiopathic steatorrhœa, 621.
- Fragilitas crinium, 1319.**
- ossium congenita, 1180.**
- Fragility of red cells, 741.**  
   in acholuric jaundice, 741.
- Framboesia, 233.**
- Freckles, 1202.**
- Frei's intradermal test in lymphogranuloma inguinale, 192.**
- Fremitus, hydatid, 1047.**
- Friction fremitus, in acute pericarditis, 879.**  
   in acute dry pleurisy, 1064.  
   in chronic pleurisy, 1066.  
   in pneumonia, 1051.
- Friderichsen-Waterhouse syndrome, 57.**
- Friedreich's ataxia, 1479.**  
   disease, 1479.
- Fröhlich's syndrome, 488.**
- Froin's syndrome, 1379.**
- Frontal bossing in congenital syphilis, 227.**
- Frontal lobe, abscess of, 1408.**  
   signs of local lesions of, 1358.  
   tumour, syndrome of, 1358.
- Frostbite, 1210.**
- Fugue, hysterical, 1673.**
- Fuller's earth, 1014.**
- Fulminate itch, 383.**
- Fundus oculi, in benign hypertension, 910.**
- Fungi, dermatitis due to, 1232-1240.**  
   in relation to pulmonary lesions, 1038.  
   pathogenic to man, 193.  
   poisoning by, 345.
- Fungicidal dusts, causing mercurial poisoning, 383.**

- Funiculitis**, endemic, 327.  
**Fur dyes** as cause of dermatitis, 1467.  
**Furuncle**, 1229.  
**Fusiformis**, sensitivity to penicillin, 7.
- Gait**, cerebellar, 1364.  
 in alcoholic neuritis, 1589.  
 in beriberi, 470.  
 in bubonic plague, 128.  
 in cerebral diplegia, 1489.  
 in chorea, 1516.  
 in disseminated sclerosis, 1474.  
 in Friedreich's ataxia, 1480.  
 in hysteria, 1672.  
 in lathyrism, 350.  
 in manganese poisoning, 385.  
 in osteomalacia, 1177.  
 in paralysis agitans, 1512.  
 in pellagra, 474.  
 in pseudo-hypertrophic muscular dystrophy, 1597.  
 in sleeping-sickness, 272.  
 in trinitrotoluene poisoning, 390.
- Galactosuria**, 444.
- Gall-bladder**, *B. coli* infection of, 689.  
 carcinoma of, 699.  
 cholesterosis of, 694.  
 diseases of, 689.  
 dyspepsia, 695, 697.  
 empyema of, 690.  
 gangrene of, 690.  
 infection, sources of, 689, 694.  
 strawberry, 694.  
 X-ray examination of, 692.
- Galloping consumption**, 1021.
- Gall-stone colic**, 695.  
 dyspepsia, 695.
- Gall-stones**, 694.  
 acholurhydria and, 690.  
 as cause of acute intestinal obstruction, 649.  
 calcium bilirubinate, 741.  
 cancer as a sequel of, 697.  
 composition of, 695, 696.  
 impaction of, 695.  
 in acholuric jaundice, 741.  
 in relation to jaundice, 661, 664.  
 in relation to pancreatic necrosis, 703, 704.  
 in typhoid fever, 103.
- Galvano-cautery** in fibroma molle, 1312.  
 in granuloma telangiectaticum, 1315.  
 in stellate hæmangioma, 1314.
- Gametocytes** of malarial parasite, 247.
- Gander cough** of tracheal obstruction, 958.
- Ganglioneuroma**, 520.
- Gangosa**, 234, 236.
- Gangrene** in acute appendicitis, 654.  
 in agranulocytosis, 756.  
 in benzene poisoning, 388.  
 in cholera, 135.  
 in diabetes, 439.  
 in diphtheria, 72, 73.  
 in endocarditis, 886.  
 in ergotism, 345.  
 in peripheral arteriosclerosis, 919.  
 in Rocky Mountain tick typhus, 294.  
 in scarlet fever, 44.  
 in thrombo-angitis obliterans, 921, 922.  
 in thrombosis, 925.
- Gangrene** in tropical ulcer, 1332.  
 in typhus, 298.  
 of the lung, 1005.  
 of parotid in mumps, 176.  
 of strangulated intestine, 651.
- Gangrenous stomatitis**, 527.  
 in agranulocytosis, 527.  
 in measles, 152, 155.
- Ganister disease**, 1009.
- Ganser syndrome**, 1674.
- Gargoylism**, 1686.
- Garland's triangle** in pleurisy with effusion, 1068.
- Gas**, deficient elimination of, 566.  
 emboli in caisson disease, 396, 397.  
 in flatulence, nature of, 566, 567.  
 produced in intestinal carbohydrate dyspepsia, 629, 630.  
 in megacolon, 647.
- Gas poisoning**, acute tracheitis caused by, 954.  
 as a cause of bronchitis, 967.  
 fibroid changes in lung in, 1006.  
 in relation to tracheitis, 954.  
 pulmonary oedema after, 983.
- Gasserian ganglion**, alcohol injection of, 1348.
- Gastrectomy**, partial, 586.
- Gastric analysis**, 559.  
 and duodenal ulcer, 575-587.  
 acute, 576.  
 ætiology of, 575.  
 carcinomatous developments in, 586, 590.  
 chronic, 577-587.  
 complications of, 578, 579.  
 diet in, 581.  
 treatment of, 580-587.  
 hæmatemesis in, 577, 579.  
 incidence of, 575.  
 pathogenesis of, 576.  
 position of, as affecting pain, 577.  
 post-ulcer régime, 585.  
 smoking in relation to, 576, 581, 583, 584.  
 strict ulcer treatment, 583.  
 surgical treatment of, 586.  
 tubercular, 588.
- crises of tabes**, 1462, 1465.  
 treatment of, 1468.
- disorders**, causes of, 557.
- diverticula**, 598.
- fever**, 97.
- flatulence**, 566.
- infection**, 557.
- irritants**, 556, 557.
- juice**, bactericidal action of the, 556.  
 excessive secretion of, 554.  
 hyposecretion of, 554.  
 normal, 553.  
 resting, 560.
- lavage**, in acute mercurial poisoning, 381.  
 in alcoholic coma, 355.  
 in chronic gastric and duodenal ulcer, 582.  
 in chronic gastritis, 574.
- motility**, 555.
- putrefaction** as a cause of flatulence, 566.
- secretion**, 553.  
 regulation of, 555.
- sensation**, 556.

- Gastric analysis, symptoms of functional nervous disorders, 557.**  
 reflex, origin of, 558.  
**ulcer, chronic, 577.**  
   carcinomatous development of, 578.  
   cicatrisation of, causing hour-glass stomach, 578.  
   healing of, causing obstruction, 578.  
   perforated, 578.
- Gastritis, acute catarrhal, 571.**  
 phlegmonous, 572.  
 suppurative, 572.  
 alcoholic, 571, 573, 574.  
 atrophic, 573.  
 chronic, 573.  
 diffuse suppurative, 572.  
 hæmatogenous, 557.
- Gastro-colic fistula after gastric operations, 587.**  
 in cancer of colon, 588, 592.
- Gastrodiscus hominis, 316.**
- Gastro-enteritis from bacterial poisoning, 121, 122, 124.**  
 in acute lead poisoning, 363.  
 in fungus poisoning, 345.
- Gastro-enterostomy, anæmia following, 732.**  
 -gastrostomy in hour-glass stomach, 594.  
 -intestinal allergy, 710.  
 catarrh in chronic alcoholism, 355.  
 infection, acute, 614.  
 -jejunal and jejunal ulcer, 587.  
 -jejunitis, post-operative, 587.  
 -jejuno-colic fistula, 587.  
 -jejunostomy, in cancer of stomach, 593.  
 in pyloric obstruction, 586.
- Gastrosocopy, 560.**
- Gastrotaxis, 569.**
- Gaucher's disease, 784, 1186.**
- Gee-Herter disease, 620, 1178.**
- Gee-Thaysen disease, 620.**
- General paralysis of the insane, 1455.**  
 dementia in, 1632.  
 juvenile, 1633.  
 Lissauer form of, 1633.  
 Wassermann test in, 1457.
- Geniculate ganglion, herpes of, 1349.**
- Genital mucous membranes, diphtheritic infection of, 70, 72.**  
 organs, defective development of, in Fröhlich's syndrome, 489.  
 in cretinism, 499.  
 in dystrophia myotonica, 1602.  
 in virilism, 512.  
 lesions of, in lymphogranuloma inguinale, 191.  
 in ulcerating granuloma, 1335.  
 tract, abacterial infection of, 310.
- Genitals, seriginous ulceration of, 1334.**
- Genian violet in clonorchiasis, 318.**  
 in enterobiasis, 335.  
 in strongyloidiasis, 326.
- Gerhardt's sign, 961.**
- German measles, 156.**
- Gesture language, 1369.**
- Ghon's focus, 1018.**
- Giardia diarrhoea, 284.**
- Giardia intestinalis, 284.**  
 lamblia, 284.
- Giddiness in carbon monoxide poisoning, 359.**  
 in epilepsy, 1499.  
 in heart disease, 794.  
 in intracranial tumour, 1388.  
 in migraine, 1509.
- Gierke's syndrome, 452, 892.**
- Gigantism, 485.**
- Gilchrist's disease, 198, 1239.**
- Gilles de la Tourette's disease, 1524, 1634.**
- Gingivitis in relation to pyorrhœa, 527, 528.**  
 marginal, 528.
- Girdle sensation in tabes, 1463.**
- Glanders, 131.**
- Glands, cervical, enlargement of, with adenoids, 942.**  
 mediastinal, enlargement of, 1092.
- Glandular fever, 305-307.**  
 purpuric type, 306.  
 typhoid type, 306.
- Glans penis, primary syphilitic sore of, 204.**
- Glanzmann's disease, 771.**
- Glass-pock, 171.**
- Glaucoma in epidemic dropsy, 348, 349.**
- Glioblastoma multiforme, 1382.**
- Glioma of brain, 1381.**
- Globin insulin, 429.**
- Globulin, antihæmophilic, 765, 766.**  
 in urine, 1102.
- Globus hystericus, 539, 1671.**
- Glomangioma, 1315.**
- Glomerulo-nephritis, 1115.**
- Glomerulosclerosis, diabetic, 442, 1125.**  
 intercapillary, 1125.
- Glossina morsitans, a trypanosome carrier, 271.**  
 palpalis, a trypanosome carrier, 271.  
 swynnertoni, 271.  
 tachinoides, 271.
- Glossitis, 1327.**  
 chronic superficial in syphilis, 208.  
 exfoliata, 1327.  
 in anæmias, 732.  
 in Paterson's syndrome, 543.  
 in pellagra, 473.  
 in pernicious anæmia, 736.  
 Moeller's, 1327.  
 rhomboidea mediana, 1327.  
 syphilitic, 208.
- Glossodynia, 1327.**  
 exfoliata, 1327.
- Glossopharyngeal neuralgia, 1354.**
- Glottic spasm, 953.**  
 in tetanus, 82.
- Glottis, œdema of, 944.**  
 in measles, 151.  
 in mumps, 176.  
 in typhus, 298.
- Glove and stocking anæsthesia, 1587.**
- Glucocorticoids, 506, 507.**
- Glucose content of cerebrospinal fluid, 1380.**  
 in hyperinsulinism, 431, 444.  
 tolerance in osteo-arthritis, 1159.  
 in rheumatoid arthritis, 1151.
- Gluten of wheat, intolerance of, in cœliac disease, 618.**  
 in idiopathic steatorrhœa, 620.

- Glyceryl trinitrate** in anginal attacks, 840.  
**Glycogen disease**, 452.  
**Glycosuria**, causes of, 422.  
     in acromegaly, 484.  
     in brain-stem lesions, 1363.  
     in Graves's disease, 493.  
     in relation to blood sugar, 423.  
     in sciatica, 1592.  
     in whooping-cough, 140.  
     pituitary gland in relation to, 483.  
     thyrotoxic, 494.  
**Gmelin's test** for bile-pigment, 662.  
**Goat's milk** as channel of infection in undulant fever, 125, 126.  
**Goeckerman régime** in psoriasis, 1272.  
**Goitre**, 499.  
     colloid, 499.  
     exophthalmic, 491.  
     malignant change in, 500.  
     nodular, 499.  
     parenchymatous, 499.  
     pressing on trachea, 500.  
     thyrotoxic nodular, 495.  
     toxic adenomatous, 495.  
**Gold poisoning**, effect of, on liver, 671.  
     therapy, complications of, 1152.  
         in arthritis, 1152.  
         in lupus erythematosus, 1263.  
         in rheumatoid arthritis, 1152, 1153.  
         in Still's disease, 1164.  
**Gonadotrophin**, 483.  
**Gonads** in acromegaly, 484.  
     in pseudo-hermaphroditism, 514, 515.  
     in Simmonds's disease, 487.  
**Gonococcal arthritis**, 1154.  
     peritonitis, 715.  
     septicæmia, 31.  
**Gonococcus**, the, 65.  
     sensitivity to penicillin, 7, 8.  
**Gonorrhœa**, 65.  
     in the female, 66.  
     in the male, 65.  
     prophylaxis with sulphonamides, 28.  
**Goodall's illness** of infection, 150.  
**Goose-gait** with alkaptonuria, 1105.  
**Gordon's sign** in spastic paraplegia, 1529.  
**Goudou**, 236.  
**Gout**, 444.  
     acute, 446.  
     alcoholism in relation to, 355, 445.  
     chalky, 446.  
     chronic, 447.  
     classical, 446, 447.  
     differentiated from rheumatic fever, 52.  
     irregular, 447.  
     mental disorders in, 1643.  
     radiographic appearances in, 447.  
     tophi in, 1301.  
**Gouty changes** in chronic lead poisoning, 426.  
**Gower's mixture** in migraine, 1511.  
**Gowers**, the "tonic atrophy" of, 1557.  
**Gradenigo's syndrome**, 1342.  
**Gramicidin**, 6.  
**Grand mal**, 1495.  
**Granular kidney**, 1124.  
**Granulocytes**, 753.  
**Granulocytopenia**, after arsphenamine therapy, 232.  
**Granulocytopenia**, primary, 756.  
**Granuloma annulare**, 1299.  
     coccidioidal, 200.  
     eosinophilic, 783, 1298.  
     in American dermal leishmaniasis, 268.  
     inguinale, 1334.  
         tropicum, 1334.  
         lipophagic, 1294.  
     paracoccidioidal, 199.  
     pyogenicum, 1315.  
     telangiectaticum, 1315.  
     ulcerating, of the pudenda, 1334.  
     venereum, 1334.  
         vel inguinale, 1250.  
**Granulomata**, infectious, of brain, 1384.  
     in beryllium poisoning, 386.  
     malaria, 249.  
**Grasping reflex** in prefrontal lobe lesions, 1358.  
**Graves's disease**, 491.  
**Grawitz tumour**, 1145.  
**Greenstick fractures** in rickets, 466.  
**Grinders' asthma**, 1009, 1015.  
     consumption, 1009.  
     rot, 1009.  
**Grit consumption**, 1009.  
**Grocco's triangle** in pleurisy with effusion, 1068.  
**Gros nez**, 236.  
**Growing pains**, significance of, 51.  
**Growth**, retarded in kwashiorkor, 479, 480.  
     stunted in glycogen disease, 452.  
**Guaiac test** for occult blood, 603.  
**Guaiacol** in arthritis, 1152.  
**Guarnieri bodies** in small-pox, 159, 166.  
**Guatemala nodules**, 329.  
**Guinea-worm disease**, 330.  
**Gumma** in congenital syphilis, 226.  
     meningeal, 1454, 1459.  
     of bone, 203, 209.  
     of brain, 1460.  
     of heart, 858.  
     of larynx, 209.  
     of liver, 209, 682, 683.  
     of lung, 1040.  
     of palate, 208.  
     of pancreas, 707.  
     of pharynx, 208.  
     of skin in syphilis, 207.  
     of skull, 203, 209.  
     of stomach wall, 589.  
     of subcutaneous tissue, 208.  
     of testicle, 209.  
     of tongue, 208.  
     of tonsil, 208.  
     of trachea, 958.  
     of vertebrae, 209.  
**Gummata** in yaws, 234.  
**Gums**, blue line on, due to bismuth, 217.  
     in lead poisoning, 368.  
     in mercurial poisoning, 382.  
     in infantile scurvy, 464.  
     in scurvy, 462.  
     in yellow fever, 187.  
     pain in, after arsphenamine therapy, 230.  
**Habit spasm**, 1522, 1523.

- Habit spasms** associated with impediments of speech, 1375.
- Habitus phthisicus**, 1029.
- Hæmangioma**, sclerosing, 1312.
- senile, 1315.
- stellate, 1314.
- Hæmangiomata** in epidemic dropsy, 348.
- Hæmangiomatosis**, 775.
- Hæmaphysalis humerosa**, 293.
- Hæmarthrosis**, intermittent, 1165.
- Hæmatemesis** and **melæna**, 569.
- following deep X-ray therapy, 410.
- in acid gastritis, 573.
- in **anæmia**, 569.
- in cancer of stomach, 591.
- in cirrhosis of liver, 569, 676.
- in duodenal ulcer, 579.
- in gastric ulcer, 569, 577.
- in gastro-jejunal ulcer, 588.
- in hæmophilia, 569.
- in œsophageal ulcer, 548, 549.
- in portal thrombosis, 688.
- in purpura, 569.
- in relation to menstruation, 569.
- in splenic **anæmia**, 569.
- treatment of, 570.
- Hæmatin**, 248, 249.
- acid, in stools, 604.
- Hæmatoma**, chronic subdural, 1450.
- Hæmatomyelia**, 1549.
- Hæmatopoiesis**, rôle of stomach in, 556.
- Hæmatoporphyrin** in stools, 604.
- in urine, 1099.
- Hæmaturia**, 1104.
- causes of, 1104, 1141, 1148.
- from *B. coli* infection, 95, 96.
- from spider bite, 339.
- in infantile scurvy, 464.
- in nephritis, 1104.
- in renal tuberculosis, 1140.
- tumours, 1145.
- in scarlet fever, 43.
- in schistosomiasis, 320.
- in sulphonamide therapy, 26.
- in tuberculosis, 87.
- recurring, 96.
- Hæmochromatosis**, 680.
- Hæmocele**, 247.
- Hæmoglobin**, affinity of carbon monoxide for, 358.
- content of blood in relation to anoxæmia, 400.
- derivatives in stools, 604.
- disintegration in blackwater fever, 261, 262.
- percentage, normal, 726.
- variations in, 726.
- types of, 740, 741.
- Hæmoglobinæmia**, nocturnal, 744.
- Hæmoglobinuria**, 1104.
- in arseniuretted hydrogen poisoning, 375.
- in blackwater fever, 261, 262.
- malarial, 260.
- paroxysmal, 744, 1104.
- toxic, 1104.
- with hæmolytic **anæmia**, 744.
- Hæmoglobinuric fever**, 260.
- Hæmo-hydrothorax**, 1076, 1077.
- Hæmolysis** as cause of **anæmia**, 730, 740.
- in blackwater fever, 261, 262.
- Hæmolysis** in malaria, 248, 249.
- in relation to jaundice, 661, 745.
- in relation to leucocytosis, 740.
- in sulphonamide therapy, 26.
- Hæmolytic anæmia**, 740.
- disease of new-born, 745.
- organisms, 730.
- Hæmopericardium**, 884.
- Hæmophilia**, 767.
- Hæmophilus ducreyi**, 143.
- influenzæ, 32, 148, 179, 966.
- meningitis due to, 62, 1393.
- sensitivity to penicillin, 7, 8.
- pertussis, 138.
- sensitivity to streptomycin, 10.
- Hæmaphysalis humerosa**, 293.
- punctata, 336.
- Hæmopneumothorax**, 1081.
- from infection, 1078.
- Hæmopoiesis**, in relation to symptomatic **anæmias**, 731.
- spleen in relation to, 778.
- Hæmoptysis**, 995.
- ætiology of, 995.
- forme hémoptoïque sèche, 995.
- from aneurysm, 995.
- in abscess of lung, 1003.
- in actinomycosis, 195.
- in adenoma of bronchus, 973.
- in atrial septal defect, 896.
- in bagassosis, 1016.
- in bronchiectasis, 984, 986, 995.
- in cystic disease of the lung, 1044.
- in gangrene of lung, 1005.
- in heart failure, 809.
- in infarction of the lung, 991, 995.
- in mitral stenosis, 866.
- in paragonimiasis, 317, 1043.
- in pneumococcal pneumonia, 1050.
- in pulmonary aspergillosis, 1039.
- in tuberculosis, 995, 1019, 1020, 1023.
- treatment of, 1036, 1037.
- in spirochaetosis icterohæmorrhagica, 240.
- in trauma, 995.
- in traumatic hæmothorax, 1078.
- in vicarious menstruation, 995.
- spurious, 995.
- Hæmorrhage** or **hæmorrhages**, as cause of **anæmia**, 725.
- capsular, 1437.
- cerebral, conditions of occurrence of, 1435.
- effects of, 729, 730.
- intestinal, in amœbic dysentery, 277.
- in typhoid, 102, 107, 110.
- into spinal cord, 1549.
- "light-headedness" due to, 1642.
- meningeal, 1448.
- shock in, 725, 726.
- spontaneous subarachnoid, 1448.
- subarachnoid, 1448.
- subdural, 1450.
- tendency to, in acute infections, 771.
- in jaundice, 662.
- "the artery of," 1437.
- Hæmorrhagic capillary toxicosis**, 774.
- diathesis, 569.
- disease of the new-born, 769.
- diseases, 767-776.

- Hæmorrhagic diseases, blood-platelets in,** 770.  
     capillaries in, 770.  
     classification of, 767.  
     endothelium in, 771.  
     pleural effusions, 1077.  
     states, symptomatic, 771.  
     telangiectasia, hereditary, 775.  
**Hæmorrhagin in snake venoms,** 341.  
**Hæmosiderin,** 262, 680.  
**Hæmosiderosis, idiopathic pulmonary,**  
     of liver and spleen in aplastic  
     anæmia, 739.  
**Hæmostasis, blood platelets in relation to,**  
     770.  
     in relation to purpura, 770.  
**Hæmothorax,** 1078.  
**Haffkine's vaccine in plague prophylaxis,**  
     129.  
**Hair, arsenic in, in poisoning cases,** 375.  
     diseases of the, 1317.  
     dyes as cause of lead poisoning, 365.  
     dyspigmentation of, in kwashiorkor, 479,  
     480.  
     early greyness of, in Graves's disease, 493.  
     growth of, in anorexia nervosa, 564.  
     in acromegaly, 484.  
     ingrowing, 1228.  
     loss of, after scarlet fever, 40.  
         after small-pox, 162.  
     in injury from radio-active substances,  
     414.  
     in kala-azar, 266.  
     in leprosy, 91.  
     in myxœdema, 496.  
     in syphilis, 206.  
     in typhoid, 101.  
     in xeroderma, 1200.  
     in X-ray injuries, 410.  
     plucking, in pink disease, 309.  
**Halitosis,** 529.  
**Hallucinations, 1614.**  
     in alcoholism, 1638.  
     in cocaineism, 1641.  
     in delirium, 1625, 1626.  
     in delirium tremens, 1638.  
     in epilepsy, 1498, 1636.  
     in hebephrenia, 1664.  
     in lesions of occipital lobes, 1360.  
     in mental depression, 1649, 1650.  
     in pellagra, 1643.  
     in schizophrenia, 1662.  
     in senility, 1629.  
     in uncinæ lesions, 1360.  
**Hallucinosis, acute, 1626.**  
     alcoholic, 1638.  
     paranoid, in mental defectives, 1685.  
**Hand, fleshy, in syringomyelia, 1547.**  
     interosseal position of, in paralysis agitans,  
     1512.  
     obstetric, in hypoparathyroidism, 504.  
**Hand-Schüller-Christian's disease, 783,**  
     1186.  
**Hands in acromegaly, 484.**  
     in mongol idiots, 1633.  
     in syringomyelia, 1546, 1547.  
**Handwriting in general paralysis, 1633.**  
     in schizophrenia, 1661.  
**Hangnails, 1322.**  
**Hanot's biliary cirrhosis, 679.**  
**Haptene, 5.**  
**Harrison's sulcus in adenoids, 942.**  
     in rickets, 465.  
**Hartmann-Ringer lactate solution in**  
     epidemic diarrhœa, 617.  
**Harvest mites, 336.**  
**Hatters' shakes, 382.**  
**Haustation of colon, 600.**  
     in colitis, 635.  
**Haut mal, 1495.**  
**Hautmaulwarf, 1334.**  
**Hay asthma, 979.**  
     fever, 939.  
**Hayem-Widal type of hæmolytic anæmia,**  
     747.  
**Head, bossed, in rickets, 466.**  
     injuries, mental symptoms in, 1635.  
     retraction in acute hepatic necrosis, 671.  
**Headache after arsphenamine therapy, 230.**  
     in apoplectic syndrome, 1449.  
     in cerebral abscess, 1407.  
     in cerebral syphilis, 1460.  
     in cerebral tumour, 1386.  
     in encephalitis lethargica, 1417.  
     in hydrocephalus, 1402, 1403, 1404.  
     in malignant hypertension, 914.  
     in migraine, 1509.  
     in poliomyelitis, 1426.  
     paroxysmal, 1509.  
     sick, 1508.  
     toxicæmic, 30.  
     vacuum, 148.  
**Heart, amyloidosis of, 892.**  
     arrhythmia, 819-834.  
         in cardiac trauma, 903.  
     beats, ectopic, 821.  
         interpolated, 821.  
     -block, 829.  
     chronic valvular disease of, 862-878.  
     congenital disease of, 893-900.  
         classification of, 894.  
         acyanotic, 894.  
         cyanotic, 897.  
         diagnosis of, 893.  
     dilatation of the, as consequence of myo-  
     carditis, 891.  
         compensatory, 807.  
         hypertension in relation to, 850, 851, 910.  
         in beriberi, 470, 903.  
         in influenza, 180.  
         in pneumonia, 1053.  
         in relation to cardiac failure, 807.  
         in scarlet fever, 43.  
         in whooping-cough, 140.  
     disease and chorea, 1517, 1518.  
     emphysema, 855.  
     hypertensive, 850.  
     in relation to rheumatism, 49, 862.  
     ischæmic, 834-851.  
     physical examination in, 794.  
     pulmonary, acute, 852.  
         chronic, 855.  
         symptoms in, 794.  
     syphilitic, 853.  
     traumatic, 903.  
     displacement of, in hydrothorax, 1077.

- Heparin in lung infarction, 992.  
   in thrombosis, 848, 926.  
 Hepatic abscess, 279.  
   *necrosis, acute*, 670, 671.  
   *subacute*, 670.  
   and nodular hyperplasia, 672.  
   veins, thrombosis of, 665.  
 Hepatisation of lung, grey, 1049.  
   red, 1049.  
 "Hépatisme," 1167.  
 Hepatitis, *amœbic*, 279, 280.  
   homologous serum, 666, 667.  
   in leptospirosis *icterohæmorrhagica*, 239.  
   in syphilis, 207.  
   *infective*, 666.  
   interstitial, chronic, 673.  
 Hepato-lenticular degeneration, 1484.  
 Hepato-licial fibrosis, 781.  
 Hepatoma, 685.  
 Hepatosis, *alcoholic*, 672.  
   *serous*, 673.  
 Hereditary and familial diseases of nervous system, 1479.  
   *hæmorrhagic states*, 767.  
 Heredity in *affective disorders*, 1845.  
   in asthma, 977.  
   in congenital heart disease, 893.  
   in dystrophia *myotonica*, 1600.  
   in epilepsy, 1494.  
   in gout, 444.  
   in familial periodic paralysis, 1607.  
   in hæmophilia, 767.  
   in hysteria, 1669.  
   in idiocy, 1683.  
   in mental deficiency, 1683.  
   in mental disorder, 1609.  
   in obsessional disorder, 1677.  
   in pulmonary tuberculosis, 1017.  
   in schizophrenia, 1656.  
 Hermaphroditism, 514.  
 Hernia, *diaphragmatic*, 550, 1096.  
   *oesophageal hiatus*, 550.  
   *chest pain in*, 839.  
 Hernia, *internal*, in intestinal obstruction, 650.  
 Herpes after *arsphenamine remedies*, 230.  
   *febrilis*, 1246.  
   *gestationis*, 1287.  
   in cerebrospinal fever, 56.  
   in malaria, 251.  
   in relapsing fever, 242.  
   in *spirochaetosis icterohæmorrhagica*, 239.  
   *labialis in acute gastritis*, 571.  
   in *arsphenamine therapy*, 230.  
   in pneumonia, 1051.  
   of geniculate ganglion, 1420.  
   *facial paralysis from*, 1349.  
   *recurrens*, 1246.  
   *simplex*, 1246, 1419.  
   *zoster*, 1247.  
   and *varicella*, 173, 1247, 1248.  
   from lesion of geniculate ganglion, 1248, 1420.  
   of cornea, 1248.  
   of ophthalmic division of fifth nerve, 1248, 1420.  
   of palate, 1248.  
   of tongue, 1248.  
 Herter-Heubner disease, 620.  
 Heterophil antibody reaction in acute leukemia, 764.  
 Heterophyes heterophyes, 318.  
   *katsuradai*, 318.  
 Heterophyiasis, 318.  
   *cardiac*, 318.  
 Hetrazan in filariasis, 328.  
   in *onchocerciasis*, 330.  
 Hexamethonium therapy in hypertension, 912, 916.  
   *pulmonary œdema in*, 912.  
 Hexylresorcinol in ascariasis, 334.  
   in distomiasis, 317.  
 Hiatus hernia, 1096.  
 Hiccough, epidemic, 1088.  
   in Addison's disease, 508.  
   in bacillary dysentery, 114.  
   in blackwater fever, 262.  
   in cholera, 134.  
   in uræmia, 1110.  
   in yellow fever, 187.  
   *nervous*, 1088.  
   *simple*, 1087.  
 Hilar dance in atrial septal defect, 896.  
 Hill diarrhoea, 626.  
 Hilum dimple, 1093.  
 Hippocratic facies in acute pernicious malaria, 252.  
   *fingers*, 1171.  
 Hippuric acid in urine, 1099.  
   *synthesis test*, 660.  
   *test of liver function*, 660.  
 Hirschsprung's disease, 646.  
 Hirsutes, 1320.  
 Hirsutism in *acromegaly*, 484.  
   in the climacteric, 522.  
   in virilism, 511, 512.  
 Histamine in relation to allergic rhinitis, 939.  
   in relation to gastric secretion, 555.  
   *urticaria*, 1255.  
 Histiocytoma, 1312.  
 Histoplasmosis, *Appendix i*.  
 Hodgkin's disease, 789.  
   *mediastinal glands in*, 1092.  
 Hone's disease, 286.  
 Hong Kong foot, 1333.  
 Hook-worm disease, 332.  
 Hormones, *adrenocorticotrophic*, 483.  
   *diabetogenic*, 483.  
   *gonadotrophic*, 483.  
   *growth*, 483.  
   *insulotrophic*, 483.  
   *lactogenic*, 483.  
   *sex*, 507.  
   *somatotrophic*, 483.  
   *steroid*, in rheumatoid arthritis, 1153.  
   *thyroid*, 491.  
   *thyrotrophic*, 483.  
 Horn, cutaneous, 1308.  
 Horner's syndrome, 1345.  
 Horse serum, sensitivity to, 4.  
 Hot-cross bun head in rickets, 466.  
 Hour-glass stomach, 578, 593.  
 Hunger-pain, 578.  
 Huntington's chorea, 1519.  
 Hutchinson's teeth, 227.  
   *triad in congenital syphilis*, 227.



- Hydatid cysts**, 324, 325, 683.  
   intracranial, 325, 1384.  
   of liver, 683.  
   rupture of, 684.  
   of lungs, 1046.  
   of mediastinum, 1094.  
**disease**, 324, 325, 683.  
   of liver, 683.  
   of lung, 1046.  
   of pleura, 1084.  
**fremitus**, 1047.  
**parapleural**, 1084.  
**thrill**, 684.
- Hydradenitis suppurativa**, 1231.  
**Hydradenoma papilliferum**, 1309.  
**Hydrarthrosis**, intermittent, 1165.  
**Hydroa aestivale, vel vacciniforme**, 1210.  
**Hydrocarbons**, halogenated, poisoning by, 393.  
**Hydrocephalic cry**, the, 1395.  
**Hydrocephalus**, 1399.  
   acquired, acute, 1403.  
   chronic, 1403.  
   cerebrospinal fluid in, 1400.  
   congenital, 1400.  
   in cerebrospinal fever, 58.  
   in post-basis meningitis, 58.  
   otic, 1404, 1410, 1452.  
   syphilis in relation to, 1398, 1459.  
**Hydrochloric acid** in gastric juice, 554.  
   in relation to anemia, 734.  
   in relation to hæmoglobin formation, 556.  
   lack of free, in cancer, 591.  
   of gastric juice, action of, on bacteria, 556, 557.  
   use of, in chronic gastritis, 575.  
**Hydrocortisone (compound F)** in infantile eczema, 1223.  
   in osteo-arthritis, 1159.  
   in pruritus, 1192, 1197.  
   in rheumatoid arthritis, 1154.  
**Hydrocyanic acid**, poisoning by, 362, 363.  
**Hydrogen-ion concentration** of blood, 418.  
**Hydronephrosis**, 1142.  
   renal contraction in, 1128.  
**Hydropericardium**, 884.  
**Hydrophobia**, 1420.  
**Hydropneumothorax**, 1082.  
**Hydrops asthmaticus**, 468.  
   congenital, 745.  
**Hydrothorax**, 1076.  
   in heart failure, 809, 1076.  
**Hymenolepis nana**, 322.  
**Hyoscyamine poisoning**, 352.  
**Hyoscine** in travel sickness, 403.  
   poisoning, 352.  
**Hyperadrenalism**, 518.  
**Hyperæmia** of lung, collateral, 987.  
   fluxionary, 987.  
**Hyperæsthesia** in hydrophobia, 1421.  
   in pre-paralytic stage of acute anterior poliomyelitis, 1427.  
   in tabes, 1463.  
   in trypanosome fever, 271.  
   pharyngeal, 539.  
   right iliac, in acute appendicitis, 655.  
**Hyperbilirubinæmia**, 661.  
   in blackwater fever, 262.
- Hyperbilirubinæmia** in malaria, 248.  
   in nutritional macrocytic anemia, 476  
   in Oroya fever, 145.  
   in relapsing fever, 242.  
**Hypercalcæmia**, idiopathic, 618.  
   in hyperparathyroidism, 501.  
**Hypercholesterolæmia**, 694.  
   in myxædema, 497.  
**Hyperidrosis**, 1198.  
**Hyperinsulinism** in tumour of islands of Langerhans, 443.  
**Hyperkeratosis**, from arsenic, 374, 1267.  
   of hair follicles in scurvy, 462.  
   of soles in arsenical poisoning, 1590.  
**Hyperkeratotic border** of Merck, 474.  
**Hypernephroma**, 1145.  
**Hyperostosis** of skull, general, 1175.  
**Hyperparathyroidism**, 501.  
**Hyperpiesia**, 909.  
**Hyperpituitarism** in acromegaly, 484.  
**Hyperpnoea** in acidæmia, 419.  
   in altitude sickness, 401.  
**Hyperpyrexia** from heat, 403.  
   in rheumatic fever, 50.  
**Hypersplenism**, 781.  
**Hypertension**, 907-916.  
   benign, 909.  
   essential, 1124.  
   diastolic, 907.  
   due to unilateral renal disease, 1112.  
   endocrine, 908.  
   essential, 908.  
   benign, 1124.  
   malignant, 912, 1124.  
   in phæochromocytoma, 518.  
   malignant, 912.  
   essential, 1124.  
   mental disorders associated with, 1630.  
   pulmonary, 916.  
   renal, 908, 1111.  
   systemic venous in right heart failure, 808.  
   811.  
   systolic, 907.  
**Hypertensive crises**, 1116.  
   heart disease, 850.  
**Hyperthyroidism**, 491.  
   auricular fibrillation in, 827, 901.  
   blood pressure in, 900, 901.  
   formes frustes of, 494.  
   in relation to heart disease, 900.  
**Hypertrichosis**, 1320.  
   in Cushing's syndrome, 517.  
   in virilism, 512.  
**Hypertrophic pulmonary osteo-arthropathy**, 1171.  
**Hyperventilation** in cardiac neurosis, 904.  
**Hypochlorhydria**, 560.  
   in tropical sprue, 624.  
**Hypochondria**, prognosis of, 1653.  
**Hypocorticalism**, 507.  
**Hypoderma bovis**, 338.  
   lineatum, 338.  
**Hypoglycæmia**, 430.  
   in Addison's disease, 508.  
   in glycogen disease, 452.  
   in tumour of islands of Langerhans, 443, 702.  
   spontaneous, 443.

- Hypogonadism, 520.  
 Hypoidrosis, 1199.  
 Hypomania, 1645, 1656.  
 Hypoparathyroidism, 503.  
 Hypopituitarism, 487.  
 Hypoproteinæmia, 1113.  
 Hypoprote thrombinæmia, 769.  
 Hypotension, 916.  
   postural, 818, 917.  
 Hypothalamus, localisation of lesions of, 1362.  
 Hypothermic crisis, 488.  
 Hypothyroidism, 496.  
   anidrosis in, 496.  
   heart in, 902.  
 Hypotonia in cerebellar lesions, 1363.  
   in tabes, 1463.  
 Hypoxanthine in urine, 1098.  
 Hysteria, 1669.  
   aphonia in, 952.  
   conversion mechanism in, 1671.  
   cutis, 1211.  
   differential diagnosis from schizophrenia, 1665.  
   disorders of sensibility in, 1671.  
   in relation to marriage, 1677.  
   litigation, 368, 369.  
   paralysis in, 1672.  
   speech disorders in, 1672.  
   war experiences in relation to, 1673.  
 Hysterical aphonia, 1672.  
   conversion, 1614.  
   dysphagia, 542.  
   fits, differential diagnosis of, 1503, 1665.  
   fugue, 1673.  
   mutism, 953.  
   paralysis, 1672.  
   personality, 1670.  
   polyuria, 489.  
   pseudo-constipation, 607.  
   spasm of diaphragm, 1088.  
   of œsophagus, 541.  
   tremor, 1672.  
   vomiting, 561.  
 Ichthammol in erysipelas, 35.  
 Ichthyosis, 1200.  
   hystrix, 1200, 1298.  
 Icteric fever of Carter, 242.  
 Icterus, *gravis*, 671.  
   neonatorum, familial, 745.  
 Idiocy, 1684.  
   amaurotic family, 1482.  
   congenital, 1488.  
   cretin type of, 498.  
   microcephalic, 1488.  
   mongoloid type of, 1685.  
   restless, 1488.  
 Idiots savants, 1684.  
 Ileal stasis, diagnosis of, 607.  
   stomach, 599.  
 Ileitis, regional, 631.  
 Ileocolitis, acute, 614.  
 Ileum, perforation of, in typhoid fever, 102.  
   tuberculous ulceration of, 638.  
 Ileus, duodenal, 597.  
 Ilotycin, 14.  
 Imbecility, 1684.  
 Immersion foot, 1209.  
 Immune bodies in yellow fever, 185.  
 Immunisation, 3, 4.  
 Immunity, 3.  
   acquired, 3.  
   active, 3.  
   in relation to vaccine therapy, 3, 4.  
   after virus diseases, 146.  
   passive, 3.  
   racial, 95.  
   spleen in relation to, 778.  
 Impetigo, Bockhart's, 1199, 1225, 1229.  
   contagiosa, 1225.  
   follicular, 1225.  
   neonatorum, 1226.  
   pityroides, 1226.  
   seborrhœic, 1225.  
   vulgaris, 1225.  
 Impotence, 521.  
   in Simmonds's disease, 487.  
 Impulses, obsessional, 1678.  
 Inanition, mental disorder in, 1642.  
 Inclusion bodies, 146.  
 Incompetence, aortic, 874.  
   mitral, 863.  
   tricuspid, 877.  
 Incontinence in cerebrospinal fever, 56.  
   in encephalitis lethargica, 1417.  
   in frontal lobe tumour, 1358.  
   in general paralysis, 1456.  
   in lathyrisms, 350.  
   in poisoning by insecticides, 380.  
   of urine and fæces in epilepsy, 1496.  
 Inco-ordination in chorea, 1517.  
   in tabes, 1464.  
 Indicanuria, 1099.  
   in acute intestinal obstruction, 652.  
   in heat-stroke, 408.  
 Indigestion, chronic intestinal, 618.  
 Infantile beriberi, 470, 471.  
   eczema, 1221.  
   hemiplegia, 1490.  
   paralysis, 1423.  
 Infantilism, 485.  
   in glycogen disease, 452.  
   in the Fanconi syndrome, 1179.  
   intestinal, 618.  
 Infarction, myocardial, 842.  
   of lungs, 989.  
 Infection, 1-5.  
   factors predisposing to, 1, 2.  
   gastro-intestinal, acute, 614.  
   invasive, 3.  
   response of the body to, 3.  
   results of bacterial, 2, 3.  
   terminal, 32.  
 Infectious diseases, 30-315.  
   hemorrhagic tendency in, 771.  
 Inflammation as result of bacterial infection, 2, 3.  
 Influenza, 178.  
   complications and sequelæ of, 180.  
   differential diagnosis of, 61.  
   febrile type of, 179.  
   malignant type of, 180.  
   respiratory type of, 179.  
   tracheitis in, 954.

- Influenzal meningitis**, 62, 1393.  
**Inhalations**, steam, in acute laryngitis, 943.  
 in acute laryngo-tracheo-bronchitis, 946.  
**Inhibin**, 521.  
**Inositol**, 460.  
**Insanity**. *See under* Psychological Medicine and Mental.  
**Insect bites and stings**, 337, 1254.  
 as cause of anaphylactic symptoms, 337.  
**Insulin**, choice of, 429.  
 dosage of, 427, 428, 429, 430.  
 control of, 430.  
 effects of overdose of, 430.  
 fat atrophy, 431.  
 globin with zinc, 429.  
 in mental disorders, 1621.  
 in schizophrenia, 1666, 1667.  
 local reactions to, 431.  
 preparations of, 428, 429.  
 protamine zinc, 428.  
 rôle of, in body, 423, 424.  
 soluble, 428.  
 standardisation of, 427.  
 treatment of diabetes by, 427-437.  
 zinc suspensions, 429.  
**Intelligence tests**, 1684, 1686.  
**Intermittent claudication**, 919.  
 fever, 245.  
 hydrarthrosis, 1165.  
**Internal capsule**, localisation of lesions of, 1361.  
**Inter-sex**, 514.  
**Interstitial neuritis**, 1576.  
**Intertrigo**, 1254.  
**Intervertebral disc**, protruding, brachial pain due to, 1578.  
 in relation to compression of cord, 1540.  
 sciatica due to, 1582.  
**Intestinal absorption**, defective, in idiopathic steatorrhœa, 620.  
 in sprue, 623.  
 anthrax, 80.  
 carbohydrate dyspepsia, 629.  
 indigestion, chronic, 603.  
 infections, achlorhydria predisposing to, 554.  
 motor functions, examination of the, 601.  
 movements, 599.  
 myiasis, 339.  
 obstruction, acute, 649.  
 sand, 628.  
 stasis in relation to constipation, 607.  
 stricture, congenital, 649.  
*ulcers in amœbic dysentery*, 277.  
 in bacillary dysentery, 113.  
 in kala-azar, 265.  
 in typhoid, 99.  
 worms as cause of appendicitis, 654.  
**Intestines**, actinomycosis of, 194.  
 diseases of the, 599-658.  
 diverticula of, 598.  
 examination of the, 601.  
 functional disorders of the, 605-631.  
 divisions of the, 599.  
 motor functions of, 601.  
 organic diseases of the, 631-658.  
 palpation of, 601.  
 perforation of, in typhoid, 102.  
**Intestines**, sigmoidoscopic examination of, 604.  
 strangulation of, 650, 651.  
 X-ray examination of, 602.  
**Intoxication**, alcoholic, diagnosis of, 353, 354, 355.  
 bacterial, 30.  
**Intoxications**, mental disorders in the, 1641.  
**Intracranial abscess**, 1405.  
 aneurysm, 1447.  
 pressure symptoms, 1384-1389.  
 tumours, 1380-1391, 1635.  
 aphasia due to, 1370.  
**Intramedullary tumours**, 1534.  
*Intrinsic factor*, 556, 734.  
 in relation to cyanocobalamin, 734.  
**Intubation** in diphtheria, 78.  
 in whooping-cough, 142.  
**Intussusception**, 650.  
 chronic, 646.  
 ileo-caecal, 650.  
**Involuntary affective disorders**, 1646.  
 paranoia, 1629.  
**Iodamœba bütschlii**, 275.  
**Iodides** in blastomycosis, 199, 200.  
**Iodine**, deficiency as a cause of goitre, 499.  
 in endemic goitre, 500.  
 in exophthalmic goitre, 494.  
 in syphilis, 221.  
 radio-active, in treatment of exophthalmic goitre, 494, 495.  
 rôle of, in thyroid activity, 491.  
**Iodism**, 683.  
**Ionisation**, treatment of hay fever, 939.  
**Iridocyclitis** as a complication of mumps, 176.  
 in gonorrhœa, 67.  
 in syphilis, 207.  
**Iridoplegia**, reflex, 1343.  
**Iris**, atrophic changes in, 1344.  
**Iritis** in bacterial urethritis, 312.  
 in congenital syphilis, 226.  
 in small-pox, 164.  
 malarial, 254.  
 punctate, in onchocerciasis, 329.  
**Iron**, deficiency anæmia, 732.  
 deposit of, in hæmochromatosis, 680.  
 in hæmorrhagic anæmia, 730.  
 in hypochromic anæmia, 733, 734.  
 in nutritional anæmia, 731.  
 in Plummer-Vinson syndrome, 543.  
 metabolism and elimination of, 680.  
*Ischæmia, acute cortical*, 1128.  
**Ischæmic heart disease**, 834-851.  
 heart-block in, 830.  
**Isoniazid** in lupus vulgaris, 1242.  
 in pulmonary tuberculosis, 1034.  
 in sarcoidosis, 1246.  
**Itch**, camel, 336.  
 copra, 336.  
 Cuban, 163.  
 ground, 332.  
 in cisson disease, 397.  
 Kaffir, 163.  
**Ito-Reenstierna test** in chancroid, 143.  
**Ixodes holocyclus**, 336.  
 ricinus, 336.

- Jacksonian fits**, 1497.  
     in cerebral syphilis, 1460.  
     in lesions of motor area, 1359.  
     in lesions of occipital lobes, 1360.  
     in lesions of temporal lobes, 1360.
- Jacquet's erythema infantum**, 1223.
- Jactitation** in epilepsy, 1497.
- Jail fever**, 295.
- Jamaica**, vomiting sickness of, 350.
- Japanese river fever**, 288.
- Jargon aphasia**, 1360, 1369, 1370.
- Jarisch-Herxheimer reaction**, 215.  
     in penicillin therapy, 220.
- Jaundice**, 661.  
     acholuric, 741.  
     catarrhal, 666.  
     differential diagnosis of causes of, 663, 664.  
     dissociated, 661.  
     due to ascandes, 334.  
     epidemic, 666.  
     faeces in, 663.  
     familial, 745.  
     haemolytic, 661.  
     homologous serum, 154, 667.  
     in acute hepatic necrosis, 671.  
     in arseniuretted hydrogen poisoning, 375.  
     in arsphenamine therapy, 230, 231, 232.  
     in blackwater fever, 261, 262.  
     in carcinoma of the bile-ducts, 700, 709.  
     in carcinoma of the liver, 685, 686.  
     in chronic pancreatitis, 705.  
     in erythroblastosis foetalis, 745.  
     in congenital obliteration of bile-ducts, 699.  
     in kala-azar, 266.  
     in leptospirosis icterohaemorrhagica, 239, 240.  
     in malaria, 251.  
     in yellow fever, 186.  
     infective, 661, 666.  
     juvenile, chronic intermittent, 665.  
     latent, 662.  
     leptospirosis and, 238.  
     mental symptoms in, 1645.  
     obstructive, 661.  
         from intestinal worms, 334.  
     post-arsphenamine, 667.  
     post-transfusion, 667.  
     post-vaccinal, 667.  
     pruritus in, 663.  
     rheumatoid arthritis and, 1151.  
     spirochaetal, 238.  
     syphilitic, 682, 683.  
     toxic, 661, 670.  
         in trinitrotoluene poisoning, 390.  
     urine in, 662.
- Jelly-fish stings**, 343.
- Jews**, frequency of amaurotic familial idiocy in, 1482.  
     of diabetes mellitus among, 423.  
     of pentosuria in, 444.  
     of suprarenal cortical hyperplasia among, 512.  
     liability of, to Gaucher's disease, 785.  
     relative immunity of, to pulmonary tubercle, 1017.
- Joint effusions (pseudo-arthritis)**, 1165.
- Joints**, diseases of the, 1150-1170.  
     effusion of fluid into, 1165.
- Joints, hæmorrhages into**, in hæmophilia, 768.  
     in infantile scurvy, 463.  
     in syphilis, 207.
- Jungle fever**, 245.
- Juxta-articular nodes**, 237.
- Kabure disease**, 320.
- Kahler's disease**, 1184.
- Kahn reaction** in glandular fever, 306.  
     for syphilis, 205.
- Kakke**, 468.
- Kala-azar**, 264.
- Kaolin**, 1014.
- Kaposi's idiopathic hæmorrhagic sarcoma**, 1313.  
     varicelliform eruption, 1249.
- Kassowitz's law** in syphilitic women, 225.
- Katayama disease**, 320.
- Kayser-Fleischer zone** of corneal pigmentation, 1484.
- Keloid**, 1311.
- Kendal's fever**, 184.
- Kennedy, Foster, syndrome of**, 1358.
- Kepler test** in Addison's disease, 509.
- Kerandel's sign** in African trypanosomiasis, 271.
- Kerasin**, 785, 1186.
- Keratin rings** in anidrosis, 1199.
- Keratinisation** in vitamin A deficiency, 455.
- Keratitis** in small-pox, 164.  
     interstitial, in congenital syphilis, 226, 229.
- Kerato-acanthoma**, 1305.
- Keratoderma blennorrhagica**, 312, 1297.  
     climacterium, 1297.  
     punctatum, 1297.
- Keratosis**, arsenical, 1297.  
     follicular, in scurvy, 462.  
     follicularis, 1280.  
     pharyngis, 540.  
     senilis, 1307.  
     solaris, 1307.  
     suprafollicularis, 1200.
- Kerion celsi**, 1233.
- Kernicterus**, 746, 1485.
- Kernig's sign** in cerebrospinal fever, 56.  
     in encephalitis lethargica, 1417.  
     in meningeal spirochaetosis, 240.  
     in paralytic brachial neuritis, 1578.  
     in tuberculous meningitis, 1396.
- Ketonuria**, 1105.  
     tests for, 1106.
- Ketosis**, diet in, 435.  
     in diabetes mellitus, 424, 435.
- Kidney**, adenocarcinoma of, 1145.  
     adenoma of, 1144.  
     amyloid, 1131.  
     atheromatous, 1125.  
     benign growths of the, 1144.  
     blastomycosis of, 199.  
     calculi in, 1141.  
     cardiac, 1108.  
     circulatory disturbances of, 1107.  
     coliform infection of, acute, 95.  
     congenital abnormalities of, 1130.  
     congestion of, 1107.  
     contracted, 1127.  
     crush, 1128.

- Kidney**, cysts of, 1146.  
diseases of the, 1098-1149.  
classification of, 1114.  
dysembryomata of, 1145.  
estimation of function of, 1101.  
fibromata of, 1144.  
function, 1100.  
estimation of, 1100.  
granular, 1124.  
infarction of, 1108.  
ischæmic atrophy of, in diabetes, 1125.  
lardaceous disease of, 1131.  
malignant tumours of, 1145.  
movable, 1147.  
polycystic disease of, 1146.  
"Rose Bradford," 1131.  
sarcoma, 1145.  
senile, 1125.  
tuberculosis of the, 1139.  
tumours of the, 1144.  
waxy, 1131.
- Kiesselbach's area**, common source of epistaxis, 938.
- Klebs-Löffler bacillus**, 67, 68, 69.
- Kline reaction** for syphilis, 205.
- Klumpke's palsy**, 1568, 1585.
- Knee-jerks** in beriberi, 469.  
in tabes, 1463, 1466.
- Knoppe spider**, 339.
- Koch's comma vibrio**, 133.
- Koebner phenomenon**, 1272, 1278.
- Koilonychia**, 1323, 1324.  
in iron deficiency *anæmia*, 732.  
in Plummer-Vinson syndrome, 543.
- Koplik's spots** in measles, 150, 151, 153.
- Korsakoff's psychosis** in alcoholic neuritis, 1590.  
syndrome, 1590, 1627, 1638.
- Krait bites**, 341.
- Kraurosis vulvæ**, 1295.
- Krukenberg's tumour**, 591.
- Kupffer cells**, 783.
- Kveim test** in sarcoidosis, 1246.
- Kwashiorkor**, 478.
- Kyphosis** in acromegaly, 484.  
in alkaptonuria, 1105.  
in cerebral diplegia, 1489.  
in emphysema, 999.  
in hypertrophic osteo-arthritis, 1172.  
in multiple myeloma, 1185.  
in osteogenesis imperfecta, 1180.  
in osteomalacia, 1177.  
in rickets, 466.  
in syringomyelia, 1547.
- Labia**, primary syphilitic sore of, 204.
- Labio-glosso-pharyngeal paralysis**, 1554.
- Labyrinthine vertigo**, 1352.
- Lacrimal gland**, swelling of, in Mikulicz's disease, 177.  
in mumps, 175.
- Lactation**, mental disorders associated with, 1645.
- Lactic acid** in resting juice in cancer of stomach, 591.
- Lactosuria**, 444.
- Lactroductus**, 339.
- Laennec's cirrhosis**, 674.
- Laennec's "perles"** in asthma, 979.  
in bronchitis, 970.
- Lævulosuria**, 444.
- Lamblia intestinalis**, 284.
- Landry's paralysis**, 1594.
- Lange's colloidal gold reaction**, 1380.  
in disseminated sclerosis, 1475.  
in syphilis of nervous system, 1380, 1457.
- Langerhans, islands of**, in diabetes, 423.
- Lardacein**, 1131.
- Lardaceous disease**, 1131.  
in bronchiectasis, 985.  
in chronic tuberculosis, 1026.
- Larva migrans**, 1334.
- Laryngeal conditions** in children, 945.  
crises, 952.  
in tabes, 1462, 1465.  
treatment of, 1468.
- diphtheria**, 71, 75.
- nerves, recurrent**, in cancer of œsophagus, 552.
- obstruction**, causes of, 75.  
in small-pox, 164.
- paralysis**, 950, 1356.  
abductor, 950, 1356.  
complete, 951.  
functional, 952.  
in mediastinal tumour, 1095.  
in poliomyelitis, 1429.  
organic, 950.
- spasm**, death from, in whooping-cough, 141.
- spasms** in hydrophobia, 1421.
- stridor**, congenital, 946.
- ulceration**, tuberculous, 949.
- Laryngismus stridulus**, 947.  
in relation to adenoids, 942.  
in rickets, 466.
- Laryngitis**, acute, 943.  
in children, 945.  
chronic, 947.  
complicating measles, 151, 155.  
membranous, 945.  
œdematous, 944.  
sicca, 948.  
spasmodic, 942.  
stridulosa, 945.  
tuberculous, 948, 1020.
- Laryngo-tracheo-bronchitis**, acute, 946.
- Larynx**, angioneurotic œdema in, 944.  
diphtheritic infection of, 71, 75, 78.  
diseases of the, 943-954.  
functional paralysis of, 952.  
œdema of, 944.  
paralysis of, 950.  
spasmodic affections of, 953.  
syphilis of the, 206.  
tuberculosis of, 948, 1020, 1024.
- Lateral bands**, in pharyngitis, 538, 540.  
recess, localising symptoms of lesions of, 1366.  
neurofibromata of, 1366.  
sinus, thrombosis of, 1453.
- Lathyrism**, 349.
- Lathyrus**, species of, associated with poisoning, 350.
- Laurence-Moon-Biedl syndrome**, 489.

- Lead**, abortifacient uses of, 365.  
 colic, 363, 364, 367, 371.  
 elimination of, 370, 371.  
 encephalopathy, 368, 371.  
 excretion of, 365, 366.  
 for protection against X-ray and radium injury, 411, 413.  
 in healthy urine, 365.  
 line, 368.  
 occupational risks from, 364.  
 palsy, 366, 367, 371, 1593.  
 poisoning, 363-372.  
   acute, 363.  
     status epilepticus in, 1502.  
     alcoholism predisposing to, 364.  
     chronic, 364-371.  
       idiosyncrasy in, 364.  
       mental disorder in, 1642.  
       prophylaxis of, 369.  
   tetra-ethyl poisoning, 371.  
**Leber's disease**, 1340.  
**Lederer**, acute hæmolytic anæmia of, 747.  
**Legs**, œdema of, chronic hereditary, 788, 928.  
**Leiomyoma**, 1313.  
**Leishmania braziliensis**, 264, 268.  
   donovani, 264, 265.  
   infantum, 264.  
   tropica, 264, 269.  
**Leishmaniasis**, 264.  
   American dermal, 268.  
   post-kala-azar dermal, 266.  
**Lenticular degeneration**, chronic, cirrhosis of liver in relation to, 674.  
   hepato-, 1484.  
   progressive, 1484.  
**Lentigo**, 1202.  
   maligna, 1310.  
**Leonine facies** of leprosy, 91.  
**Leontiasis ossea**, 1175.  
**Lepothrix**, 1238.  
**Lepra reaction**, 92, 94.  
**Lepromin test**, 92.  
**Leprosy**, 90.  
   anæsthetic, 91.  
   Asturian, 472.  
   bronchial, 973.  
   mixed, 91.  
   nodular, 91.  
   of trachea, 959.  
   tuberculoid, 91.  
**Leptocytosis**, hereditary, 740, 743.  
**Leptomeningitis**, 1391.  
**Leptospira autumnalis**, 238.  
   canicola, 237, 238.  
   grippo-typhosa, 237, 238.  
   hebdomadis, 237, 238.  
   icterohæmorrhagiae, 237.  
     sensitivity to penicillin, 7.  
   pyrogenes, 238.  
**Leptospirosis**, 237.  
   atypical, 240.  
   with jaundice, 238.  
   without jaundice, 238.  
**Leptospirosis icterohæmorrhagica**, 238.  
**Lesègue's sign**, 1582.  
**Lethargic encephalitis**, 1414.  
**Letterer-Siwe's disease**, 784.  
**Leucocytes**, 752.  
**Leucocytosis**, 752.  
**Leucoderma centrifugum acquisitum**, 1204.  
   syphilitic, 205.  
**Leuco-erythroblastic anæmia**, 747.  
**Leuconychia**, 1323.  
**Leucopenia**, 755.  
**Leucoplakia**, 209, 1326.  
**Leucotomy**, frontal, in treatment of mental disorders, 1621.  
   in treatment of schizophrenia, 1668.  
**Leukæmia**, 757.  
   acute, 762.  
   aleukæmic, 761, 763.  
   chronic lymphatic, 761.  
     lymphocytic, 761.  
     myeloid, 758.  
   classification of, 758.  
   eosinophilic, 754.  
   leucopenic, 761, 763.  
   mixed, 749.  
   monocytic, 758.  
   myelocytic, 758.  
   spleno-medullary, 758.  
**Leukanæmia**, 747, 749.  
**Leukosis**, 757.  
**Levi-Lorraine syndrome**, 485.  
**Lewisite**, poisoning by, 376.  
**Libman-Sacks disease**, 889.  
**Lice** in relation to relapsing fever, 241, 242.  
   in relation to trench fever, 300.  
   in relation to typhus fever, 295.  
**Lice-borne relapsing fevers**, 242.  
**Lichen amyloidosis**, 1281, 1300.  
   nitidus, 1279.  
   plano-pillaris, 1278.  
   planus, 1277.  
     atrophicus, 1278.  
     follicularis, 1278.  
     hypertrophicus, 1278.  
     verrucosus, 1278.  
   sclerosus et atrophicus, 1279.  
   scrofulosorum, 1244, 1281.  
   simplex chronicus, 1193.  
   spinulosus, 1278.  
   striatus, 1280.  
   tropicus, 1328.  
   urticatus, 1256, 1281.  
**Lichenoid eruption of axillæ**, 1281.  
**Lightning stroke**, death from, 403, 404.  
   injuries in, 404.  
**Lignac's disease**, 468.  
**Lindau's disease**, 1383.  
**Lineæ atrophicæ** in typhoid, 104.  
**Lineæ distensæ** in Cushing's syndrome, 517.  
**Lingua geographica**, 1327.  
   nigra, 1327.  
   plicata, 1327.  
**Linguatula serrata**, 336.  
**Lipase**, 701.  
**Lipodystrophia progressiva**, 451.  
**Lipodystrophy**, intestinal, 632.  
**Lipoid deposit diseases**, 783-786.  
   granulomatosis, 1186.  
   infiltration in renal tumours, 1145.  
   metabolism in atherosclerosis, 835.  
   storage spleno-hepatomegaly, 784.

**Lipoidosis, phosphatide, 785.**  
**Lipoma of skin, 1313.**  
**Lipomatoses, 452.**  
**Lips and mouth, diseases of, 1324.**  
**Lipophagia granulomatosis, 632.**  
**Lissauer type of general paralysis, 1633.**  
**Listeria monocytogenes, 305.**  
**Litten's sign in pleural adhesion, 1066.**  
**Little's area as common site of epistaxis, 938.**  
**disease, 1487, 1488.**  
**Livedo reticularis, 1209.**  
**Liver, acute and subacute necrosis of,**  
**causes of, 670.**  
**necrosis of, 670.**  
**yellow atrophy of, 671.**  
**amoebic abscess of, 277, 279-283.**  
**attacks, 673.**  
**biopsy, 659.**  
**carcinoma of, 685.**  
**primary, 685.**  
**secondary, 686.**  
**cirrhosis, 673.**  
**etiology of, 674.**  
**alcohol in relation to, 355, 674, 675.**  
**associated with progressive lenticular**  
**degeneration, 1484.**  
**biliary, 679.**  
**compensatory portal circulation in, 675.**  
**hematemesis in, 569, 676.**  
**in children, 674.**  
**Laennec's, 674.**  
**multilobular, 674.**  
**pericellular, 681.**  
**portal, 674.**  
**syphilitic, 681.**  
**tuberculous disease with, 678.**  
**condition of, in relation to jaundice, 664.**  
**congestion of the, 665.**  
**disease, fatty, 478.**  
**diseases of the, 658-689.**  
**enlarged, in acute necrosis, 671.**  
**in blackwater fever, 261, 262.**  
**in cancer, 686.**  
**in chronic lymphatic leukæmia, 761.**  
**in chronic pancreatitis, 705.**  
**in cirrhosis, 676.**  
**in congenital syphilis, 226, 681.**  
**in congestion, 666.**  
**in essential thrombocytosis, 770.**  
**in fatty infiltration, 673.**  
**in Gaucher's disease, 785.**  
**in glycogen disease, 452.**  
**in heart failure, 811.**  
**in hydatid disease, 684.**  
**in infective hepatitis, 668.**  
**in kala-azar, 266.**  
**in kwashiorkor, 479.**  
**in malaria, 249, 251.**  
**in Niemann-Pick's disease, 785.**  
**in nutritional macrocytic anemia, 475.**  
**in pernicious anemia, 736.**  
**in suppurative pyelephlebitis, 689.**  
**in typhoid fever, 99.**  
**in yellow fever, 185, 186.**  
**fatty infiltration of, 672.**  
**fibrosis of, 673.**  
**function tests, 658.**  
**gummata of, 682, 683.**

**Liver, hobnailed, 675.**  
**hydatid disease of the, 683.**  
**inflammation of, 666.**  
**lesions of, following arsphenamine treat-**  
**ment, 231, 670.**  
**necrosis of, acute and subacute, 670.**  
**in carbon tetrachloride poisoning, 394.**  
**in infective hepatitis, 667.**  
**in tetrachlorethane poisoning, 395, 670.**  
**in trinitrotoluene poisoning, 390, 670.**  
**nodular hyperplasia of, 671, 672.**  
**nutmeg, 665.**  
**pericarditic pseudo-cirrhosis of (Pick's**  
**disease), 717, 881.**  
**poisons acting on the, 670, 671.**  
**primary growths of the, 685.**  
**pulsating, in congestion, 666.**  
**replacement fibrosis of, 671.**  
**secondary growths of the, 686.**  
**syphilis of, 681, 682.**  
**tropical, 673.**  
**umbilication of, in carcinoma, 686, 687.**  
**"Liverishness," 672.**  
**Loa loa, 326, 328.**  
**Lobstein, post-natal fracture of, 1180.**  
**Localisation of cerebral lesions, 1336.**  
**Lockjaw, 81.**  
**Locomotor ataxia, 1461.**  
**Loculation syndrome, 1379.**  
**Loeffer's syndrome, 753.**  
**Long thoracic nerve, anatomy and physi-**  
**ology of, 1567.**  
**lesions of, 1568.**  
**Longitudinal sinus, thrombosis of, 1453.**  
**Lordosis in achondroplasia, 1182.**  
**in cerebral diplegia, 1489.**  
**in Cushing's syndrome, 517.**  
**in osteomalacia, 1177.**  
**in pseudo-hypertrophic paralysis, 1597.**  
**Louse-borne typhus fever, 295.**  
**Ludwig's angina, 538.**  
**Lumbago, 1166.**  
**Lumbago-sciatica syndrome, 1449.**  
**Lumbar puncture, 1378.**  
**importance of, for diagnosis of menin-**  
**gitis, 63.**  
**in apoplectic syndrome, 1449.**  
**in apoplexy, 1442.**  
**in cerebral abscess, 1409.**  
**in cerebrospinal fever, 59, 64.**  
**in heat hyperpyrexia, 409.**  
**in hypertensive encephalopathy, 1445.**  
**in meningitis, 1396.**  
**in trypanosomiasis, 272.**  
**in whooping-cough, 142.**  
**technique of, 1378.**  
**Lumbo-sacral cord paralysis after parturi-**  
**tion, 1585.**  
**Lumbo-sacral plexus, lesions of, 1573.**  
**Lung, abscess of, 1002.**  
**bacteriology of, 1002.**  
**differential diagnosis of, 1003.**  
**in bronchiectasis, 983, 984.**  
**in typhoid, 103.**  
**absence of, congenital, 994.**  
**absorption collapse of, 992.**  
**acquired collapse of, 992.**  
**actinomycosis of, 195, 1038.**

- Lung, active collapse of, 992.**  
 acute interstitial emphysema of, 1002.  
     vesicular emphysema of, 1001.  
 albinism of, 998.  
 aluminium, 1014.  
 aspergillosis of, 1039.  
 atrophic emphysema of, 1000.  
 blastomycosis of, 1039.  
 brown induration of, 988.  
 carcinoma of, 1041.  
     neurological syndromes in, 1042.  
 carnification of, 1067.  
 cirrhosis of, 1006.  
 collapse of, 992.  
 collateral hyperæmia of, 987.  
 compensatory emphysema of, 1001.  
 compressive collapse of, 992.  
 congenital collapse of, 992.  
 congestion of, use of term, 987.  
 consolidation of, in pulmonary tuberculosis, 1024.  
     in silicosis, 1009.  
 cystic disease of, 1044.  
 diseases of, 987-1062.  
 distomatosis of, 1043.  
 dust disease of, 1008.  
 embolism of, 852, 989.  
 emphysema of, 997.  
     acute interstitial, 1001.  
         vesicular, 1001.  
     atrophic, 1000.  
     bullous, 998, 999.  
     compensatory, 1001.  
     complications of, 999.  
     focal, 1011.  
     hypertrophic, 997.  
     idiopathic, 997.  
     in relation to broncho-pneumonia, 1059.  
     large-lunged, 997.  
     localised, 1001.  
     secondary, 1001.  
     senile, 1000.  
     small-lunged, 1000.  
     subcutaneous, from sudden decompression, 397.  
     substantive, 997.  
     varieties of, 997.  
 eosinophilic, 313.  
 farmers', 1015.  
 fibroid disease of, 1006.  
 fibrosis of, pneumoconiosis in relation to, 1009, 1011, 1013.  
 fluke disease of, 1043.  
 fluxionary hyperæmia of, 987.  
 gangrene of, 1005.  
     following infarction, 991.  
     in bronchial obstruction, 974.  
     in bronchiectasis, 984.  
     in typhoid, 103.  
     putrefactive products formed in, 1005.  
 gummata of, 1040.  
 hepatisation of, in pneumonia, 1049, 1051.  
 histoplasmosis of, *Appendix i.*  
 honeycomb, 983.  
 hydatid disease of, 1046.  
 hyperæmia of, 987.  
 hypertrophic emphysema of, 997.  
 hypostatic congestion of, ætiology of, 987.  
 hypostatic congestion of, in scarlet fever, 43.  
     in typhoid, 99, 100, 103.  
     in typhus, 296, 298.  
 infarction, 989.  
 lobar collapse of, 993.  
 lobular collapse of, 992.  
 massive collapse of, 993.  
 mottling, radiographic, in coal miners' pneumoconiosis, 1011.  
     in tropical eosinophilia, 314.  
 mycosis of, 1038.  
 new-growths of the, 1041.  
 nodulation of, in coal miners' pneumoconiosis, 1011.  
 oat-celled tumour of, 1041.  
 œdema of, 987.  
     acute or hyperacute, 988.  
     chronic, 989.  
     in acute nephritis, 1116.  
     in heart failure, 809.  
 oligæmic, in congenital heart disease, 893.  
 Pancoast tumour of, 1042.  
 pancreatisation of, 1040.  
 paragonimiasis of, 1043.  
 passive collapse of, 992.  
 peribronchial fibrosis of, 970.  
 pleonæmic, in congenital heart disease, 893, 894.  
 relaxation collapse of, 992.  
 resection in pulmonary tuberculosis, 1036.  
 sarcoidosis of, 1045.  
 "snow-storm" in miliary tuberculosis, 90.  
 syphilis of, 1040.  
 torulosis of, 198.  
 tropical diseases of, 1043.  
 tuberculosis of, 1016.  
 tumours of, 1041.  
**Lupus, bat's wing, 1262.**  
 disseminated, 889, 933.  
 erythematous, 1261.  
     chronic discoid, 1261.  
     systematized, 1263.  
 miliaris, 1241.  
     disseminatus faciei, 1245.  
 of nose, 1241.  
 pernio of Besnier, 1246.  
     of Hutchinson, 1262.  
 phenomenon, 934.  
 verrucosus, 1243.  
 vulgaris, 1240.  
**Lutembacher's syndrome, 896.**  
**Lymph glands or nodes, diseases of the, 787.**  
     in glandular fever, 305.  
     in Hodgkin's disease, 789, 790.  
     in leukæmia, 761, 762.  
     in rat-bite fever, 244.  
     in rheumatoid arthritis, 1151.  
     in sarcoidosis, 1246.  
     in scarlet fever, 39, 40.  
     in small-pox, 164.  
     in syphilis, 204.  
     in trypanosomiasis, 271.  
     in tsutsugamushi disease, 239.  
     in typhoid fever, 99.  
     neoplasm, of, 783.  
     structure of, 787.



- Lymphadenitis**, acute generalised, 788.  
 local, 788.  
 in syphilis, 207, 226.  
 tuberculous, 788.
- Lymphadenoma**, 789.
- Lymphadenomatous nodules**, 789.
- Lymphadenosis**, benigna cutis, 1317.
- Lymphangiectasis**, 928.
- Lymphangioma cavernosum**, 1315.  
 circumscriptum, 1315.
- Lymphangitis**, 787.  
 causative organism of, 34.  
 filarial, 326, 327.  
 in erysipelas, 35.  
 in glanders, 132.  
 in malignant pustule, 80.  
 in oriental sore, 269.  
 in rat-bite fever, 244.  
 in scarlet fever, 41, 42.  
 in tsutsugamushi disease, 289.
- Lymphatic obstruction**, 928.  
 system, diseases of, 787-792.  
 varix in filariasis, 327.  
 vessels, diseases of the, 787.
- Lymphatics in rat-bite fever**, 244.
- Lymphoblastomatosis**, erythroderma in, 1268.
- Lymphocytes**, 752, 754.
- Lymphocytoma**, follicular, 1317.  
 miliary, 1317.
- Lymphocytosis**, 754.
- Lymphœdema**, 788, 928.  
 inflammatory, 928.  
 præcox, 928.
- Lymphogranuloma inguinale**, 191.  
 venereum vel inguinale, 191, 1250.  
 pseudo-arthritis associated with, 1165.
- Lymphogranulomatosis**, benign, 1245.
- Lymphoid hyperplasia in chronic lymphatic leukaemia**, 761.
- Lymphopathia venereum**, 191.
- Lymphorrhages in myasthenia gravis**, 1604.
- Lymphosarcoma**, 791.  
 reticulum cell type, 792.
- Lyssa**, 1420.
- MacBurney's point**, 655.
- Macewen's sign in hydrocephalus**, 58.
- Macrocheilia**, 1324.
- Macrococytes**, 727.
- Macrogenitosomia**, 523.
- Macula cærulea**, 1254.
- Madura foot**, 196.
- Maduramycosis**, 196.
- Magnamycin**, 14.
- Magnesium sulphate in bacillary dysentery**, 119.  
 trisilicate in gastric and duodenal ulcer, 582, 583.
- Maidismus**, 472.
- Main en griffe in progressive muscular atrophy**, 1556.  
 in syringomyelia, 1546.  
 in ulnar paralysis, 1572.  
 succulente in syringomyelia, 1547.
- Maize as cause of pellagra**, 472.
- Majocchi's disease**, 1259.
- Malattia della Miseria**, 472.
- Mal de la rosa**, 472.  
 del sole, 472.
- Mal de los pintos**, 1333.
- Maladie de Carrion**, 144.  
 de Roger, 896.  
 de Woillez, 987.
- Malaise**, toxæmic, 30.
- Malaria**, 245-260.  
 abdominal, 252.  
 acute pernicious, 249, 251, 259, 260.  
 ætiology of, 246.  
 algid, 252.  
 benign tertian, 246, 253.  
 blackwater fever in relation to, 254, 260.  
 cachexia in, 253.  
 cardiac, 252.  
 cerebral, 251.  
 chronic, 249.  
 clinical types of, 251.  
 complications and sequelæ of, 254.  
 diagnosis of, 254.  
 distribution of, 246.  
 gastro-intestinal, 252.  
 history of, 245.  
 incubation period, 250.  
 latency period, 252.  
 malignant tertian, 246, 253.  
 mosquitoes which transmit, 248.  
 parasites, 246.  
 differentiation of species of, 248.  
 human phase of, 247.  
 in blood smears, 248.  
 life cycle of, 247.  
 mosquito phase of, 247.  
 staining of, 248.  
 pathology of, 248.  
 pernicious, 249, 251.  
 primary fever, 250.  
 prognosis of, 255.  
 prophylaxis of, 255.  
 purpuric, 252.  
 quartan, 246, 253.  
 recrudescence and relapse in, 253.  
 renal, 252.  
 symptoms of, 249.  
 tertian, 246.  
 treatment of, 255.
- Malassez**, pityrosporon of, 1216.
- Malassezia furfur**, 1238.  
 tropica, 1333.
- Malattia della miseria**, 472.
- Malignant œdema**, 80.  
 pustule, 80.
- Malingering**, 1672.
- Mallein test for glanders**, 132.
- Malnutrition as a factor in infection**, 2.  
 malignant, 478.
- Malta fever**, 125.
- Mandelic acid preparations in pyelitis**, 1135.
- Manganese poisoning**, 385.
- Mania**, 1645.  
 and catatonia contrasted, 1664.  
 symptoms of, 1648.  
 treatment of, 1654.
- Mania à potu**, 353, 1637.
- Manic-depressives**, liability and responsiveness of, 1646.
- Mansonella ozzardi**, 326.

- Mantoux intradermal test for tuberculosis**, 88, 1028.
- Marasmus**, 617.  
idiopathic hypercalcaemia in, 618.  
in congenital syphilis, 227.  
infantile renal acidosis in, 618.
- Marble bone disease of Albers-Schönberg**, 748.
- Marchiafava-Micheli type of hæmolytic anaemia**, 744.
- Marie's delayed cortical cerebellar atrophy**, 1481.  
disease, 1171.
- Marie-Strumpell disease**, 1160.
- Marriage, epilepsy in relation to**, 1505.  
hysteria in relation to, 1677.  
syphilis in relation to, 224, 225.
- Marsh fever**, 245.
- Masons' disease**, 1009.
- Mass reflex**, 1542.
- Massage of carotid sinus**, 824.
- Mastoid inflammation in measles**, 152.  
symptoms in scarlet fever, 42, 47.
- Maurer's spots in malarial parasite**, 248.
- Meal, opaque, in examination of bowel**, 602.
- Measles**, 149.  
age-incidence of, 149.  
complications of, 151.  
congenital, 149.  
German, 156.  
hæmorrhagic type of, 151.  
incubation period in, 150.  
Koplik's spots in, 150, 151, 153.  
mortality in, 154.  
prophylaxis of, 29, 154.  
pulmonary type of, 151.  
quarantine after, 155.  
rash in, 150, 151, 153.  
second attacks of, 153.  
serum prophylaxis of, 154.  
toxic type of, 151.  
varieties of, 151.
- Meat poisoning**, 111, 120, 122.
- Meckel's diverticulum as cause of acute intestinal obstruction**, 650.
- Median nerve, lesions of**, 1570.
- Mediastinal abscess**, 1091.  
cause of bronchial stenosis, 977.  
glands, enlarged, 1092.  
in Hodgkin's disease, 1092.  
tracheal obstruction due to, 962.  
in pneumoconiosis, 1092.  
tubercular, 1092.  
new-growths, 1093.  
syndrome, the, 1090, 1094.
- Mediastinitis**, 1089.  
acute simple, 1089.  
suppurative, 1089.  
chronic, 1091.  
indurative, 1091.
- Mediastinum, carcinoma of the**, 1094.  
causes of pressure in, 962.  
diseases of the, 1089.  
emphysema of the, 1091.  
gangrene of, 1090.  
malignant tumours of the, 1093.
- Mediterranean anaemia**, 743.  
fever, 125.
- Medulla, localisation of lesions of**, 1363.
- Medulloblastoma**, 1382.
- Megacolon**, 646.
- Megalerythema epidemicum**, 305.
- Megaloblasts**, 729.
- Megalocephaly**, 1175.
- Megalocytes**, 729.
- Megalocytic anaemia**, 729.
- Megalocytosis in pernicious anaemia**, 736.
- Meigs' syndrome**, 1076.
- Meinicke reaction in syphilis**, 205.
- Melena**, 569.  
neonatorum, 576, 769.
- Melancholia**, 1645.
- Melania libertina in relation to hetero-phydiasis**, 318.  
in relation to paragonimiasis, 317.
- Melanin, formation of**, 1201.
- Melanoblasts**, 1201.
- Melanophores**, 1201.
- Melanoma, malignant**, 1310.
- Melanuria**, 1105.
- Melanuric fever**, 260.
- Meleney's ulcers**, 1231.
- Melioidosis**, 133.
- Membrane, in diphtheria**, 69, 70, 71, 74, 75, 534.  
in muco-membranous colic, characters of, 628.  
in Vincent's angina, 74, 537.  
of thrush, 527.  
on throat in scarlet fever, 38.
- Memory**, 1613.
- Ménière's disease**, 1353.
- Meningeal hæmorrhage**, 1448.  
syphilis, 1454, 1459.  
tumours in relation to compression of cord, 1535.
- Meningioma**, 1382.
- Meningism**, 60, 1399.
- Meningitic syndrome**, 1449.  
torulosis, 198.
- Meningitis**, 1391-1399.  
acute syphilitic, 1461.  
anthrax bacillus causing, 1393.  
benign aseptic, 1397.  
lymphocytic, 1397.  
carcinomatous, 1382.  
cerebrospinal, 54.  
classification of, 1392.  
differentiated from cerebral abscess, 1409, 1410.  
from toxæmia, 60.  
epidemic cerebrospinal, 54.  
serous, 1397.  
gonococcal, 1393.  
in coccidioidosis, 200.  
in erysipelas, 35.  
in scarlet fever, 42.  
in typhoid fever, 104.  
infantile syphilitic, 1398.  
influenzal, 62, 1393.  
treatment with penicillin, 8.
- leptospirosis**, 240.  
plague, 128.  
pneumococcal, 62, 1392.  
cerebrospinal fluid in, 1392.  
in pneumococcal pneumonia, 1053.

- Meningitis, post-basic of infants**, 58.  
   purulent, from screw-worm, 338.  
   pyogenic, 1393.  
   *serosa circumscripta*, 1537.  
   streptococcal, 62.  
   suppurative, from bone disease, 1393.  
   syphilitic, 1398, 1461.  
     cerebrospinal fluid in, 1398.  
   tuberculous, 62, 1394.  
   typhoid, 62, 101.
- Meningococcal arthritis**, 1155.  
   septicæmia, chronic, 1155.
- Meningococci**, Gordon's grouping of, 55.  
   in cerebrospinal fluid, 55, 60.
- Meningococcus**, 55.  
   "carriers," 55.  
   meningitis, cerebrospinal fluid in, 59, 60.  
   sensitivity to penicillin, 7.  
   types of, 55.
- Meningo-typhoid variety of typhoid fever**, 101.
- Menopausal arthritis**, 1159, 1166.
- Menopause**, 522.  
   changes in body fat at, 449.  
   in relation to idiopathic hypochromic  
     anæmia, 732.  
   in relation to mental disorders, 1645, 1647.
- Menstrual disturbances in melancholia**, 1645.
- Menstruation in relation to asthma**, 978.  
   in relation to epilepsy, 1494.  
   in relation to mental disease, 1645.  
   in relation to pulmonary tuberculosis, 1024.  
   vicarious, 569, 938, 995.
- Mental age**, 1684, 1686.  
   and bodily illness, relationship between,  
     1609.  
   defectives, educational and social care of,  
     1618.  
   deficiency, 1682.  
     bodily anomalies associated with, 1684.  
     classification of, 1683.  
     mental tests in, 1686.
- Disorders**, 1608-1688.  
   associated with acute carbon monoxide  
     poisoning, 1642.  
   with alcoholism, 1637.  
   with altitude sickness, 400, 401.  
   with barbiturate poisoning, 1641.  
   with bromide intoxication, 1641.  
   with castration, 1645.  
   with cerebral atheroma, 1443.  
     diplegia, 1488.  
     tumour, 1635.  
   with child-bearing, 1644, 1646.  
   with chronic alcoholism, 356, 1637.  
   with climacteric, 1645, 1647.  
   with cocaineism, 1641.  
   with cœliac disease, 619.  
   with congenital syphilis of nervous  
     system, 1471.  
   with degenerative and hereditary brain  
     disease, 1903.  
   with disseminated lupus erythema-  
     tosus, 936.  
   with disseminated sclerosis, 1475, 1635.  
   with drug addiction, 1640.  
   with encephalitis lethargica, 1415.
- Mental disorders, associated with endocrine  
 disorders**, 1643.  
   with epilepsy, 1500, 1636.  
   with exhaustion and inanition, 1642.  
   with exophthalmic goitre, 1643.  
   with general paresis, 1456.  
   with head injuries, 1635.  
   with hydrocephalus in children, 1401.  
   with hysteria, 1673.  
   with infantile hemiplegia, 1491.  
   with infections and exhaustive dis-  
     orders, 1642.  
   with infectious toxæmias, 1642.  
   with intoxications, 1637.  
   with intracranial tumours, 1635.  
   with lactation, 1645.  
   with menopause, 1645, 1647.  
   with menstruation, 1645, 1646.  
   with metabolic disorders, 1643.  
   with morphinism, 1640.  
   with paralysis agitans, 1635.  
   with parturition, 1644.  
   with pellagra, 474.  
   with pregnancy, 1644, 1646.  
   with puberty, 1646.  
   with puerperium, 1644.  
   with Schilder's disease, 1635.  
   with senility, 1628.  
   with sexual epochs, 1644.  
   with somatic tension, 324.  
   with syphilis of central nervous system,  
     1632.  
   with Tay-Sachs disease, 1483.  
   with trauma, 1635.  
   with tsutsugamushi disease, 290.  
   with tuberosc sclerosis, 1487.  
   with typhoid fever, 104.  
   with visceral disease, 1645.
- bodily disease in relation to**, 1609.
- cerebral arterial disease and hypertension  
 causing**, 1630.  
   classification of, 1622.  
   convulsion therapy in, 1621.  
   effect of war upon incidence of, 1615.  
   endocrine factors in, 1611.  
   extrinsic causes of, 1611.  
   heredity and constitution in, 1609.  
   intrinsic causes of, 1609.  
   mental experiences in relation to, 1613.  
   organic, general description of types of,  
     1624.  
   physical experiences in relation to, 1612.  
   prophylactic treatment of, 1616.  
   sexual instinct in relation to, 1614.  
   treatment of, 1616.
- experiences in relation to mental disorders**,  
   1613.  
   tests, 1684, 1686.
- Mepacrine in blackwater fever**, 263, 264.  
   in flagellate diarrhoea, 284.  
   in lupus erythematosus, 1263.  
   in malaria, 255, 257.  
   in teniasis, 323.
- Meralgia paræsthetica**, 1574.
- Mercurial diuretics in heart disease**, 815.  
   inunction, for syphilis, 216.  
   poisoning, 381.  
     acute, 381, 816.

- Mercurial poisoning**, chronic, 382.  
     mental disorders in, 1642.  
     preparations for treatment of syphilis, 216.  
     stomatitis, 233, 382, 383.
- Mercurialism**, 382, 816.
- Mercury compounds**, organic, poisoning by, 383.  
     eruptions, 382, 383.  
     fulminate, poisoning by, 383.  
     preparations, in syphilis, 216.  
     toxic effects of, 233.  
     vapour lamp, in treatment of rickets, 467.
- Merk, hyperkeratotic border of**, in pellagra, 474.
- Merozoites of malaria parasite**, 247.
- Mersalyl** in heart disease, 815.
- Mescaline intoxication**, 1657.
- Mesenteric glands**, affections of, in kala-azar, 265.  
     in tuberculous peritonitis, 718, 719.  
     in typhoid, 99, 103.  
     in undulant fever, 125.  
     calcified, in tuberculous peritonitis, 719.  
     thrombosis simulating intestinal obstruction, 653.  
     tuberculosis of, 718, 719, 788.  
     veins, thrombosis of, 688.
- Metabolic disorders** in relation to mental health, 1643.  
     rate, basal, 415.
- Metabolism**, diseases of, 415-453.  
     in dinitro-ortho-cresol poisoning, 392.  
     in dinitrophenol poisoning, 391.  
     in exophthalmic goitre, 493.  
     in myxœdema, 497.  
     in relation to epilepsy, 1492.  
     in relation to obesity, 449.  
     thyroid, in relation to, 449.
- Metagonimus yokogawai**, 318.
- Metazoa**, diseases due to, 316.
- Meteorism**, 102.
- Methæmoglobin in urine**, 262, 1104.
- Methæmoglobinæmia**, 751.  
     hereditary, 752.
- Methanol**, poisoning by, 357.
- Methyl alcohol**, poisoning by, 357.  
     androstenediol in treatment of infantilism, 486.  
     bromide, poisoning by, 394.  
     chloride, poisoning by, 393.  
     mercury compounds, poisoning by, 383.  
     testosterone in treatment of infantilism, 486.
- Methylene-blue**, effect of, on urine, 1106.
- Metritis** in gonorrhœa, 67.
- Meulengracht diet**, 570.
- Meuse fever**, 300.
- Mibelli**, porokeratosis of, 1297.
- Microcephalic type of idiocy**, 1488.
- Microcytes**, 727.
- Microfilaria streptocerca**, 1329.
- Microgyria** as cause of mental defect, 1684.
- Micromelia fœtalis**, 1182.
- Micro-organisms**, antibiotic products from, 6.
- Micropsia**, 1638.
- Microsporon audouini**, 1233.  
     canis vel felineum, 1233.
- Microsporon furfur**, 1238, 1333.  
     gypseum, 1233.
- Microsporosis**, 1233.
- Micturition**, frequency of, in anoxæmia, 401.  
     in coliform infections, 95.  
     in diverticulitis, 644.  
     in gonorrhœa, 65.  
     in heat hyperpyrexia, 408.  
     in pyelitis, 1134.  
     in trench fever, 301.  
     in tuberculosis of kidney, 1139.  
     reflex, 1532.
- Mid-brain**, localisation of lesions of, 1362.
- Midge bites**, 337.
- Migraine**, 1508.  
     mental, 1637.
- Miliaria**, crystallina, 1198.  
     profunda, 1199.  
     rheumatic, 50.  
     rubra, 1199, 1225, 1328.
- Miliary tuberculosis**, acute, 1019.  
     chronic, 1019.
- Milk drip**, 587.  
     in relation to tubercular infection, 85, 89.  
     in treatment of mild plumbism, 370.  
     in treatment of rickets, 467.
- Milkers' nodes**, 1250.
- Mill fever**, 1015.
- Milroy's disease**, 788, 928.
- Mineralocorticoids**, 506, 507.
- Miners' asthma**, 1009, 1012.  
     phthisis, 1009, 1012.
- Miracid D**, in schistosomiasis, 321.
- Mirbane**, oil of (nitrobenzene), 389.
- Mite typhus**, 288.
- Mites** as transmitters of disease, 288, 336.  
     in relation to tsutsugamushi disease, 288.
- Mitral disease**, 862.  
     incompetence, 863.  
     stenosis, 863, 865.  
     and incompetence, 868.  
     auricular fibrillation in, 827, 868.  
     congenital, 863.  
     hæmoptysis in, 866.  
     hypertrophy of left auricle in, 866.  
     of right ventricle in, 866.  
     in relation to pulmonary tuberculosis, 1017.  
     murmurs in, 867.  
     pulse in, 867.  
     thrombosis in, 868.  
     valve, funnel-shaped, 863.  
     valvotomy, 870.  
     valvulitis, 889.
- Moles**, 1310.  
     fleshy hairy, 1310.  
     non-hairy, 1202.
- Mollities ossium**, 1176.
- Molluscum contagiosum**, 1302.  
     fibrosum, 1486.  
     sebaceum, 1303.
- Moloney toxoid test** for diphtheria susceptibility, 77.
- Mönckeberg's degeneration**, 919.
- Monday fever**, 1015.
- Mongolian spot**, 1202, 1311.
- Mongolism**, 1685.
- Mongoloid type of idiocy**, 1685.

- Monilethrix**, 1317.  
**Monilia** affecting lungs, 1040.  
     skin, 1237.  
**Monocytes**, 752, 755.  
**Monocytic angina**, 305.  
**Monocytosis**, 755.  
**Mononeuritis multiplex**, 932.  
**Mono-nitrobenzene poisoning**, 389.  
**Mononucleosis, acute**, 754.  
     infectious, 305.  
**Monoplegia** in cerebrospinal fever, 58.  
**Mood**, in anxiety states, 1651.  
     in mental depression, 1649.  
     lability of, in mania, 1648.  
**Moon's teeth**, 227.  
**Moral defectiveness**, 1683, 1684, 1685.  
     effects of morphinism, 1640.  
**Morbilli**, 149.  
**Morbis cœruleus**, 897.  
     coxæ senilis (of hip), 1157.  
     maculosus hæmorrhagicus of Werlhof, 771.  
**Morphine** in heart failure, 813.  
     poisoning, acute, 351.  
**Morphinism**, 1640.  
**Morphœa**, 935, 1291.  
**Morton's disease**, 1151.  
**Morvan's disease**, 1547.  
**Mosquito bites**, 337.  
     worm, the, 338.  
**Mosquitoes** as conveyers of mosquito worm, 338.  
     in relation to dengue, 189.  
     in relation to filariasis, 326.  
     in relation to malarial infection, 247, 248.  
     in relation to yellow fever, 184.  
     measures for control and destruction of, 255.  
**Motor area**, lesions of, localising signs of, 1359.  
     neurone disease, 1554.  
     symptoms in hysteria, 1672.  
**Mountain sickness**, 400.  
**Mouth affections** in syphilis, 206.  
     diseases of the, 525-530, 1325.  
     dry, 530.  
     in pink disease, 309.  
     in scarlet fever, 38, 40.  
     in scurvy, 462.  
     in syphilis, 206.  
     lesions in agranulocytosis, 757.  
     in pellagra, 473.  
     lupus of the, 1241.  
**Mouth-breathing** in adenoids, 942.  
     in relation to bronchitis, 963.  
**Movements** in schizophrenia, 1663.  
     involuntary, in chorea, 1516.  
     in Friedrich's ataxia, 1480.  
     in encephalitis lethargica, 1416, 1417.  
     perverse, in cerebral diplegia, 1488.  
**Mucin**, test for, 1102.  
**Muco-membranous colic**, 627.  
**Mucor mucedo** infecting lungs, 1040.  
**Mucous "catarrh"** in epidemic diarrhœa, 615.  
     erosions in syphilis, 207.  
     patches, 206.  
     of mouth and throat, 206.  
**Mucus** in colitis, 633, 634.  
**Mucus** in gastric secretion, rôle of, 554.  
     in stools in bacillary dysentery, 114.  
     in stools in muco-membranous colic, 628.  
**Mugil cephalus** in relation to heterophyiasis, 318.  
**Mumps**, 174.  
     cerebral, 174.  
     complications of, 175.  
     submaxillary, 175.  
**Muræna bite**, 343.  
**Murmur**, Austin Flint, 859, 876.  
     Carey Coombs, 889.  
**Murmurs, auricular systolic**, 798.  
     cardiac, 797, 798.  
     continuous, 798.  
     diastolic, 798.  
     mid-diastolic, 798.  
     mid-systolic, 797.  
     pan-systolic, 798.  
     pre-systolic, 798.  
     systolic, 797.  
**Muscle**, Zenker's degeneration of, 99, 296, 1169.  
**Muscles, diseases of**, 1596-1607.  
     voluntary, inflammation of, 1169.  
**Muscular atrophy** in acute poliomyelitis, 1427, 1428.  
     in beriberi, 470.  
     in dermatomyositis, 936.  
     in dystrophia myotonica, 1601, 1602.  
     in lead palsy, 1593.  
     in rheumatoid arthritis, 1151.  
     in syringomyelia, 1546.  
     neuritic type, 1563.  
     of children, progressive spinal, 1565.  
     peroneal, 1563.  
     progressive, 1554.  
     changes in the myopathies, 1596.  
     dystrophies, 1596.  
     dystrophy, pseudo-hypertrophic, 1596.  
     pain in leptospirosis icterohæmorrhagica, 239.  
     rheumatism, 1165.  
**Mushroom poisoning**, 345.  
     as cause of hepatic necrosis, 671.  
**Mussels** as source of infection in typhoid, 98.  
**Mustard gas** in relation to bronchitis, 967.  
     tracheitis caused by, 954.  
**Mutism**, hysterical, 1672.  
**Myalgia**, epidemic, 193, 1166.  
     in undulant fever, 1156.  
**Myasthenia gravis**, 1603.  
     dysphagia in, 542.  
     ocular palsy in, 1604.  
**Mycetoma**, 196.  
**Mycides**, 1239.  
**Mycobacterium lepræ**, 90.  
     tuberculosis, 84, 85, 1017.  
     in sputum, 87, 1021.  
     isolation and recognition of, 87.  
**Mycoses**, 193-201.  
     pulmonary, 1038.  
**Mycosis fungoides**, 1316.  
**Mydriasis**, 1343.  
**Myelinoclasia**, perivascular, 1411.  
**Myelitis**, acute syphilitic, transverse, 1469.  
     acute transverse, 1542.  
     diffuse, with optic neuritis, 1478.

- Myelitis**, sub-acute and chronic syphilitic, 1470.  
**Myeloblasts**, 748, 759.  
**Myelocytes** in chronic myeloid leukaemia, 759.  
     in diphtheria, prognostic significance of, 72.  
     in leuco-erythroblastic anaemia, 748.  
     in whooping-cough, 139.  
**Myelofibrosis**, 748.  
**Myeloma**, *haematogenous*, 1184.  
     multiple, 748, 1184.  
     osteogenetic, 1175.  
**Myelomatosis**, 1184.  
**Myelosclerosis**, 748.  
**Myelosis**, chronic leukaemic, 758.  
**Myiasis**, 337.  
     dermal, 337.  
     intestinal, 339.  
     linearis, 1334.  
**Myleran** in chronic myeloid leukaemia, 760.  
**Myocardial infarction**, 842.  
**Myocarditis**, 890.  
     diphtheritic, 891.  
     Fiedler's, 891.  
     idiopathic, 891.  
     isolated, 891.  
     primary, 891.  
     rheumatic, 891.  
**Myocardium**, degeneration of, in coronary disease, 836.  
     diseases of the, 890.  
     non-inflammatory disease of the, 892.  
     primary amyloidosis of the, 892.  
**Myoclonus**, 1520.  
     epilepsy, 1497, 1520.  
     Unverricht's, 1520.  
**Myoidema**, 1026.  
**Myokimia**, 1560.  
**Myopathic atrophy**, 1596.  
     face, 1601.  
**Myopathies**, the, 1596.  
**Myosis**, diagnostic significance of, 1342.  
     pontine, 1363.  
**Myositis**, 1169.  
     dermato-, 936, 1293.  
     in rat-bite fever, 244.  
     in trichiniasis, 331.  
     non-suppurative, 1169.  
     ossificans progressiva, 1170.  
     suppurative, 1169.  
**Myotonia atrophica**, 1600.  
     congenita, 1599, 1602.  
**Myotonic reaction of Erb**, 1603.  
**Myxoedema**, 496.  
     blood in, 497.  
     hair in, 1318.  
     mental disorders in, 496, 1644.  
     metabolism in, 497.  
     skin in, 1301.  
**Nævi**, epidermal, 1298.  
     in hereditary hæmorrhagic telangiectasia, 775.  
**Nævo-xantho-endothelioma**, 1299.  
**Nævus**, blue, 1311.  
     caverno-capillary, 1314.  
     flammeus, 1313.  
     linear, 1298.  
**Nævus**, physiological, 1313.  
     sebaceus (Jadasshon), 1308.  
     senile sebaceous, 1308.  
     unius lateralis, 1298.  
     Unna's, 1313.  
     vasculosus, 1314.  
**Naga sore**, 1331.  
**Nail plate**, disorders of, 1323.  
**Nails**, claw, 1323.  
     diseases of, 1321.  
     drumstick, 1172.  
     lesions of, due to arsenic, 374.  
     due to X-rays, 410.  
     psoriasis of, 1274.  
**Nalorphine** in acute morphine poisoning, 351.  
**Nanukayami disease**, 237.  
**Naphthalene**, chlorinated, poisoning by, 395.  
     as a cause of acute hæmolytic anaemia, 747.  
**Napier's aldehyde test** in kala-azar, 267.  
**Napkin eruption**, 1223.  
     in congenital syphilis, 225.  
**Narcolepsy**, 1507.  
**Nares**, plugging the, 938.  
**Nasal causes of asthma**, 977.  
     diphtheria, 71.  
     irritation, as symptom of intracranial tumour, 1388.  
     obstruction from adenoids, 941, 942.  
     in gonorrhoea, 236.  
     in rhinosporidiosis, 201.  
     septum, erosions of, 227.  
     in chromium poisoning, 384.  
**Naso-pharynx**, diseases of the, 941.  
**Naunyn's sign** in cholecystitis, 691.  
**Nausea**, 565.  
     in chronic cholecystitis, 691.  
     in infective hepatitis, 668.  
     in pulmonary tuberculosis, 1024.  
     hysterical, 565.  
**Necator americanus** as human parasite, 332.  
**Neck**, actinomycosis affecting, 194.  
     rigidity of, in cerebrospinal fever, 56.  
     in meningitis, 1395, 1397.  
     in poliomyelitis, 1426.  
**Necrobiosis lipoidica**, 1300.  
**Necrosis**, acute medullary, 1127.  
     tubular, 1128.  
     following infection, 3.  
     of bone in leprosy, 91.  
     of jaw in chronic phosphorus poisoning, 378.  
**Negativism** in schizophrenia, 1660, 1663.  
**Negri bodies**, 146.  
     in rabies, 146, 1421.  
**Negroes**, sickle-celled anaemia in, 743.  
**Neill-Mooser reaction** in flea typhus, 287.  
**Neisseria catarrhalis** in relation to bronchitis, 963.  
     in relation to influenza, 179.  
     in relation to tracheitis, 954.  
     gonorrhoeae, 65.  
     meningitidis, 55.  
**Nelson bed** for postural drainage, 986.  
**Nematodes**, diseases due to, 325-335.  
**Neoarsphenamine** in gangrene of the lung, 1006.  
     in relapsing fever, 244.

- Neoarsphenamine in syphilis, 213.  
in yaws, 235.
- Neosalvarsan, 213.
- Neostibosan in filariasis, 328.
- Nephritis, acute diffuse, 1115.  
focal, 1118.  
interstitial, 1128.  
hæmorrhagic, 1115.  
ascaris, 334.  
classification of, 1114.  
glomerular, 1115.  
hæmaturia in, 1104.  
high blood pressure in, 1116, 1122, 1124.  
hydropigenous, 1120.  
in carbon tetrachloride poisoning, 394.  
in chronic lead poisoning, 368.  
in scarlet fever, 43.  
interstitial acute focal, 1128.  
nephrotic, 1120.  
parenchymatous, 1120.  
renal contraction in, 1127.  
"salt-losing," 1137.  
trench, 1115.  
Type I, 1115.  
Type II, 1120.
- Nephrocalcinosis, 1130.
- Nephrolithiasis, 1140.
- Nephropathy, diabetic, 442.
- Nephropepy, 1149.
- Nephroptosis, 1147.
- Nephrosis, bilateral cortical, 1130.  
eclamptic 1130.  
lipoid, 1120.  
lower nephron, 1128.  
mercurial, 1129.  
simple, 1129.  
toxic, 1129.
- Nephrosclerosis, benign, 909, 1124.  
malignant, 912, 1124.  
without hypertension, 1125.
- Nephro-typhoid variety of typhoid fever, 101.
- Nerve, auditory, 1351.  
axillary, 1573.  
cervical sympathetic, paralysis of, 1345.  
cochlear, 1351.  
common peroneal, 1575.  
eighth, damage to, in streptomycin therapy, 11.  
eleventh, 1356.  
facial, 1348.  
femoral, 1574.  
fifth, 1345.  
fourth, paralysis of, symptoms of, 1341.  
glossopharyngeal, 1354.  
hypoglossal, 1357.  
lateral femoral cutaneous, 1574.  
long thoracic, 1567.  
median, paralysis of, 1570.  
musculo-cutaneous, 1573.  
ninth, 1354.  
obturator, 1574.  
olfactory, and tract, 1338.  
optic, 1338.  
phrenic, 1567.  
radial, paralysis of, 1569.  
recurrent laryngeal, in relation to paralysis, 950, 951.
- Nerve roots and nerve trunks, local lesions of, 1567-1576.  
sciatic, paralysis of, 1574.  
seventh, 1348.  
sixth, anatomy of, 1341.  
spinal accessory, 1356.  
tenth, 1355.  
third, anatomy of, 1341.  
tibial, 1575.  
trigeminal, 1345.  
twelfth, 1357.  
ulnar, lesions of, 1572.  
vagus, 1355.  
lesions of, 1355.  
vestibular, 1351.
- Nerve-deafness, 1351.
- Nerve lesions, local, treatment of, 1575.  
roots and nerve trunks, lesions of, 1567-1576.
- Nerves, auditory and vestibular, symptoms of lesions of, 1351.  
cranial, disorders of the, 1338-1357.  
syphilitic paralysis of, 1399.  
oculo-motor, affections of the, 1340-1345.  
peripheral, lesions of the, 1567-1576.
- Nerve-suture, 1576.
- Nervous dyspepsia, 567.  
system, congenital syphilis of, 1471.  
diseases of the, 1336-1607.  
in pulmonary tuberculosis, 1024.  
syphilis of the, 1454-1472.  
mental disorders associated with, 1632.  
vascular disorders of, 1435-1454.  
virus diseases of, 1414-1434.
- Neuralgia, brachial, in aortic aneurysm, 860.  
glossopharyngeal, 1354.  
post-herpetic, 1248.  
trigeminal, 1346.
- Neurapraxia, 1567.
- Neurasthenia, 1625.  
and trench fever, 301.  
syphilitic, 1632.
- Neuritis, alcoholic, 1589.  
arsenical, 1590.  
associated with arthritis, 1576.  
brachial, 1166, 1577.  
interstitial, 1578.  
paralytic, 1577.  
causing laryngeal paralysis, 952.  
cervico-occipital, 1577.  
diabetic, 425, 1592.  
diphtheritic, 1590.  
interstitial, 1576.  
multiple diphtheritic, 1591.  
peripheral, 1586.  
of sacral plexus, 1573.  
optic, 1339.  
retrobulbar, 1339, 1475.  
sciatic, 1582.
- Neuroblastoma, 520.
- Neurodermatitis circumscripta, 1193.  
disseminated, 1197.
- Neurofibroma of brain, 1382.  
of spine, 1536.
- Neurofibromatosis, 1485.  
skin lesions in, 1312.
- Neuro-fibrositis, 1576.
- Neuroma, plexiform, 1486.

- Neuromyelitis optica, 1478.  
 Neuropathy, diabetic, 442.  
     in beriberi, 469.  
 Neuro-retinitis, 1339.  
 Neuroses, occupation, 1525.  
 Neurosis, cardiac, 904.  
     colon, 627.  
     vegetative, 308.  
 Neurotmesis, 1567.  
 Neutropenia, malignant, 756.  
     primary splenic, 756.  
 Neutrophilia, 753.  
 Nevrodermite, 1193.  
 Nicotinamide (vitamin B<sub>3</sub>), 458.  
     in ulcerative stomatitis, 526.  
 Nicotine poisoning, acute, 346.  
 Nicotinic acid (vitamin B<sub>3</sub>), 458.  
     in pellagra, 474.  
 Niemann-Pick's disease, 785.  
 Nightshade poisoning, 344, 352.  
 Night sweats in pulmonary tuberculosis, 1022.  
     terrors in adenoids, 942.  
 Nihilistic delusions, 1653.  
 Nikolsky's sign, 1286.  
 Nipple, Paget's disease of, 1306.  
 Nissl bodies, disappearance of, in progressive muscular atrophy, 1555.  
 Nitrites in anginal attacks, 840.  
     in cardiospasm, 545.  
 Nitritoid crises in arsphenamine therapy, 230.  
 Nitrobenzene, poisoning by, 389.  
 Nitrogen excretion in urine, 1098.  
     retention, extra-renal, 1111.  
     saturation of tissues with, the essential in caisson disease, 396, 397.  
     solubility of, in fat, 396.  
 Nitro-prusside test for ketonuria, 1106.  
 Nits, 1252.  
 Nodal extra-systoles, 822.  
     rhythm, auriculo-ventricular, 823.  
 Nodes, juxta-articular, 237, 1315.  
     milkers', 1250.  
 Nodular goitre with hyperthyroidism, 495.  
 Nodules, "apple jelly," in lupus vulgaris, 1241.  
     fibrous, 1165, 1166.  
     filarial, 327.  
     in amebic dysentery, 276.  
     in erythema nodosum, 1260.  
     in localised Bartonellosis, 145, 146.  
     in multiple myeloma, 1185.  
     in mycetoma, 197.  
     in oriental sore, 269.  
     leprotic, 91.  
     periosteal, in congenital syphilis, 227.  
     subcutaneous, in teniasis, 324.  
     subcutaneous rheumatic, in children, 51.  
 Noma, 527.  
     in measles, 152, 155.  
 Nominal deficiency, 1370.  
 Noradrenaline, hypersecretion of, in pheochromocytoma, 518.  
     in cardiac infarction, 846.  
 Normoblasts, 729.  
 Normocytes, 727.  
 Nose, affections of, in glanders, 132.  
     Nose, diseases of the, 938-943.  
         in gangosa, 236.  
         lupus of the, 1241.  
         syphilis of the, 206, 227.  
 Nothnagel's syndrome, 1362.  
 Novarsenobillon in tropical eosinophilia, 315.  
 Nuclear fission, injuries from, 413.  
     ophthalmoplegia, 1362.  
 Nucleus pulposus, herniation of, 1582.  
 Nummular sputum, 966, 1021.  
 Nutmeg liver, 469.  
 Nystagmus in acute poliomyelitis, 1429.  
     in barbiturate poisoning, 360.  
     in cerebellar apoplexy, 1440.  
     in cerebellar lesions, 1364, 1409.  
     in cerebral abscess, 1409.  
     in cerebral diplegia, 1489.  
     in disseminated sclerosis, 1474, 1475.  
     in Friedreich's ataxia, 1480.  
     in hydrocephalus in children, 1402.  
     in Ménière's disease, 1353.  
     in subacute combined degeneration, 1552.  
     in syringomyelia, 1546.  
     positional, 1354.  
 Obesity, 449.  
     basal metabolism in, 449.  
     diet in, 450.  
     endocrine aspects of, 449.  
     in Cushing's syndrome, 516.  
     in Fröhlich's syndrome, 489.  
 Object-blindness, 1371.  
 Obsessional disorders, 1677.  
     and schizophrenia contrasted, 1665.  
     ideas or images, 1678.  
     impulses, 1678.  
     rumination, 1679.  
 Obstetrical paralysis, 1584.  
 Obstruction, chronic venous, 927.  
     intestinal, acute, 649.  
         in ascariasis, 334.  
         in cancer of the colon, 641, 642.  
         in Crohn's disease, 632.  
     peritoneal adhesions in relation to, 719.  
     peritonitis complicating, 715.  
 Obturator nerve, 1574.  
 Occipital lobe, abscess of, 1409.  
     localising signs of lesions of, 1359.  
 Occult blood in stools, examination for 60  
*Occupational cramps*, 1525.  
     palsy, 1525.  
     treatment of mental disorder, 161  
 Ochronosis in alkaptonuria, 1105.  
     in carboluria, 1106.  
 Ocular changes in hypertension, 910, 914, 915.  
     muscles in botulism, 124.  
     nerve palsies, causes and varieties of, 1340.  
         conjugate, 1342.  
         nuclear, 1342.  
         supranuclear, 1342.  
     symptoms in cerebral syphilis, 1460.  
         in chorea, 1517.  
         in disseminated sclerosis, 1474.  
         in Friedreich's ataxia, 1480.  
         in malaria, 254.



- Ocular symptoms in myasthenia gravis, 1605.  
in subacute combined degeneration, 1552.  
in tabes, 1464.  
in tuberculous meningitis, 1396.
- Oculogyric crises in encephalitis lethargica, 1418.
- Oculo-motor nerves, affections of, 1340-1345.
- Oddi's sphincter, achalasia of, 698.  
in relation to biliary crises, 698.
- Oedema, angioneurotic, 1255.  
chronic nasal, 939.  
cold, in syphilis, 204.  
in beriberi, 469, 470.  
in cirrhosis of liver, 677.  
in epidemic dropsy, 348.  
in heart failure, 811.  
in kwashiorkor, 479, 480.  
in nephritis, 1116, 1121.  
in trichiniasis, 331.  
in trypanosome fever, 271, 274.  
malignant, 80.  
pathology of, 1113.  
pulmonary, 809, 988, 1068.  
Quincke's, 1255.  
"raw beef," in pink disease, 309.  
renal, 1113.
- Oesophageal hiatus hernia, 550.  
obstruction, 550.  
ulcer, 548.  
varices in Banti's syndrome, 781.
- Oesophagitis peptic, and oesophageal ulcer, 548, 549.  
simple, 547.
- Oesophagostomiasis, 331.
- Oesophagostomum apicostomum, 331.  
stephanostomum, 332.
- Oesophagus, cancer of the, 551.  
diseases of the, 541-553.  
diverticula of, 546.  
normal, 541.  
short, 550.  
spasm of the, 541, 543, 544.  
stricture of the, 550.  
ulcer of, 548.
- Oestrogens in acne vulgaris, 1283.  
in sexual precocity, 524.  
in the climacteric, 523.
- Oestrus ovis, 338.
- Ohara's disease, 130.
- Olfactory nerve and tract, 1338.
- Oliguria in acute nephritis, 1116.  
in bacillary dysentery, 114.  
in heart failure, 808.  
in sulphonamide therapy, 26.
- Ollier's disease, 1184.
- Onanisme pruritique, 1195.
- Onchocerca excavatus, 329.  
tumours in head, 329.  
volvulus as a human parasite, 329.
- Onchocerciasis, 329.
- Onychauxis, 1323.
- Onychia maligna, 1322.  
syphilitic, 225.
- Onychogryphosis, 1323.
- Onychoheterotopia, 1323.
- Onycholysis, 1324.
- Onychomadesis, 1324.
- Onychophagia, 1323.
- Onychoptosis, 1324.
- Onychorrhaxis, 1323.
- Onychoschizia, 1323.
- Onychotillomania, 1323.
- Oophoritis in mumps, 176.
- Ophiasis, 1318.
- Ophidiiasis, 340.
- Ophthalmoplegia, chronic progressive external, 1342.  
exophthalmic, 493.  
in chicken-pox, 173.  
in encephalitis lethargica, 1416.  
in migraine, 1510.  
in tabes, 1464, 1465.  
nuclear, 1362.
- Ophthalmoscopic changes in optic atrophy, 1340.  
in papilloedema, 1338.  
in retrobulbar neuritis, 1339.
- Opisthorchis sinensis, 317.
- Opisthotonos in cerebrospinal fever 56.  
in epilepsy, 1496.  
in hydrophobia, 1421.  
in tetanus, 82.  
of infants, cervical, 58.
- Oppenheim's disease, 1599.  
sign in spastic paraplegia, 1529.
- Opioid, 3.
- Optic atrophy, 1340.  
from arsenical preparations, 1468.  
in acromegaly, 484.  
in cerebral diplegia, 1488.  
in familial spastic paralysis, 1482.  
in mumps, 176.  
in oxycephaly, 1181.  
in pituitary tumour, 1365.  
in relapsing fever, 243.  
in subacute combined degeneration, 1552.  
in tabes, 1463, 1465, 1468.  
chiasma, localisation of lesions of, 1365.  
nerve, the, 1338.  
affections of the, 1338.  
neuritis, 1339.  
in chicken-pox, 173.  
in malaria, 254.  
in typhoid, 104.  
retrograde, 1340.  
thalamus, lesions of, localising signs of, 1361.
- Orbicularis palpebrarum, the "ultimum monens" of facial muscles, 1350.
- Orchitis, isana, 327.  
in congenital syphilis, 227.  
in mumps, 175, 176.  
in paratyphoid fever, 111.  
in small-pox, 164.  
in typhoid, 104.  
in typhus fever, 298.  
in undulant fever, 126.
- Orf, 1250.
- Oriental plague, 127.  
sore, 268.
- Ornithosis virus, sensitivity to penicillin, 7.
- Oroya fever, 144.
- Orpiment, 373.
- Orthopnea in cardiac failure, 809.

- Osler's nodes in subacute bacterial endocarditis, 886.
- Osler-Vaquez disease, 750.
- Osteitis deformans, 1172.
- radiographic appearances in, 1173, 1174.
- fibrosa circumscripta*, 1175.
- cystica*, generalised, 501.
- diffusa*, 501.
- focal*, 1175.
- radiation*, 412.
- Osteo-arthritis, 1157.
- of spine, 1162.
- Osteo-arthropathy, hypertrophic, 1171.
- pulmonary, 1026, 1171.
- following empyema, 1074.
- in bronchiectasis, 984.
- Osteochondritis in congenital syphilis, 226.
- Osteoclastoma, 1175.
- Osteoclastomatous tumours in hyperparathyroidism, 501, 502.
- Osteogenesis imperfecta, 1180.
- Osteogenetic myeloma, 1175.
- Osteomalacia, 1176.
- in idiopathic steatorrhœa, 1178.
- with renal glycosuria, 1179.
- Osteomyelitis differentiated from rheumatic fever, 51.
- Osteoperiostitis in typhoid fever, 99, 104.
- Osteophytes in osteo-arthritis, 1157, 1158.
- Osteoporosis circumscripta, 1174.
- congenita*, 1180.
- in hyperparathyroidism, 502.
- in rickets, 466.
- in Still's disease, 1164.
- in syringomyelia, 1547.
- Osteospathyrosis, 1180.
- Osteosclerotic anæmia, 747.
- Ostio-folliculitis, 1199, 1229.
- Otitis media in congenital syphilis, 227.
- in diphtheria, 74.
- in influenza, 180.
- in kala-azar, 266.
- in measles, 152.
- in mumps, 176.
- in pneumonia, 1053.
- in relation to meningitis, 1394.
- in scarlet fever, 41, 42.
- in small-pox, 164.
- suppurative, in glandular fever, 306.
- in typhoid, 104.
- Ouabaine, 814.
- Ovalocytosis, 740.
- Overhydration, 417.
- Oxalate of lime calculi, 1141.
- crystals in urine, 1107.
- Oxalic acid, poisoning by, 362, 363.
- Oxophenarsine in syphilis, 213, 214.
- administration of, 215.
- toxic effects of, 229.
- Oxycephaly, 1181.
- Oxygen, deficiency, effects of, 399.
- in acute laryngo-tracheo-bronchitis, 946.
- in carbon monoxide poisoning, 360.
- in cardiac failure, 816.
- in treatment of pneumonia, 1055.
- saturation of arterial and venous blood, 400.
- Oxytetracycline, 14.
- in bacterial urethritis, 312.
- Oxytetracycline in amœbic dysentery, 279.
- in chancre, 144.
- in flea typhus, 287.
- in folliculitis barbae, 1228.
- in gonorrhœa, 66.
- in impetigo vulgaris, 1226.
- in leptospirosis icterohæmorrhagica, 241.
- in "Q" fever, 304.
- in Rocky Mountain tick typhus, 295.
- in tsutsugamushi disease, 292.
- in yaws, 235.
- Oxytocin, 483.
- Oxyuris vermicularis, 335.
- Oysters in relation to typhoid infection, 98.
- Ozœna, 956.
- as a cause of halitosis, 329.
- Pachydermia laryngis, 948.
- Pachymeningitis, 1391.
- externa*, 1538.
- hæmorrhagica*, 1450.
- hypertrophica cervicalis*, 1469.
- in acute alcoholism, 355.
- interna*, 1392.
- Pachonychia congenita, 1323.
- Paget's disease of bone, 1172.
- of the nipple, 1306.
- Pahvant Valley fever, 130.
- Pains, lightning, 1462, 1463.
- Palate, arched, in adenoids, 942.
- soft, diphtheritic paralysis of, 1591.
- syphilitic perforation of, 208.
- ulceration of, in gangosa, 236.
- in yaws, 234.
- Palmar fascia, fibrosis of, 1167.
- Pallor, circum-oral, in scarlet fever, 38.
- Palpitation in cardiac neurosis, 905.
- in exophthalmic goitre, 794.
- in heart disease, 794.
- in nutritional macrocytic anæmia, 476.
- in thyrotoxicosis, 900.
- Palsy, Bell's, 1349.
- craft*, 1525.
- Erb's*, 1568.
- Klumpke's*, 1568.
- lead*, 366, 367, 1593.
- occupation*, 1525.
- shaking*, 1511.
- Paludism, 245.
- Pamaquin (plasmoquin) in malaria, 257, 259.
- Panarteritis, 931.
- Pancoast tumour of lung, 1042.
- Pancreas, acute necrosis of, 702.
- carcinoma* of, 708.
- diseases* of the, 700-710.
- fibrocystic disease* of the, 706.
- fibrosis* of, in infants, 706.
- hydatid* of, 708.
- in kwashiorkor, 479.
- in mumps, 175.
- in relation to carbohydrate metabolism, 702.
- to glycosuria, 702.
- to jaundice, 701.
- secretions* of, 700.
- subacute necrosis* of, 704.
- syphilis* of the, 707.
- Pancreatic calculi, 704, 707.
- colic, 703, 705.

- Pancreatic cysts**, 707.  
 digestion, deficient, stools in, 701.  
 ducts, anatomy of, 701.  
 ferments in intestines, faeces and urine, 701.  
 juice, 701, 702.
- Pancreatitis**, acute hæmorrhagic, 702.  
 chronic, 704.  
 in relation to gall-stones, 697, 704,  
 jaundice in, 662.  
 relapsing, 708.  
 in mumps, 176.
- Panhypopituitarism**, 487.
- Panniculopathy**, 738.
- Panniculitis**, 1165, 1166.
- Panophthalmitis in small-pox**, 164.
- Pantothenic acid**, 459.
- Papataci fever**, 188.
- Papillitis in cerebrospinal fever**, 59.
- Papilloedema**, 1338, 1385, 1386.  
 in anæmia, 1386.  
 in cerebral abscess, 1385, 1408.  
 in cerebral syphilis, 1460.  
 in cerebrospinal fever, 56.  
 in chloroma, 763.  
 in encephalitis lethargica, 1416.  
 in hydrocephalus, 1402, 1403, 1404.  
 in hypertensive encephalopathy, 1444.  
 in intracranial tumour, 1385, 1388.  
 in malignant hypertension, 915.  
 in measles, 152.  
 in meningitis, 1386.  
 in mumps, 176.  
 in oxycephaly, 1181.  
 in relation to vision, 1338.  
 in renal disease, 1386.  
 in suppurative encephalitis, 1408.  
 in tuberculous meningitis, 1396.  
 ophthalmoscopic appearances in, 1339.  
 optic atrophy following, 1340.  
 results of, 1340.
- Papilloma**, basal cell, 1301.  
 squamous cell, 1301.
- Papules**, granulomatous in yaws, 234.  
 moist, in syphilis, 205.
- Papulo-squamous lesions in syphilis**, 203.
- Para-aminobenzoic acid**, 460.
- Para-aminosalicylic acid**, *see* Sodium aminosalicylate.
- Paracentesis in ascites**, 723.  
 in cancer of peritoneum, 721.  
 in chronic nephritis, 1123.  
 in pleurisy with effusion, 1070.  
 technique of, 1070, 1071.  
 in tuberculous peritonitis, 720.  
 of pericardium, 880.
- Paræsthesia in Landry's paralysis**, 1595.  
 in subacute combined degeneration, 1551.
- Paraffinoma**, 1315.
- Paraganglioma**, 518.
- Paragonimiasis**, 317.  
 of lungs, 317.
- Paragonimus westermani**, 317.
- Parakeratosis variegata**, 1275.
- Paraldehyde**, addiction to, 1642.  
 in chronic alcoholism, 356.
- Paralyses**, crossed, 1363.  
 localised, in herpes zoster, 1420.
- Paralyses**, toxæmic, 30.
- Paralysis**, acute ascending, 1594.  
 advance of, in Landry's paralysis, 1594, 1595.  
 agitated, 1511.  
 mental disorders in, 1635.  
 alternate, 1363.  
 ascending, in poliomyelitis, 1427.  
 brachial plexus, 1568, 1569.  
 common facial, 1349.  
 congenital spastic, 1487, 1488.  
 conjugate, 1342.  
 crossed, 1363.  
 diphtheritic, 73, 78, 1590.  
 due to tick-bites, 336.  
 familial periodic, 1607.  
 spastic, 1482.  
 flaccid, diagnosis of, 1672.  
 hysterical, 1672.  
 in beriberi, 469.  
 in hydrocephalus in children, 1401.  
 in poisoning by tri-ortho-cresyl phosphate, 379.  
 in poliomyelitis, 1427, 1428, 1429.  
 in Tay-Sachs disease, 1483.  
 infantile, 1423.  
 juvenile general, 1472.  
 labio-glosso-pharyngeal, 1554.  
 Landry's, 1594.  
 laryngeal, 1356.  
 lead, 367, 1593.  
 local, in diphtheria, 1590.  
 obstetrical, 1584.  
 oculo-motor, 1341.  
 of accommodation in diphtheria, 1591.  
 of cranial nerves in encephalitis lethargica, 1416.  
 of diaphragm, 1088, 1432.  
 of reaction with accommodation, 1344.  
 of soft palate, 1591.  
 of sternomastoid, 1356.  
 of trapezius, 1356.  
 of vocal cords, 952.  
 pharyngeal, bilateral, 1356.  
 unilateral, 1355.  
 progressive bulbar, 1554.  
 pseudo-hypertrophic, 1596.  
 Saturday night, 1567.  
 simple, as an epileptic fit, 1498.  
 spinal atrophic, 405.  
 Todd's, 1441, 1497.  
 toxæmic, 30.
- Paramphistomiasis**, 316.
- Paramyoclonus multiplex**, 1520.
- Parangi**, 233.
- Paranoia**, and allied states, 1668.  
 alcoholic, 1639.  
 involutional, 1629.
- Paranoid form of schizophrenia**, 1664.
- Paraphasia**, 1370.
- Paraphrenia**, 1664.
- Paraplegia**, congenital spastic, 1487.  
 Erb's syphilitic spastic, 1469.  
 general management of, 1533.  
 in caisson disease, 398.  
 "in extension," 1528.  
 "in flexion," 1528.  
 in subacute combined degeneration, 1552, 1554.

- Paraplegia, senile, 1543.**  
   spastic, in compression of the cord, 1538.  
   treatment of, 1533.  
**Paraplegic rigidity, 1489.**  
**Parapraxia, 1376.**  
**Parapsoriasis, 1274.**  
   discoides, 1275.  
   en plaque, 1275.  
   guttata, 1274.  
   lichenoides, 1275.  
**Parathormone in hypoparathyroidism, 505.**  
**Parathyroid glands, diseases of the, 501-506.**  
   effect of removal, 503.  
   in relation to calcium metabolism, 501-503.  
   tetany, 503, 504.  
**Parathyroidectomy, effects of, 504.**  
   in relation to tetany, 503, 504.  
**Paratyphoid fever, 110.**  
**Paresis and rigidity in cerebral diplegia, 1488.**  
   dysarthria in, 1374.  
   general, 1455.  
   in chorea, 1517.  
**Parietal lobes, abscess of, 1409.**  
   localising signs of lesions of, 1359.  
**Parkinsonism as a sequel of encephalitis lethargica, 1417, 1513.**  
   manganese poisoning as cause of, 1642.  
   ptyalism in, 530.  
**Parkinson's disease, 1511.**  
**Paronychia, 1321.**  
   in X-ray injuries, 410.  
   monilial, 1238.  
**Parotid glands in Mikulicz's disease, 177.**  
   non-infective recurrent swelling of, 532.  
   suppuration, 176.  
**Parotitis, 174, 531.**  
   acute, 531.  
   epidemic, 174.  
   in bacillary dysentery, 116.  
   in lobar pneumonia, 1053.  
   in paratyphoid fever, 112.  
   in small-pox, 164.  
   in typhoid, 110.  
   in typhus fever, 298.  
   infectious, 174.  
   subacute, 532.  
**Paroxysmal headache, 1508.**  
   tachycardia, 823.  
**Parrot's nodes, 227.**  
**Parrots as transmitters of psittacosis, 183.**  
**Parry's disease, 491.**  
**Parturition, mental disorders of, 1644.**  
**Paschen, elementary bodies of, in vaccinal lesions, 159, 169.**  
**Pasteurella pestis, 127.**  
   resistance to penicillin, 7.  
   sensitivity to streptomycin, 10.  
   Pastia's sign in scarlet fever, 39.  
**Paterson's graduated exercises for tuberculosis, 1033.**  
   (so-called Plummer-Vinson) syndrome, 542.  
**Pathogenicity of parasitic organisms, 1.**  
**Pathogens, facultative, 1.**  
**Pathogens, obligatory, 1.**  
**Paul's test for small-pox, 166.**  
**Paul-Bunnell reaction in glandular fever, 306.**  
   in rubella, 158.  
**Pautrier micro-abscesses, 1316.**  
**"Peasants' skin," 1210, 1295.**  
**"Pea-soup stools" of typhoid, 100.**  
**Pectoriloquy, whispering in pulmonary fibrosis, 1008.**  
   in pulmonary tuberculosis, 1025.  
**Pediculi, forms of human, 1252.**  
**Pediculosis, 1252.**  
   capitis, 1252.  
   corporis, 1253.  
**Pel-Ebstein type of pyrexia, 790.**  
**Peliosis rheumatica, 39, 774.**  
**Pellagra, 472.**  
   atypical, 474.  
   infantile, 478.  
   mental symptoms of, 474, 1643.  
   vitamins in relation to, 472.  
**Pelvic deformity in idiopathic steatorrhea, 621.**  
**Pemphigoid, 1289.**  
**Pemphigus, benign familial (Gougerot and Hailey-Hailey), 1290.**  
   benign, of mucous membranes, 1290.  
   erythematodes, 1289.  
   foliaceus, 1289.  
   neonatorum, 1226.  
   ocular, 1290.  
   syphilitic, 225.  
   vegetans, 1288.  
   vulgaris, 1288.  
**Pendek sore, 268.**  
**Penicillin, 6-10.**  
   action on bacteria, 6.  
   administration, local, 9.  
   oral, 9.  
   principles, 8.  
   systemic, 8, 9.  
   bacterial resistance to, 7, 8.  
   sensitivity to, 7, 8.  
   benzyl, 6, 218.  
   cream, 9.  
   dosage, 8, 9.  
   duration of effect of, 8, 9.  
   excretion in urine, 8.  
   in abscess of the lung, 1005.  
   in accessory-sinus suppuration, 941.  
   in actinomycosis, 196, 1240.  
   in acute suppurative bronchitis, 966.  
   in agranulocytosis, 757.  
   in amebic dysentery, 279.  
   in anthrax, 81.  
   in cerebral syphilis, 1461.  
   in cerebrospinal fever, 64.  
   in congenital syphilis, 228.  
   in diphtheria, 78.  
   in empyema, 1075.  
   in erysipelas, 35.  
   in erysipeloid, 1232.  
   in folliculitis barbae, 1228.  
   in general paralysis of the insane, 1458.  
   in gonorrhoea, 65, 66.  
   in impetigo, 1226.  
   in leptospirosis icterohæmorrhagica, 241.

- Penicillin** in measles, 155.  
 in parotitis, 532.  
 in perinephritis, 1138.  
 in peritonitis, 716.  
 in pharyngitis, acute septic, 539.  
 in pleural actinomycosis, 1085.  
 in pneumococcal meningitis, 1393.  
 in pneumonia, 1056.  
 in psittacosis, 184.  
 in pyelitis, 1135.  
 in quinsy, 535.  
 in rat-bite fever, 245.  
 in relapsing fever, 244.  
 in scarlet fever, 47.  
 in subacute bacterial endocarditis, 888.  
 in syphilis, 218-224, 228, 1461, 1469.  
 in syphilitic meningitis, 1461.  
 in tabes, 1468.  
 in tracheitis, 956.  
 in tropical ulcer, 1332.  
 in ulcerative colitis, 637.  
 in Vincent's angina, 538.  
 stomatitis, 526.  
 in yaws, 235.  
**International standard**, 6.  
 masking effect of, 220.  
 nature and properties of, 6.  
 pastilles, 9.  
 preparations of, 9.  
 procaine, 9.  
 prolongation of effect of, 9, 219.  
 sensitivity to, 10.  
 snuff, 9.  
 susceptible and insusceptible organisms, 7, 8.  
 toxic effects, 10, 219.  
 varieties, 6.  
 with bismuth in syphilis, 222.  
 with caronamide, 9.  
 with neosarsphenamine in syphilis, 222.
- Penicillinase**, 6.  
**Penicillium chrysogenum**, 6.  
 notatum, 6.
- Penis**, enlargement of, in sexual precocity, 523.  
 granuloma of, in schistosomiasis, 320.  
 herpetiform ulcers on, in lymphopathia venereum, 192.  
 papillomatous of, in rhinosporidiosis, 201.  
 syphilitic herpes of, 210.
- Pentamidine isethionate** in trypanosomiasis, 273.
- Pentaquine** in malaria, 257.
- Pentosuria**, 444.
- Pepsin**, 554.
- Peptic oesophagitis and ulcer**, 548.
- Peptone** in urine, 1103.
- Perforating ulcers**, in leprosy, 91.  
 in peroneal muscular atrophy, 1564.  
 in tabes, 1462, 1465, 1469.
- Periadenitis** in lymphopathia venereum, 192.
- Periarteritis nodosa**, 931.
- Peri-arthritis**, 1163.
- Pericarditis**, acute, 878.  
 acute benign, 880.  
 fibrinous, 878.  
 chronic adhesive, 883.  
 constrictive, 717.
- Pericarditis**, exudate in, 878.  
 friction sounds in, 879.  
 idiopathic, 880.  
 non-specific, 880.  
 purulent, 881.  
 rheumatic, 50, 881.  
 septic in bronchiectasis, 985.  
 traumatic, 884.  
 tuberculous, 880.  
 virus, 880.  
 with effusion, 878.
- Pericardium**, adherent, 883.  
 "bread-and-butter," 878.  
 diseases of the, 878-884.  
 effusion into, 879.  
 paracentesis of, 880.  
 trauma of, 904.  
 tuberculosis of, 880.
- Perichondritis** of tracheal cartilage, 956.
- Pericolic suppuration**, *B. coli* in, 95.
- Pericolitis**, 633.
- Perifolliculitis capitis abscedens**, 1320.
- Perihepatitis**, 717.  
 general chronic, 717.  
 in cancer, 686.  
 in cirrhosis of liver, 676.  
 syphilitic, 682.
- Perinephritis and perinephric abscess**, 1137.
- Peri-neuritis**, 1165.
- Periodontitis**, chronic, 527.
- Periostitis**, in congenital syphilis, 226.  
 in paratyphoid fever, 112.  
 in syphilis, 207.  
 in typhoid, 104, 110.
- Peripheral nerves**, disorders of, 1567-1607.  
 neuritis, 1586.  
 vascular disease, 17.
- Perisplenitis**, 676, 780.
- Peristalsis**, gastric, in pyloric obstruction, 596.  
 in colon, 600.  
 in small intestines, 600.  
 visible, 596.
- Peritoneal adhesions**, 718, 719.  
 in relation to obstruction, 719.
- Peritoneoscopy**, 723.
- Peritoneum**, cancer of, 720.  
 diseases of the, 711-724.
- Peritonitis**, 711-721.  
 acute, 711-717.  
 fulminant generalised, 712.  
 localised, 714.  
 spreading, 713.  
 adhesions due to, 719.  
 benign paroxysmal, 717.  
 bile, 717.  
 chronic, 717.  
 fibro-purulent, 716.  
 fibrous tuberculous, 718.  
 gonococcal, 715.  
 in acute appendicitis, 656.  
 in acute suppurative gastritis, 572.  
 in paratyphoid fever, 112.  
 in perforating ulcers of stomach and duodenum, 579.  
 in relation to acute intestinal obstruction, 652.

- Peritonitis** in typhoid fever, 103.  
in ulcerative colitis, 635.  
*malignant*, 686, 720.  
*pelvic*, 715.  
*perforative*, in typhoid, 101, 103.  
*pneumococcal*, 714.  
*rheumatic*, 50.  
*staphylococcal*, 712.  
*streptococcal*, 715.  
*tuberculous*, 718.  
*adhesive or fibrous*, 718.  
*ascitic form of*, 718.  
in cirrhosis of liver, 678.  
*loculated*, 718.  
*obliterative*, 718.
- Peritonsillar abscess**, 534.  
*"Perles," Laennec's*, 970.
- Pernicious anemia**, 734.
- Perniones**, 1205.
- Peroneal muscular atrophy**, 1563.
- Perseveration**, 1377.
- Personality**, as showing tendency to mental disorder, 1610.  
*dissociation of*, in hysteria, 1673.  
*hysterical*, 1670.  
in schizophrenia, 1663.  
*psychopathic*, 1680.
- Pertussis**, 137.
- Pes cavus** in cerebral diplegia, 1488.  
in familial spastic paralysis, 1482.  
in Friedreich's ataxia, 1480.  
in peroneal muscular atrophy, 1564.
- Pest**, 127.
- Pestis minor**, 128.
- Petechiæ** in hæmorrhagic diphtheria, 70.  
in heat-stroke, 407.  
in plague, 128.  
in *spirochaetosis icterohæmorrhagica*, 240.  
in subacute bacterial endocarditis, 886.  
in whooping-cough, 139.  
in yellow fever, 187.
- Petechial rash** in measles, 151.  
in scarlet fever, 39, 41.  
in typhus, 297.
- Petit mal**, 1499, 1506.  
*electro-encephalogram in*, 1493.
- Peyer's patches** in *Salmonella enteritis*, 120.  
in typhoid fever, 97, 99.
- Pfeifferella mallei**, 131.  
*whitmorei*, 133.
- Phæochromocytoma**, 518.
- Phagedena**, tropical sloughing, 1331.
- Phagocytic cells**, rôle of, in red cell destruction, 727.
- Phagocytosis** in relation to tetanus, 82.  
in the spleen, 778.
- Phakoma**, 1487.
- Pharyngeal hyperæsthesia**, 539.  
*paralysis*, 1356, 1591.
- Pharyngitis**, acute catarrhal, 538.  
*acute septic*, 538.  
*chronic*, 539.  
*gangrenous*, 538.  
*granular*, 540.  
*lateral*, 540.  
*œdematous*, 538.  
*phlegmonous*, 538.  
*sicca*, 540.
- Pharyngo-laryngitis**, septic, 944.
- Pharyngo-œsophageal sphincter**, *achalasia of*, 541, 543.
- Pharynx**, diseases of, 538.  
*diverticula of*, 546.  
*syphilis of*, 206.
- Phenarsazine chloride**, poisoning by, 376.
- Phenobarbitone**, addiction to, 1641.  
in the treatment of epilepsy, 1505, 1506.  
poisoning by, 360.
- Phenol**, poisoning by, 362, 363.  
*sulphonaphthalein excretion test in renal function*, 1101.
- Phenylbutazone** in acute gout, 448.  
in fibrositis, 1168.  
in osteo-arthritis, 1159.  
in rheumatoid arthritis, 1152.
- Phenyl dichlorarsine**, poisoning by, 376.
- Phenylenediamine poisoning**, 393.
- Phenyketonuria**, 1686.
- Phenytoin sodium** in epilepsy, 1506.
- Phlebitis**, gouty, 447.
- Phlebogram** in cor pulmonale, 852.
- Phlebothrombosis** in cardiac infarction, 845.
- Phlebotomus fever**, 188.  
*noguchi*, 144.  
*papatasi*, 188.  
*sargenti*, 269.  
*verrucarum*, 144.
- Phlyctenular conjunctivitis** with adenoids, 942.  
*ulceration in measles*, 152.
- Phobias**, 1678.
- Phonation**, laryngeal disorders of, 950.
- Phonocardiography**, 798.
- Phosphatase**, plasma, increased in hyperparathyroidism, 502.  
*serum alkaline in liver function*, 660.
- Phosphates**, in urine, 1099.
- Phosphatic calculi**, 1140.
- Phosphaturia**, 1099.
- Phosphorus content of blood** in tetany, 505.  
*insecticides, poisoning by*, 379.  
*metabolism in hyperparathyroidism*, 502.  
*plasma, increased in hypoparathyroidism*, 505.
- poisoning**, 376.  
*acute*, 376.  
*as cause of hepatic necrosis*, 670.  
*chronic*, 377.
- Phossy jaw**, 377.
- Photophobia** in cerebrospinal fever, 56.  
in measles, 150.  
in *tuberculous meningitis*, 62.  
in yellow fever, 186.
- Phrenic nerve**, anatomy and physiology of, 1567.  
*evulsion of*, in pulmonary tuberculosis, 1035.
- Phrynodermis**, 1201.
- Phthalylsulphathiazole**, 18.  
in bacillary dysentery, 118.  
in ulcerative colitis, 637.
- Phthiriasis pubis**, 1253.
- Phthisis**, 1017.  
*syphilitic*, 1040.
- Physiotherapy** in osteo-arthritis, 1159.  
in rheumatoid arthritis, 1152.

- Physiotherapy in spondylitis, 1162.  
 Physostigmine in myasthenia gravis, 1606.  
 Pian, 233.  
   Bois, 268.  
   Cayenne, 268.  
 Pick's dementia, 1629.  
   disease, 717, 881.  
 Picrotoxin in barbiturate poisoning, 361.  
 Piedra, 1334.  
 Pigment calculi, 695.  
 Pigmentation in Cushing's syndrome, 517.  
   of skin, anomalies of, 1201-1208.  
     in Addison's disease, 508.  
     in arsenical eruptions, 1203.  
     poisoning, 374.  
     in dermatomyositis, 1294.  
     in Gaucher's disease, 785.  
     in generalised scleroderma, 935.  
     in hæmochromatosis, 681, 1204.  
     in kwashiorkor, 479, 480.  
     in leprosy, 91.  
     in malaria, 249.  
     in mepacrine therapy, 1204.  
     in metallic poisoning, 1205.  
     in neurofibromatosis, 1485.  
     in Niemann-Pick's disease, 785.  
     in pellagra, 473.  
     in pinta, 1333.  
     in Still's disease, 1164.  
     in syphilis, 205.  
     in systemic sclerosis, 1292.  
     in subacute combined degeneration, 1552.  
     in yaws, 234.  
   physical causes of, 1202.  
   randrop, 374.  
 Pili incarnati, 1229.  
   torti, 1317.  
 Pin worm, 335.  
 Pingueculæ in Gaucher's disease, 785.  
 Pink disease, 308.  
 Pinta, 1333.  
   fever, 293.  
 Pirquet's test for tuberculosis, 88, 1028.  
 Pitressin, 483.  
   in diabetes insipidus, 490.  
 Pituitary cachexia, 487.  
   extracts, effects of, 483.  
   gland, 483-491.  
     diseases of, 483.  
     hormones of, 483.  
     in relation to obesity, 449.  
     in relation to polyuria and polydipsia, 489.  
     localisation of lesions of, 1365.  
     mental disorders in diseases of, 1644.  
     posterior lobe of, 483.  
   tumours of, 1365, 1383.  
     differential diagnosis of, 1387.  
 Pityriasis alba, 1226.  
   rosea, 1275.  
   rubra pilaris, 1276.  
   lichenoides chronica, 1274.  
   lichenoides et varioliformis acuta, 1275.  
   simplex, 1217.  
   steatoides, 1217.  
   versicolor, 1333.  
 Plagiocephaly, 1181.  
 Plague, 127.  
   abortive, 128.  
   Plague, ambulatory type of, 128.  
     anginal, 128.  
     bubonic, 128.  
     cellulo-cutaneous type of, 128.  
     cerebral, 128.  
     complications of, 128.  
     intestinal type of, 128.  
     pneumonic, 128.  
     septicæmic, 128.  
     tonsillar, 128.  
     types of, 128.  
     varioid, 128.  
     vesicular, 128.  
 Planorbis holtsyi in relation to schisto-  
   somiæ, 319.  
   cænosis in relation to fascioliasis, 316.  
   metidjensis in relation to schistosomiæ,  
     319.  
 Plantar fascia, fibrosis of, 1167.  
 Plants, poisonous, 344.  
 Plasma bilirubin, 659.  
   proteins, 660.  
 Plasmacytoma, 1184.  
 Plasmodium cynomolgi, 247.  
   falciparum, 245, 246, 261.  
   knowlesi, 246.  
   malariae, 246, 261.  
   ovale, 246, 261.  
   tenue, 246.  
   vivax, 246, 261.  
 Pleura, actinomycosis of, 195, 1085.  
   B. coli infection of, 97.  
   carcinoma of, 1086.  
   diseases of the, 1063.  
   dropsy of the, 1076.  
   endothelioma of, 1086.  
   hydatid disease of, 1084.  
   hydrops of the, 1076.  
   in pneumonia, 1049.  
   in pulmonary tuberculosis, 1021.  
   injury of, 1087.  
   malignant tumours of, 1086.  
   sarcoma of, 1086.  
   simple tumours of, 1086.  
 Pleural adhesions, in fibro-caseous tuber-  
   culosis, 1020.  
   effusion in primary atypical pneumonia,  
     1057.  
   effusions, anomalous, 1072.  
     characters of, 1067, 1070.  
     chylous and other milky, 787, 1079.  
     hæmorrhagic, 1077.  
     in malignant disease, 1077, 1086.  
   shock, 1071.  
 Pleurisy, 1063.  
   acute dry, 1063.  
   acute fibrinous, 1063.  
   as a tubercular manifestation, 1020.  
   chronic dry, 1066.  
   classification of, 1063.  
   diaphragmatic acute dry, 1065.  
     chronic, 1067.  
   eosinophil, 1070.  
   hæmorrhagic, 1077.  
   in pneumococcal pneumonia, 1050, 1053.  
   in relation to tuberculosis, 1020, 1022, 1026,  
     1063.  
   interlobar dry, 1066.

- Pleurisy, plastic, 1063.**  
   primary dry, 1063.  
   purulent, 1072.  
   secondary dry, 1063.  
   sero-fibrinous, 1067.  
   with effusion, 1067.  
**Pleuritis, 1063.**  
**Pleurodynia, 1064, 1166.**  
   epidemic or infectious, 193.  
**Pleurogenous cirrhosis, 1006.**  
**Pleurothotonus in tetanus, 82.**  
**Plumbism, 364.**  
**Plummer-Vinson (Paterson's) syndrome, 542.**  
**Pneumatia, 1107.**  
**Pneumo-bacillus of Friedländer in acute tracheitis, 954.**  
**Pneumococcal arthritis, 1155.**  
   meningitis, 61, 1392.  
   peritonitis, 714.  
**Pneumococcus, the, 1048.**  
   in acute tracheitis, 954.  
   in relation to lobar pneumonia, 1048.  
   meningitis, 61.  
   pathogenicity of the, 1048.  
   septicæmia, 31.  
   types of the, 1048.  
**Pneumoconiosis, the, 1008-1016.**  
   benign, 1009, 1014.  
**Pneumoconiosis, barium, 1014.**  
   in bauxite smelters, 1015.  
   in coal miners, 1011.  
   mediastinal glands in, 1092.  
   sericite, 1013.  
   sillimanite, 1013.  
**Pneumoliths, 1019, 1021.**  
   as cause of bronchial obstruction, 974.  
**Pneumonia, apical, 1052.**  
   ascaris, 334.  
   aspiration, 1059.  
   atypical, 1056.  
   carriers, 1049.  
   central, 1052.  
   chronic interstitial, 1053.  
   contusional, 1052.  
   creeping, 1052.  
   "critical evacuations" in, 1050.  
   differential diagnosis of, 61.  
   Friedländer bacillus, 1056.  
   hæmorrhagic vesicular, in psittacosis, 183.  
   hypostatic, 987.  
   in children, 1052.  
   in the aged, 1052.  
   in the insane, 1052.  
   influenzal, 1056.  
   lobar, 1048.  
   lobular, 1059.  
   massive, 1052.  
   migratory, 1052.  
   post-operative, 1052.  
   pneumococcal, 1048.  
     lobular, 1058.  
   primary atypical, 1056.  
   relation of pneumococcus to, 1048.  
   secondary, 1052.  
   staphylococcal, 1056.  
   streptococcal, 1056.  
**Pneumonia, traumatic, 1052.**  
   virus, 1056.  
   wandering, 1052.  
   white, of Virchow, 1040.  
**Pneumonias, the, 1047-1062.**  
**Pneumonitis, 1062.**  
**Pneumonomycoses, 1038.**  
**Pneumopericardium, 883.**  
**Pneumoperitoneum in pulmonary tuberculosis, 1035.**  
**Pneumothorax, 1080.**  
   artificial, dangers of, 1035.  
   for dry pleurisy, 1065.  
   for pulmonary tuberculosis, 1034.  
   technique of, 1034.  
   benign, 1081.  
   complications and sequelæ of, 1083.  
   extra-pleural, 1036.  
   in cystic disease of the lung, 1045.  
   in emphysema, 999.  
   in pulmonary tuberculosis, 1026, 1037, 1080.  
   simple, 1081.  
**Pneumo-typhoid variety of typhoid fever, 101.**  
**Podophyllin in treatment of warts, 1302.**  
**Poikilocytes, 727.**  
**Poikilocytosis, 727.**  
**Poikiloderma, 1296.**  
   vasculare atrophicans (Jacobi-Lane), 1296.  
**Poikilodermato-mycosis, 1296.**  
**Poisons acting on the liver, 670, 671.**  
   causing aplasia of bone-marrow, 737.  
**"Poker back," 1161.**  
**Polio-encephalitis, 1427.**  
**Poliomyelitis, acute anterior, 1423.**  
   abortive forms of, 1426.  
   blood cell count in, 1426.  
   brain-stem form of, 1428.  
   bulbar, 1428, 1433.  
   carriers of, 1424.  
   complications of, 1432.  
   differentiation from cerebrospinal fever, 62.  
   myelitic form, 1428.  
   nerve-cell destruction in, 1425.  
   neuritic form of, 1428.  
   non-paralytic, 1427.  
   paralytic, 1427.  
   pre-paralytic, 1426.  
   prophylaxis in, 1434.  
   spinal form of, 1427.  
   virus of, 1424.  
**Polyadenitis in sleeping sickness, 271.**  
**Polyarteritis nodosa, 931.**  
**Polyarthritis, 1150.**  
**Polycholia in malaria, 251.**  
**Polychromasia, 729.**  
**Polycythæmia, 749.**  
   vera, 750.  
   with leukæmia, 748.  
   with osteosclerosis, 748.  
**Polydipsia in cerebrospinal fever, 56.**  
   in diabetes insipidus, 489.  
   in hypoparathyroidism, 502.  
**Polymorphonuclear cells, 752.**  
**Polymixin, 15.**  
   in whooping-cough, 142.



- Polyneuritis**, 1586.  
acute febrile, 1592.  
infective, 1592.  
after arsenamine remedies, 230, 232.  
endemic, 468.  
in beriberi, 469, 1586.  
in polyarteritis nodosa, 931.  
Korsakoff syndrome associated with, 1589.  
progressive hypertrophic, 1592.
- Polyposis of colon**, 639.
- Polyps in rhinosporidiosis**, 201.
- Polyserositis**, 717.
- Polyuria**, 489, 1102.  
causes of, 489, 1102.  
hysterical, 489.  
in asthma, 979.  
in diabetes insipidus, 489.  
in hypoparathyroidism, 502.  
in lardaceous disease, 1132.  
in the Fanconi syndrome, 1179.
- Pompholyx**, 1220.
- Pons, localisation of lesions of**, 1363.
- Poradenitis**, 191.
- Pork as source of infection in tape-worm**, 331.
- Poroccephalus armillatus**, 336.
- Porokeratosis of Mibelli**, 1297.
- Porphyria, acuta congenita**, 453.  
cutanea tarda, 453.
- Porphyria metabolism, disorders of**, 452.
- Porphyria, acuta**, 453.
- Portal circulation in relation to cirrhosis**, 675.  
pyæmia, 32.  
thrombosis, 688.  
vein, diseases of the, 688.
- Port-wine stains of skin**, 1313.
- Post-basis meningitis of infants**, 58.  
-epileptic automatism, 1500.  
-gastroctomy syndrome, 587.  
-vaccinal encephalo-mycelitis, 170.
- "Pot Belly" in kwashiorkor**, 480.
- Potassium, body**, 420, 421.  
chloride in familial periodic paralysis, 1607.  
iodide to accelerate elimination of lead, 370.  
in leprosy, 94.  
in pulmonary actinomycosis, 1039.  
in pulmonary aspergillosis, 1039.  
in syphilis, 221, 1461.  
oedematous laryngitis caused by, 944.
- Potters' rot**, 1009.
- Pott's disease in relation to compression of spinal cord**, 1538.
- "Powder holes,"** 383.
- Precocity, sexual**, 523.
- Prefrontal lobes, lesions of, localising signs of**, 1358.
- Pregnancy, acute necrosis of liver in**, 671.  
and chorea, 1515, 1634.  
in relation to anæmia, 749.  
to arthritis, rheumatoid, 1151.  
to diabetes mellitus, 438.  
to disseminated sclerosis, 1477.  
to epilepsy, 1505.  
to osteomalacia, 1176, 1177.  
jaundice in, 663, 671.  
leucocytosis in, 753.  
mental disorders of, 1644, 1646.  
nausea of, 565.
- Pregnancy, pernicious anæmia of**, 475, 749.  
scarlet fever in, 41.  
small-pox and, 159.  
syphilis and, 228.  
typhoid and, 102.  
vomiting of, 562.
- Prematurity, anæmia of**, 731.
- Prepuce, chicken-pox on**, 173.  
diphtheria of, 72.  
lichen sclerosus of, 1280.  
primary syphilitic sore of, 204.
- Presbyophrenia**, 1629.
- Presenile and senile dementia**, 1628.
- Price-Jones curve**, 727, 728.
- "Prickles", the, in caisson disease**, 397.
- Prickly heat**, 1199.
- Primaquine in malaria**, 257, 259.
- Primidone in epilepsy**, 1506.
- Probenecid in chronic gout**, 448.
- Procaine, susceptibility to**, 220.
- Proctalgia fugax**, 629.  
paroxysmal, 629.
- Proctitis from constipation**, 607.  
in amœbic dysentery, 277.  
in gonorrhœa, 67.
- Proctoscopic examination**, 604.
- Prodromal rashes**, 45.
- Producer gas**, 358.
- Progeria**, 486, 487.
- Prognathism in acromegaly**, 484.
- Progressive bulbar paralysis**, 1554.  
lenticular degeneration, 1484.  
muscular atrophy, 1554.  
spinal muscular atrophy of children, 1565.
- Proguanil in blackwater fever**, 263, 264.  
in malaria prophylaxis, 256.  
in treatment of malaria, 258.
- Progesterone, hypersecretion of, in acne vulgaris**, 1282.
- Projectile vomiting**, 596.
- Prolan A, action of**, 483.  
B, action of, 483.
- Promethazine in travel sickness**, 403.
- Proptosis as symptom of intracranial pressure**, 1389.  
in infantile scurvy, 464.  
in oxycephaly, 1181.  
in sinus thrombosis, 1453.
- Prostate, lesions of, in schistosomiasis**, 320.
- Prostatic disease, nausea in**, 565.
- Prostatitis in coliform infection of urinary tract**, 96.  
in typhoid, 104.
- Protamine zinc insulin**, 428.
- Protein content of cerebrospinal fluid**, 1379.  
deficiency, 477.  
shock in rheumatoid arthritis, 1153.  
therapy, non-specific, 1164.
- Proteins, digestion of**, 556.  
plasma, measurement of, 660.  
sensitiveness to, in relation to asthma, 978.
- Proteinuria**, 1102.  
congestive, 1103.  
febrile, 1103.  
functional, 1102.  
orthostatic, 1102.  
physiological, 1103.

- Proteose in urine, 1103.  
 Proteus, resistance to penicillin, 7.  
   *morganii*, 112.  
   *vulgaris*, susceptibility to penicillin, 8.  
*Prothrombin*, 765.  
   test, 766.  
 Protozoan infections, 245-284.  
 Pruning spider, 339.  
 Prurigo, 1193.  
   *æstivale*, 1210.  
   *ferox*, 1197.  
   *flexural*, 1195.  
   *hiemalis*, 1209.  
   *Hutchinson's summer*, 1210.  
   *nodularis*, 1197.  
   of Besnier, 1195.  
   of Hebra, 1197.  
 Pruritus, 1190.  
   *ani*, 1191.  
   due to threadworms, 335.  
   general, 1190.  
   in diabetes, 424.  
   in Hodgkin's disease, 790.  
   in jaundice, 663.  
   in polycythæmia vera, 750.  
   in serum sickness, 5.  
   localised, 1191.  
   perineal, 1192.  
   psychogenic, 1190, 1191, 1193.  
   scrotal, 1192.  
   vulvæ, 1192.  
   with lichenification, 1193.  
*Psammoma*, 1536.  
*Pseudo-Argyll Robertson pupil*, 1344, 1466.  
   -*arthritis*, 1165.  
   -*bulbar palsy*, 1373, 1443.  
   -*chylous effusions*, 1080.  
   -*chyluria*, 1107.  
   -*constipation, hysterical*, 607.  
   -*crisis in lobar pneumonia*, 1050.  
     in typhus, 297.  
   -*cyesis*, 567.  
   -*dementia in hysteria*, 1674.  
   -*diarrhoea*, 611, 649.  
   -*diphtheria bacilli*, 69.  
   -*flatulence*, 567.  
   -*hermaphroditism*, 514.  
     ovarian, 515.  
     testicular, 515.  
   -*hypertrophic muscular dystrophy*, 1596.  
   -*pancreatic cysts*, 708.  
   -*paralysis in syphilitic epiphysitis*, 226.  
   -*paresis, alcoholic*, 356.  
   -*Parkinsonism*, 1443.  
   -*sclerosis*, 1484.  
   -*tubes, alcoholic*, 356.  
     diabetic, 442.  
   -*tubercles, in schistosomiasis*, 320.  
   -*typhoid of Delh*, 288.  
   -*xanthoma elasticum*, 1296.  
*Pseudologia phantastica*, 1670.  
*Pseudomonas pyocyaneus*, septicæmia due to, 31.  
   susceptibility to penicillin, 8.  
   resistance to penicillin, 7.  
   sensitivity to streptomycin, 10.  
*Psilosis*, 623.  
*Psilosis, pigmentosa*, 472.  
*Psittacosis*, 183.  
*Psoriasis*, 1270.  
   *flexural*, 1271.  
   *guttate, in children*, 1270.  
   *localised extensor*, 1271.  
   of nails, 1274.  
   of palms and soles, 1273.  
   *pustular*, 1273.  
   *rupioid*, 1272.  
   *widespread*, 1272.  
*Psycho-analysis*, 1620.  
*Psychological medicine*, 1608-1688.  
*Psychoneurosis*, chest pain in, 839, 904, 905.  
*Psychopathology*, 1609.  
*Psychotherapy*, 1619.  
   in ulcerative colitis, 636.  
*Pteroylglutamic acid*, 460.  
*Ptoxis*, 1341.  
   *cervical sympathetic*, 1345, 1547.  
   in botulism, 124.  
   in encephalitis lethargica, 1416.  
   in myasthenia gravis, 1604.  
   *sympathetic*, 1345, 1547.  
   *tabetic*, 1464.  
*Pus in amœbic liver abscess*, 282.  
*Ptyalin*, rôle of, in digestion, 629.  
*Ptyalism*, 530.  
*Pubertas præcox*, 523.  
*Puberty*, incidence of goitre at, 499.  
   in relation to functional proteinuria, 1102.  
   to mental disorders, 1645.  
   psychological crises of, affective disorders in, 1646.  
*Pubic hairs*, loss of, in Simmonds's disease, 487.  
*Puerperal fevers*, 31.  
   *peritonitis*, 712, 715.  
   *psychoses*, 1644.  
*Puerperium as predisposing to erysipelas*, 34.  
   *mental disorders of*, 1644.  
*Pulmonary actinomycosis*, 1038.  
   *amœbiasis*, 1044.  
   *anthrax*, 80.  
   *apoplexy*, 989, 990.  
   *artery, congenital malformations of*, 897, 898, 899.  
     *diseases of*, 857.  
     obstruction of, in cor pulmonale, 852.  
   *aspergillosis*, 1039.  
   *atresia*, 898.  
   *calculi*, 1021.  
   *coccidioidosis*, 200.  
   *collapse*, 992.  
   *distomatosis*, 317.  
   *embolism*, 852.  
   *fibrosis*, 1006.  
     *bronchiectasis in*, 1007.  
     following broncho-pneumonia, 1006.  
     in relation to tuberculosis, 1006, 1019, 1025.  
   *heart disease*, 851-858.  
     *acute*, 852.  
     *causes of*, 857.  
     *chronic*, 855.  
   *histoplasmosis, Appendix i.*  
   *infarction*, 989.  
   *mycoses*, 1038.

- pulmonary oedema**, 988.  
 in heart failure, 809.  
 in pleurisy with effusion, 1068, 1069.  
**oligæmia** in congenital heart disease, 893.  
**osteo-arthritis**, 1171.  
 chronic, in empyema, 1074.  
 in bronchiectasis, 984.  
 in pulmonary tuberculosis, 1026.  
**pleonæmia**, in congenital heart disease, 894.  
**schistosomiasis**, 1043.  
**torulosis**, 198.  
**tuberculosis**, 1017-1038.  
 acquired resistance in, 1018.  
 acute caseous, 1019.  
     miliary, 1019, 1024.  
 ætiology of, 1016.  
 age in relation to, 1017.  
 breath sounds in, 1025.  
 bronchial glands in, 1020.  
 calcification of tubercles of, 1018.  
 caseation in, 1018, 1019.  
 causal organism of, 1017.  
 cavitation in, 1018, 1024.  
 chronic miliary, 1019, 1024.  
 circulatory symptoms of, 1023.  
 classification of stages of, 1028.  
 climatic treatment of, 1032.  
 collapse therapy in, 1034.  
 complications and sequelæ of, 1026.  
 cough in, 1021.  
 course of, 1028.  
 diagnosis of, 1027.  
 dietetic treatment of, 1032.  
 dust in relation to, 1009.  
 dyspnoea in, 1021.  
 early signs of, 1024.  
 environment in relation to, 1017.  
 excavation in, 1025.  
 exercise in treatment of, 1032.  
 expectoration in, 1021.  
 fever in, 1022.  
 fibroid, 1020.  
 fibrosis in relation to, 1006, 1020, 1025.  
 following influenza, 180, 1020.  
 genito-urinary system in, 1024.  
 hæmoptysis in, 1018, 1020, 1023, 1030, 1036.  
 heredity in relation to, 1017.  
 influence of other diseases upon, 1017.  
 in relation to asthma, 979.  
     to coal miners' pneumoconiosis, 1012.  
     to emphysema, 999.  
     to silicosis, 1010.  
 incubation period of, 1018.  
 marriage and, 1029.  
 mass radiography in, 1031.  
 medicinal treatment of, 1033.  
 mental disorders in, 1042.  
 minimal, 1037.  
 mode of spread of, 1019.  
 nervous system in, 1023.  
 occupation in relation to, 1017.  
 pathology of, 1018.  
 physical signs of early, 1024.  
 pleurisy in, 1021, 1022, 1026, 1063.  
 post-primary lesions in, 1018.  
 predisposing causes, 1017.
- Pulmonary tuberculosis**, primary lesion in 1018.  
 prognosis of, 1029.  
 prophylaxis of, 1031.  
 psychical factors in, 1017.  
 racial susceptibility to, 1017.  
 radiography in, 1026.  
 rest in treatment of, 1032.  
 sanatorium treatment of, 1031.  
 sedimentation test in, 1027.  
 senile, 1021.  
 sex-incidence of, 1017.  
 signs of consolidation in, 1024.  
 signs of excavation in, 1025.  
 signs of fibrosis in, 1025.  
 sputum in, 1021, 1022, 1030.  
 symptoms of, 1020.  
 trauma in relation to, 1017.  
 treatment of, 1031.  
 tuberculin tests for, 1028.  
 valve, stenosis of, 895.  
     with right-to-left interatrial shunt, 898.  
 valvotomy, 896.  
**Pulse**, 795, 796.  
 anacrotic, 795.  
 arterial, 795.  
 bisferiens, 795.  
 Corrigan's, 873.  
 venous, 795.  
 water-hammer, 795.  
**Pulses**, unequal, in cervical ribs, 1580.  
 in mediastinal tumour, 1095.  
**Pulsus bigeminus**, 822.  
 bisferiens, 795.  
 trigeminus, 879, 882.  
**Pupil**, abnormalities of, 1342.  
 Argyll Robertson, 1343.  
 myotonic, 1344.  
**Pupils**, in alcoholic coma, 354.  
 in apoplexy, 1438.  
 in cerebral thrombosis, 1438.  
 in cerebrospinal fever, 56, 59.  
 in chronic alcoholism, 356.  
 in encephalitis lethargica, 1416.  
 in general paralysis of the insane, 1456, 1457.  
 in heat hyperpyrexia, 408.  
 in mediastinal tumour, 1095.  
 in syringomyelia, 1547.  
 in tabes, 1464.  
 pin-hole, in typhus, 298.  
**Purgatives** as a cause of diarrhoea, 609.  
 habitual use of, as cause of colitis, 633.  
 the use and abuse of, 607.  
**Purine bodies**, 1098.  
 in relation to gout, 445, 448.  
**Purpura**, 770, 1259.  
 anaphylactoid, 774.  
 annularis telangiectodes, 1259.  
 arthritic, 774.  
 blood platelets in relation to, 770.  
 fulminans, 771.  
 Henoch's, 774.  
 idiopathic, thrombocytopenic, 771.  
 infective, 771.  
 in acute hepatic necrosis, 671.  
 relation of, to other diseases, 771.  
 simplex, 774.

- Purpura**, thrombotic thrombocytopenic, 772.  
 variolosa, 162.  
**Purpuric eruptions** in children, 51.  
   in sprue, 625.  
   rheumatic, 50.  
   states, Rumpel-Leede phenomenon in, 39.  
**Pustule**, malignant, 81.  
**Pyæmia**, 31, 32.  
   arterial, 32.  
     in relation to septic endocarditis, 32.  
     differentiated from rheumatic fever, 51.  
     from abscess of lung, 1004.  
     from local infection, 3.  
     intracranial abscess in, 1405.  
   portal, 32.  
   relation of, to septicæmia, 32.  
   scarlatinal, 41.  
   systemic venous, 32.  
   types of, 32.  
**Pyelitis**, 1132.  
**Pyelonephritis**, chronic, 1136.  
   in coliform infection, 96.  
   renal contraction in, 1127.  
**Pyknic habitus** in relation to affective psychoses, 1646.  
**Pyknolepsy**, 1502.  
**Pylephlebitis**, non-suppurative, 688.  
   suppurative, 32, 688.  
**Pyloric obstruction**, 594.  
   ulcers as cause of, 578, 594.  
   stenosis, hypertrophic, 596.  
**Pylorus**, benign hypertrophy of, 595.  
   congenital hypertrophy of the, 596.  
   "tumour" in, 596.  
**Pym's fever**, 188.  
**Pyoderma gangrenosum**, 1231.  
**Pyonephrosis**, 1144.  
**Pyo-pneumothorax**, 1073, 1082.  
**Pyorrhœa alveolaris**, 527.  
**Pyothorax**, 1075.  
**Pyrexia**, undulant, in Hodgkin's disease, 790.  
**Pyridoxine** (vitamin B<sub>6</sub>), 459.  
**Pyrimethamine** in malaria prophylaxis, 256.  
**Pyruvic acid** in brain, excess of, effects of, 457.  
**Pyuria**, 1106.  
  
**"Q" fever**, 293, 302.  
**Quadriceps paralysis**, 1574.  
**Queckenstedt's phenomenon**, 1378.  
   test, 1379, 1534.  
**Queyrat's erythroplasia**, 1307.  
**Quinidine** in auricular fibrillation, 828.  
   flutter, 826.  
   tachycardia, 824.  
   in paroxysmal tachycardia, 824.  
   in ventricular tachycardia, 828.  
   toxic symptoms from use of, 828.  
**Quinine** as cause of optic atrophy, 1340.  
   in dystrophia myotonica, 1602.  
   in malaria, 255, 256, 259.  
   in myotonia congenita, 1603.  
   in relation to blackwater fever, 256, 257, 261.  
**Quinsy**, 534.  
**Quintan fever**, 300.  
  
**Rabies**, 1420.  
  
**Radiation therapy** in coccidioidosis, 200.  
   in follicular lymphocytoma, 1317.  
   in Hand-Schüller-Christian's disease, 784.  
   in Hodgkin's disease, 791.  
   in lymphosarcoma, 792.  
   in Queyrat's erythroplasia, 1307.  
   in rodent ulcer, 1304.  
   in squamous cell carcinoma, 1305.  
**Radio-active substances**, injuries from, 411.  
**Radiography** of the chest, 1026.  
   of the heart, 802-805.  
   of the intestines, 602.  
   of the stomach, 559.  
**Radium dermatitis**, 412.  
   injuries, protection from, 413.  
**Râles**, in pulmonary tuberculosis, 1025.  
   leathery, in bronchiectasis, 984.  
**Rammstedt's operation** for congenital hypertrophy of the pylorus, 597.  
**Rashes**, drug, 1265.  
**Raspberry tongue** in scarlet fever, 39.  
**Rat-bite disease**, 244.  
   fever, 244.  
**Rat flea**, 127.  
**Rats** as disseminators of rat-bite fever, 244.  
   in relation to flea typhus, 287.  
   to leptospirosis, 238, 239.  
   to plague, 127.  
   measures of destroying, 129.  
**Rauwolfia serpentina** in benign hypertension, 912.  
**Ray-fungus disease**, 193.  
**Raynaud's disease**, 923.  
   phenomenon, 922.  
**Reaction**, mixed electrical, in progressive muscular atrophy, 1560.  
   of degeneration in acute poliomyelitis, 1428.  
**Rebound phenomenon** in cerebellar lesions, 1363.  
**Recklinghausen's disease**, 1485.  
**Rectal crises** in tabes, 1462, 1465.  
   examination, value of, in acute appendicitis, 655.  
   hæmorrhage from polypi of colon, 640.  
**Rectum**, the, 684.  
   disturbances of, and spinal cord lesions, 1531.  
   dyschezia in relation to the, 602, 605-609.  
   lesions of, in lymphogranuloma inguinale, 191.  
   in schistosomiasis, 319.  
   pain in, in paroxysmal proctalgia, 629.  
**Red blood cells**, 726.  
   fragility of, in acholuric jaundice, 741, 742.  
**Reed-Sternberg cells** in lymphadenoma, 789.  
**Reflex epilepsy**, 1502.  
   grasping, 1358.  
   mass, 1542.  
   radial, inversion of, 1530.  
**Regurgitation of food**, 546, 551, 552, 562.  
**Reiter's syndrome**, 312, 1156.  
**Relapsing fever**, 241.  
   American, 242.  
   Asiatic, 242.  
   Central African, 243.

- elapsing fever, Central and South American, 241.  
 European, 242.  
 lice-borne, 242.  
 N. African, 242.  
 Palestinian and Syrian, 241.  
 Panama, 241.  
 Persian and N.W. Indian, 243.  
 Spanish, 243.  
 tick-borne, 243.  
 "Release phenomena," 1337.  
 remittent fever, 243.  
 renal agenesis, 1131.  
 aplasia, 1131.  
 asthma, 979.  
 calculi, 1140.  
 colic, 1141, 1142.  
   in pyelitis, 1133.  
 disease, hypertension in relation to, 908, 909, 912, 1111.  
   in relation to cerebral thrombosis and hæmorrhage, 1435.  
   papilloedema in, 1386.  
 failure, 1110.  
   in blackwater fever, 261.  
   in subacute bacterial endocarditis, 887.  
 function, estimation of, 1100.  
 hypertension, 1111.  
 hypoplasia, 1131.  
 oedema, 1113.  
 rickets, 467.  
 vascular disease, 1124.  
 Rendu-Osler-Weber disease, 775.  
 depression, 1614.  
 respiration, acidotic, 419.  
 adenoids in relation to, 941.  
   in acidæmia, 419.  
   in intracranial tumour, 1388.  
   Kussmaul's, 419.  
 respiratory centre, failure in poliomyelitis, 1432.  
   system, diseases of, 938-1097.  
 rest pain, 919.  
 reticulocyte count, normal, 729.  
   crisis, 731.  
 reticulocytes, 729.  
   in blood in pernicious anæmia, 736.  
 reticulo-endothelial cells, 783.  
   lipoid in, in Niemann-Pick's disease, 785.  
 system, diseases of the, 783-786.  
   role of, in relation to immunity reactions, 778.  
   spleen as part of, 778.  
   tissue, 778.  
   -endothelium in lymph glands, 787.  
 reticuloses, cutaneous, 1316.  
   benign, 1317.  
   malign, 1316.  
 retina, phakoma of, 1487.  
 retinal changes in amaurotic family idiocy, 1483.  
   in diabetes mellitus, 441.  
 hæmorrhages, in leukæmia, 759, 763.  
   in malaria, 254.  
   in nephritis, 1116.  
   in small-pox, 164.  
   in whooping-cough, 140.  
 Retinopathy, diabetic, 441, 1126.  
 Retinopathy, hypertensive, 910.  
 Retrobulbar neuritis, 1399, 1475.  
 Retrocollic spasm, 1521.  
   -pharyngeal abscess, 75, 539.  
     in glandular fever, 306.  
 Retrosternal soreness in tracheitis, 955.  
 Rh factor, 728.  
 Rhabditis pellio, 326.  
 Rhabdomyosarcoma, 789.  
 Rhagades in congenital syphilis, 225.  
 Rhesus factor, 728.  
   in erythroblastosis foetalis, 745, 746.  
 Rheumatic carditis, 49, 51, 863.  
   fever, 48.  
     complications of, 50.  
     differentiation from meningitis, 62.  
     in children, 51.  
     prophylaxis with sulphonamides, 28, 29.  
   infection of heart in childhood, 51.  
   nodules, 51.  
 Rheumatism and chorea, 1515, 1517.  
   cardiac disease in relation to, 51.  
   gonorrhœal, 67, 1154.  
   manifestations of, in children, 51.  
   muscular, 1165.  
   non-articular, 1165.  
   palindromic, 1165.  
   psychogenic, 1166.  
   scarlatinal, 43.  
   tonsillitis in relation to, 533.  
 Rheumatoid arthritis, 1150.  
 Rhinitis, acute catarrhal, 147.  
   allergic, 939.  
   in cadmium poisoning, 387.  
   psychogenic influence in, 939.  
 Rhino-pharyngitis, destructive ulcerating, 236.  
 Rhinophyma, 1207, 1208.  
 Rhinorrhœa, in scarlet fever, 40, 42.  
 Rhinosporidiosis, 201.  
 Rhinosporidium seeberi, 201.  
 Rhipicephalus sanguineus, 293.  
 Rhythm, cardiac, abnormal, 819.  
   gallop, 810.  
   in paroxysmal tachycardia, 823.  
   nodal, auriculo-ventricular, 823.  
   sinus, 819, 820.  
   triple, 810.  
 Rib-notching in coarctation of aorta, 895.  
 Riboflavin, 457, 472, 475.  
   deficiency, effects of, 458.  
   in pellagra, 472, 475.  
 Ribs, cervical, 1579.  
 Rice, polished, use of, a cause of beriberi, 468.  
 Rice-water stools in cholera, 134.  
   in epidemic diarrhœa, 615.  
 Rickets, 465.  
   acrobatic, 466.  
   acute, 468.  
   adult, 1176.  
   congenital, 468.  
   foetal, 468.  
   hypophosphatæmic, with renal glycosuria, 1179.  
   in coeliac disease, 619.  
   in relation to broncho-pneumonia, 1058.  
     to epidemic diarrhœa, 616.  
   late or adolescent, 467.

- Rickets, renal, 467.  
   scurvy, 468.  
   vitamin-resistant, 468.  
 Rickettsia bodies, 285.  
   burneti, 285, 293, 302.  
   diseases, 285-304.  
   mooseri, 285, 287, 295.  
   orientalis, 285, 288.  
   prowazeki, 285, 295, 296.  
   quintana, 285, 300.  
   rickettsi, 285.  
   tsutsugamushi, 288.  
 Rickety rosary, 465.  
   spine, 466.  
 Riedel's lobe, 1146, 1148.  
 Rigor, in arspenamine therapy, 230.  
   in small-pox, 160.  
 Ringworm, 1233.  
   black dot, 1234.  
   cattle, 1235.  
   of the beard, 1235.  
   of the foot, 1236.  
   of the glabrous skin, 1235.  
   of the nails, 1237.  
   of the scalp, 1233.  
 Rinne's test for nerve deafness, 1351.  
 Risus sardonius, 82.  
 Ritter's disease, 1226.  
 Rock tuberculosis, 1009.  
 Rocky Mountain spotted fever, 293.  
   tick typhus, 293.  
 Rodent ulcer, 1303.  
 Romberg's sign, 1464.  
   in Friedrich's ataxia, 1480.  
   in sleeping sickness, 272.  
   in tabes, 1464.  
 Rosacea, 1207.  
 Rose spots in paratyphoid fever, 111.  
   in trench fever, 301.  
   in typhoid, 100.  
 Roseolar rash of syphilis, 205.  
 Rötheln, 156.  
 Rothera's nitroprusside test for acetone  
   bodies, 1106.  
 Round-worms, diseases due to, 325-335.  
 Rubella, 156.  
   differentiation from measles, 153, 157.  
   from scarlet fever, 45.  
 Rumination, obsessional, 1679.  
 Rumpel-Leede phenomenon, 39.  
 Rupia, 205.  
 Rusty sputum, 1050.  
 Sabre-scabard tibia, 227.  
   in jaws, 234.  
 Saddle-nose of congenital syphilis, 227.  
 "Sailor's skin," 1210.  
 St. Vitus' dance, 1515.  
 Salicylates in rheumatic fever, 52.  
 Saliva, deficient secretion of, 530.  
   drugs inhibiting secretion of, 530.  
   drugs stimulating secretion of, 530, 531.  
   excessive secretion of, 530.  
 Salivary glands, diseases of the, 530.  
   in mumps, 175.  
 Salivation, conditions associated with, 530.  
   in cadmium poisoning, 387.  
   in chronic arsenical poisoning, 374.  
   Salivation in foot-and-mouth disease, 183.  
   in iodism, 221.  
   in progressive muscular atrophy, 1558.  
   in pyorrhoea alveolaris, 528.  
   Salk vaccine in poliomyelitis, 1434.  
   "Salmon patch," 226.  
   Salmonella enteritidis (Gaertner), 94, 120.  
   resistance to penicillin, 7.  
   typhi, 97, 98.  
   susceptibility to penicillin, 8.  
   typhimurium, 120.  
   Salpingitis in gonorrhoea, 67.  
   Salt required to make up for loss in sweat, 407,  
   408, 409.  
   Salt-free diet in ascites, 724.  
   Salvarsan, 213.  
   Sand-flies in relation to kala-azar, 265.  
   to oriental sore, 269.  
   to Oroya fever, 144.  
   to phlebotomus fever, 188.  
   Sand-fly fever, 188.  
   Sante manœuvre, 994.  
   Santonin in ascariasis, 334.  
   São Paulo fever, 293.  
   Sarcoidosis, 1245.  
   of Boeck, 1246.  
   Sarcoids, Darier-Roussy, 1246, 1261.  
   in epidemic dropsy, 346, 349.  
   Sarcoma, idiopathic hæmorrhagic, of Kaposi,  
   1313.  
   myeloid, 1175.  
   of liver, 685.  
   of mediastinum, 1094.  
   of spleen, 781.  
   Sarcoptes scabiei, 1250.  
   Saturnism, 364.  
   Scabbard trachea, 962.  
   Scabies, 1250.  
   crusted, 1251.  
   Norwegian, 1251.  
   Scalp, ringworm of the, 1233, 1234.  
   seborrhoeic dermatitis of, 1217.  
   treatment of, 1219.  
   Scaphocephaly, 1181.  
   Scapula, winged, 1568.  
   Scarlatina, 36.  
   miliaris, 39.  
   sine eruptione, 41.  
   Scarlet fever, 36-48.  
   acute nephritis in, 1115.  
   and diphtheria, 44.  
   complications of, 42.  
   Dick test for susceptibility, 37.  
   differentiation from rubella, 157.  
   hæmorrhagic, 41.  
   in relation to chicken-pox, 171.  
   in relation to measles, 45, 150.  
   prophylaxis of, 29, 37.  
   Schultz-Charlton blanching test in, 38.  
   septic or anginous, 40.  
   simple, 40.  
   surgical, 41.  
   toxic or malignant, 41.  
   types, 40.  
   Schamberg's disease, 1260.  
   Scheele's green, 373, 376.  
   Schick's test for susceptibility to diphtheria,  
   76.

- Schilder's disease**, 1412.  
 mental disorders in, 1635.
- Schistosoma bovis**, 319.  
*hæmatobium*, 319, 320.  
*japonicum*, 319, 320.  
*mansoni*, 319, 320.  
*mathei*, 319.
- Schistosomiasis**, 319.
- Schistosomidae**, life cycle of, 319.
- Schizogony of malarial parasite**, 247.
- Schizoid personality**, 1657.
- Schizont of malarial parasite**, 247.
- Schizophrenia**, 1656.  
 varieties of, 1664.
- Schizotrypanosomiasis**, 274.
- Schüller-Christian's disease**, 783, 1186.
- Schultz-Charlton blanching test in scarlet fever**, 38, 44.
- Sciatic pain, referred**, 1584.
- Sciatica**, 1166, 1581.  
 as symptom of osteo-arthritis, 1158.  
 associated with subarachnoid hæmorrhage, 1449.
- Scleredema adultorum (Buschke)**, 1294.
- Sclerema neonatorum**, 1294.  
 nodular, 1294.
- Sclerodactyly**, 935.
- Scleroderma**, 1291.  
 circumscribed, 1291.  
 generalised, 935.  
 Raynaud's phenomenon, 935.  
 in relation to, 923, 935, 1292.
- Scleroma of trachea**, 959.
- Sclerosis, amyotrophic lateral**, 1554.  
 disseminate in childhood, 1412.  
 disseminated, 1472.  
 mental disorders in, 1635.  
 retrobulbar neuritis in, 1339.  
 insular, 1472.  
 lobar atrophic, 1487.  
 multiple, 1472.  
 systemic, 1292.  
 tuberosa, 1486.
- Sclerotics, blue, in osteogenesis imperfecta**, 1180.
- Scoliosis in acromegaly**, 484.  
 in cerebral diplegia, 1489.  
 in Friedreich's ataxia, 1481.
- Scolopendra gigantea**, 340.
- Scorpion stings, treatment of**, 340.
- Scorpions, diseases due to**, 340.
- Scotoma, central**, 1360, 1475.
- Screw worm**, 337.
- Scrofuloderma**, 1243.
- Scrotum, filarial lesions of**, 327.  
 gangrene of, in Rocky Mountain tick typhus, 294.
- Scrub typhus**, 288.
- Scurf**, 1217.
- Scurvy**, 461.  
 Alpine, 472.  
 bachelor's, 462.  
 infantile, 463.
- Scurvy-rickets**, 468.
- Sea-sickness and allied conditions**, 401.
- Sebaceous cysts**, 1303.
- Seborrhœa**, 1200.  
 and acne, 1200.
- Seborrhœa, baldness in**, 1200.  
 in schizophrenia, 1663.  
*sicca*, 1217.
- Seborrhœides**, 1218.
- Sedimentation rate in pulmonary tuberculosis**, 1027, 1031.  
 in rheumatoid arthritis, 1151.
- Seminal emission in epileptic fit**, 1496.  
 vesicles affected in schistosomiasis, 319.  
 in amœbic dysentery, 277.
- Semon's law of laryngeal paralysis**, 950.
- Senear-Usher syndrome**, 1289.
- Senile atrophy of skin**, 1295.  
 and presenile dementia, 1628.  
 paraplegia, 1543.  
 tuberculosis, 1021.
- Sensory defects and mental deficiency**, 1683.  
 disturbances in acroparæsthesia, 1581.  
 in acute poliomyelitis, 1428.  
 in alcoholic neuritis, 1589.  
 in beriberi, 469, 470.  
 in hæmatomyelia, 1549.  
 in hysteria, 1671.  
 in Landry's paralysis, 1595.  
 in median nerve lesions, 1571.  
 in parietal lobe lesions, 1359.  
 in radial nerve lesions, 1570.  
 in subacute combined degeneration, 1551.  
 in syringomyelia, 1545.  
 in tabes, 1462.  
 in ulnar nerve lesions, 1573.  
 tract disturbances, 1529.
- Sepsis, focal**, 30.
- Septicæmia**, 30, 31.  
 as result of bacterial activity, 3.  
 from *Bact. coli*, 97.  
 from local infection, 3.  
 from streptococcus infection, 34.  
 by insect bites, 337.  
 from typhoid bacillus, 97.  
 gonococcal, 67.  
 in cerebrospinal fever, 58.  
 in erysipelas, 35.  
 in peritonitis, 715.  
 in scarlet fever, 39, 40.  
 in small-pox, 164.  
 local infections leading to, 31.  
 microbes chiefly concerned in, 31.  
 pneumococcus, 31.  
 post-operative, 31.  
 puerperal, 31.  
 relation to, of pyæmia, 31.
- Septicæmic arthritis**, 1155.
- Sera, antitoxic**, 4.
- Serilicite pneumoconiosis**, 1013.
- Serum proteins and albumin-globulin ratio in liver tests**, 660.  
 prophylaxis of measles, 154.  
 sickness, 5.
- Sex as a factor in psychogenesis**, 1614.  
 as causal factor in schizophrenia, 1658.  
 glands, 520.
- Sexual aberrations in moral imbecility**, 1629, 1685.  
 desire in mania, 1649.  
 in pulmonary tuberculosis, 1024.  
 loss of, in tabes, 1464.  
 development, arrest of, in dwarfism, 486.

- Sexual development as affected by orchitis**  
   in mumps, 176.  
   failure of, in Fröhlich's syndrome, 489.  
**dystrophy in diseases of pituitary, 484, 485, 487.**  
   epochs in relation to mental disorder, 1611, 1644.  
   instinct in relation to mental disorder, 1614, precocity, 523.  
**Shaking palsy, 1511.**  
**Shaver's disease, 1015.**  
**Sheehan-Simmonds's disease, 487.**  
**Shell-fish as vehicle of typhoid infection, 98.**  
**"Shift to the left," 753.**  
**Shiga's dysentery, 113, 114.**  
**Shigella, boyd, 113.**  
   flexneri, 113.  
   resistance to penicillin, 7, 8.  
   schmitzi, 113.  
   shigæ, 112, 113.  
**Shin-bone pain in trench fever, 301.**  
**Shingles, 1247, 1419.**  
**Shock, 818.**  
   blood-volume in relation to, 725, 726.  
   in cardiac infarction, 843.  
   in hæmorrhage, 725.  
   syndrome, 725.  
   treatment of, 726.  
   of schizophrenia, 1621.  
   of schizophrenia, 1667.  
**Shoulder, dropped, in pulmonary tuberculosis, 1025.**  
   frozen, 845, 1167.  
   -hand syndrome, 845.  
**Sialodochitis, 531.**  
**Sickle-cell trait, 743.**  
**Siderosis, welders', 1014.**  
**Sigmoidoscopic examination, technique of, 604.**  
**Sigmoidoscopy in bacillary dysentery, 116.**  
   in ulcerative colitis, 635.  
**Silica in relation to pneumoconiosis, 1008, 1013.**  
**Silicosis, 1009.**  
**Sillimanite pneumoconiosis, 1013.**  
**"Silver wire" arteries, 910.**  
**Simmonds's disease, 487.**  
   mental disorders associated with, 1644.  
**Simulium damnosum as transmitter of onchocerciasis, 329.**  
**Sino-auricular heart-block, 821.**  
   node, 793.  
**Sinus, accessory, suppuration of, 940.**  
   arrest, 821.  
   arrhythmia, 821.  
   bradycardia, 820.  
   cavernous, thrombosis of, 1366, 1453.  
   lateral, thrombosis of, 1453.  
   longitudinal, thrombosis of, 1453.  
   rhythm, 819.  
   tachycardia, 820.  
   thrombosis, 1366, 1452-1454.  
   infective venous, 1410.  
**Sinuses, affections of, in the common cold, 148.**  
   cerebral, thrombosis of, 1366, 1452.  
**Sinusitis, frontal, 940.**  
   in influenza, 180.  
**Skeleton, diseases of, 1171-1187.**  
**Skenitis in gonorrhœa, 67.**  
**Skew deviation, 1364.**  
**Skin, actinomycosis of, 195, 1240.**  
   affections after arsphenamine remedies, 230, 231.  
   anatomy of the, 1188.  
   atrophy of, 1295.  
   blastomycosis of, 198, 199, 1239.  
   café-au-lait in congenital syphilis, 225.  
   in neurofibromatosis, 1486.  
   carcinoma, secondary of, 1305.  
   coccal infections of, 1224-1232.  
   degenerative conditions of, 1298.  
   dermoid cysts of, 1303.  
   diphtheria, infections of, 72, 1232, 1330.  
   diseases, 1188-1335.  
   tropical, 1327-1335.  
   erythematous conditions of, 1254-1265.  
   eruptions, chronic bullous, 1286-1291.  
   drug, 1265-1268.  
   due to drugs, 27, 1265-1268.  
   to filtrable viruses, 1246.  
   to sulphonamide preparations, 27.  
   functions of the, 1188.  
   fungus infections of, 1232-1240.  
   " glossy," 1295.  
   hypertrophy of, 1297.  
   in acromegaly, 484.  
   in ankylostomiasis, 332.  
   in filarial elephantiasis, 327.  
   in morphinism, 1640.  
   in myxedema, 496.  
   in neurofibromatosis, 1486.  
   in pellagra, 473.  
   in Simmonds's disease, 487.  
   in tuberosc sclerosis, 1487.  
   monilial infections of, 1237.  
   navi of, 1313.  
   parasitic infections of, 1250-1254.  
   pigmentary anomalies of, 1201-1205.  
   primary chancres of, 204.  
   protective function of the, 1188.  
   reticulos, 1316.  
   secretions of the, 1198.  
   secretory disorders of, 1198-1201.  
   senile elastosis of the, 1293.  
   sensory disorders of, 1189-1197.  
   sporotrichosis of, 1239.  
   staining of, in dinitrophenol poisoning, 391.  
   tags, 1312.  
   test for tuberculosis, 88, 1027, 1028.  
   tuberculosis of, 1240.  
   tumours of the, dermal, 1310-1316.  
   epidermal, 1301-1310.  
   vasomotor disorders of, 1205-1208.  
   virus infections of, 1246-1250.  
   X-ray injuries of the, 410.  
**Skoda, veiled puff of, 984.**  
**Skull, abnormalities of, in cerebral diplegia, 1488.**  
   anterior fossa, lesions in, 1364.  
   general hyperostosis of, 1175.  
   in achondroplasia, 1182.  
   in acromegaly, 484.  
   in cretinism, 498, 499.  
   in Hand-Schüller-Christian's disease, 1186, 1187.



- Skull** in hydrocephalus, 1400, 1401.  
 in osteitis deformans, 1173.  
 in oxycephaly, 1181.  
 in rickets, 466.  
 middle fossa, lesions in, 1365.  
 posterior fossa, lateral recess, tumours in, 1366.  
 worm-eaten, in syphilis, 203, 209.
- Sleep** in anxiety states, 1651.  
 in mania, 1649.  
 in mental depression, 1650.  
 rhythm, reversed in encephalitis lethargica, 1416.
- Sleeping sickness**, 270.  
 of Tübingen, 1414.
- Sleeplessness** in delirium tremens, 1638.  
 in morphinism, 1640.  
 in pneumonia, 1050.
- "Sleeved jacket"** anæsthesia, 1546.
- Slough**, wash leather, in syphilis, 208.
- Small-pox**, 158-168.  
 complications of, 164.  
 confluent, 162.  
 differentiation from glanders, 132.  
 from measles, 153.  
 hæmorrhagic, 162.  
 malignant, differentiation from meningitis, 61.
- Smegma bacillus**, differentiation of, from tubercle bacillus, 88.
- Smell**, loss of sense of, 1338, 1358, 1364.
- Smith's sign** in enlarged mediastinal glands, 1093.
- Smoking**, a cause of chronic pharyngitis, 540.  
 a cause of pyralism, 530.  
 effect on cardiovascular system, 346.  
 on gastro-intestinal system, 347.  
 on nervous system, 347.  
 on respiratory system, 346.  
 effects of, 346.  
 excessive, enterospasm in, 605.  
 harmfulness of, in intestinal spasm, 627, 628.  
 in relation to gastric and duodenal ulcer, 576, 579.  
 to gastric irritation, 557.  
 to laryngitis, 947.  
 to pulmonary new growths, 1041.  
 to thrombo-angiitis obliterans, 921.
- Snake poisoning**, 340.  
 venom for hæmophilus, 768.  
 for hæmorrhagic diseases, 768.  
 venoms, 340, 341.
- Snakes**, diseases due to, 340.
- Snapper-Witts syndrome**, 487.
- Snoring** in adenoids, 941.
- Snuffles**, 226.
- Soap diarrhoea**, 613.
- Sodium aminosalicylate** in pulmonary tuberculosis, 1033.  
 arsenite, uses of, 373.  
 bicarbonate in methyl alcohol poisoning, 357.  
 biurate deposits in gout, 446, 447.  
 chloride in urine, 1099.  
 citrate to accelerate elimination of lead, 371.  
 dehydration, 416.  
 iodide in syphilis, 221.
- Sodium retention**, 1114.  
 sulphate in bacillary dysentery, 119.  
 salicylate in chronic gout, 448.  
 in rheumatic fever, 52.
- Sodoku**, 244.
- Softening**, cerebral, red, 1436.  
 yellow, 1436.
- Sokoshio**, 244.
- Solanine poisoning**, 344.
- Sonne's dysentery**, 113, 115.
- Sparganosis**, ocular, 323.
- Sparganum mansoni**, 323.  
 proliferum, 323.
- Spasm**, carpo-pedal in laryngismus stridulus, 947.  
 in tetany, 504.  
 epidemic diaphragmatic, 193.  
 habit, 1522.  
 in craft palsy, 1525.  
 in first stage of epileptic fit, 1496, 1497.  
 in hour-glass stomach, 593.  
 of anal sphincter, 609.  
 of œsophagus, chest pain in, 839.  
 peripheral facial, 1351.  
 respiratory in rabies, 1421.  
 retro-colic, 1521.  
 torsion, 1484.
- Spasmodic torticollis**, 1521.
- Spastic ataxia** in cerebrospinal fever, 59.  
 dysarthria, 1373.  
 paralysis, congenital, 1487.  
 familial, 1482.  
 general congenital, 1488.  
 paraplegia, 1528.  
 congenital, 1488.  
 syphilitic, 1469.
- Spasticity**, development of, after hemiplegia, 1439.  
 in encephalitis lethargica, 1417.
- Spatulate hand** in cretins, 499.
- Specific gravity test** of renal efficiency, 1101.
- Spectroscopic examination** of stools for blood, 604.  
 of urine for blood, 1104.
- Speech**, anatomical considerations, 1368.  
 articulate muscular mechanism of, 1364.  
 defects, 1367-1376.  
 disorders in cerebral abscess, 1408.  
 in general paralysis of the insane, 1456.  
 in hysteria, 1672.  
 in myoclonus, 1520.  
 function of, 1367.  
 patterns, 1370, 1371.  
 perseveration of, 1370.  
 physiological mechanism of, 1369.  
 region of the brain, 1360.  
 scanning or staccato in cerebellar lesions, 1364.
- Spes phthisica**, the, 1024, 1642.
- Sphenoidal fissure**, syndrome of, 1341.  
 ridge, syndromes of, 1366.
- Spherocytosis**, hereditary, 740, 741.
- Sphincter control**, loss of, in epilepsy, 1496.  
 troubles in disseminated sclerosis, 1475.  
 in encephalitis lethargica, 1417.  
 in syringomyelia, 1547.  
 in tabes, 1464, 1468.
- Spiders**, diseases due to, 339.

- Spiegler-Fendt sarcoïd**, 1317.  
**Spina bifida**, 1544.  
**Spinal arthritis**, 1160.  
     caries, in relation to compression of cord, 1538.  
     tuberculous, 1026, 1538.  
**cord, compression of**, 1535.  
     extrathecal, 1537.  
     intrathecal, 1535.  
     traumatic, 1540.  
     hæmorrhages into, 1549.  
     local lesions of, 1527-1544.  
     localisation of lesions, by myelography, 1533.  
     by reflexes, 1530.  
     motor localisation of, 1530.  
     segmental diagnosis of, 1530.  
     sensory localisation of, 1530.  
     neurofibromata of, 1536.  
     subacute combined degeneration of, 1550.  
     surface anatomy of, 1532.  
     tumours of, 1534.  
     vascular lesions of, local, 1543.  
**myosis**, 1342.  
     symptoms in encephalitis lethargica, 1417.  
**syphilis**, 1470, 1471.  
     tumours of, 1534, 1535.  
**Spine, arthritis of**, 1160.  
     fracture and dislocation of, in relation to compression, 1540, 1541.  
     osteo-arthritis of, 1162.  
     tuberculous disease of, 1538.  
**Spirillum fever**, 241.  
     minus, 244.  
**Spirochæta pallida**, 202.  
**Spirochætal infections**, 202-245.  
     jaundice, 238.  
**Spirochætæ** likely to be confused with *Sp. pallida*, 210.  
**Spirochætosis**, 241.  
     ictero-hæmorrhagica, 238.  
**Spashing in stomach**, 558.  
**Spleen, abnormalities of**, 778.  
     ague-cake, 249, 254.  
     amœbiasis of, 276.  
     circulation in, 777.  
     congenital lobulation of, 779.  
     cysts of, 779, 780.  
     diseases of, 777-783.  
     dislocated, 779.  
     enlargement of, 780.  
     floating, 779.  
     functions of, 778.  
     hæmopoietic tissues of, 778.  
     in anthrax, 79.  
     in blackwater fever, 261, 262.  
     in carcinoma of the liver, 685.  
     in cirrhosis of the liver, 676.  
     in congenital syphilis, 226.  
     in glandular fever, 305.  
     in kala-azar, 266.  
     in malaria, 249, 251, 253, 254.  
     in malarial cachexia, 253, 254.  
     in nutritional macrocytic anæmia, 475.  
     in polycythæmia vera, 750.  
     in relapsing fever, 242.  
     in Still's disease, 1164.  
     in syphilis of the liver, 681.  
     in trypanosomiasis, 271.  
     in typhoid, 99, 100.  
     infarction of, 779.  
     in undulant fever, 125.  
     movable, 779.  
     rupture of, 779.  
         complicating malaria, 254.  
     sarcoma of, 780.  
     tumours of, 780.  
**Spleens, accessory**, 778, 779.  
**Splenic anæmia**, 781.  
     fever of animals, 79.  
**Spleniculi**, 778.  
**Spleno-hepatomegaly**, lipoid storage, 784.  
**Splenomegaly**, 780.  
     bilharzial, 320.  
     in relation to tropical macrocytic anæmia, 475, 476.  
     congestive, 781.  
     eosinophilia with, 754.  
     in acholuric jaundice, 742.  
     in Banti's syndrome, 782.  
     in Gaucher's disease, 785.  
     in kala-azar, 266.  
     in leukæmia, 759.  
     in malaria, 251.  
     in Niemann-Pick's disease, 785.  
     in nutritional macrocytic anæmia, 476.  
     in Oroya fever, 144.  
     in plague, 128.  
     in subacute bacterial endocarditis, 886.  
     in trench fever, 301.  
     myeloid, non-leukæmic, 748.  
**Splenunculi**, 778.  
**Splinting in beriberi**, 472.  
     in infantile scurvy, 465.  
     in osteitis deformans, 1174.  
     in rheumatoid arthritis, 1152.  
     in rickets, 467.  
**Spondylitis**, 1160.  
     ankylopoietica, 1160.  
     ankylosing type of, 1160.  
     in abacterial urethritis, 312.  
     atrophic type of, 1160.  
     degenerative, 1162.  
     hypertrophic, 1162.  
     osteo-arthritis type of, 1162.  
     rheumatoid, 1160.  
     types of, 1160.  
**Spondylose rhizomélîque**, 1160.  
**Spondylosis**, 1162.  
**Sporogony of malarial parasite**, 247.  
**Sporotrichosis**, 196.  
     of skin, 1239.  
**Sporotrichum beurmanni**, 196.  
     schenki, 196.  
**Sporozoites of malaria parasite**, 247.  
**Spotted fever of Eastern type**, 293.  
**Sprue, non-tropical**, 620.  
     tropical, 623.  
**Sputum, anchovy paste in pulmonary amœbiasis**, 1044.  
     black in miners' pneumoconiosis, 1011.  
     culture, 1022.  
     currant jelly, 1042.  
     in bronchiectasis, 984, 985.  
     in influenza, 180.

- Sputum in tropical eosinophilia, 313.  
   nummular, 966, 1021.  
   prune-juice, 1042, 1050, 1095.  
   rusty, 1050.  
   tubercle bacilli in, 87, 1021, 1030.  
 Squatting in congenital heart disease, 898.  
 Staccato speech in cerebellar lesions, 1364.  
 Stammering, 1374.  
   hysterical, 1672.  
 Stanford-Binet test, 1686.  
 "Staggers" in decompression sickness, 398.  
 Stannosis, 1014.  
 Staphylococcal food poisoning, 122.  
   infections, 33.  
 Staphylococci as cause of pyæmia, 32.  
   in relation to septicæmia, 31.  
 Staphylococcus aureus in food poisoning, 122.  
   infection, 33.  
   sensitivity to penicillin, 7, 8.  
   infections, 33.  
   pyogenes, 31, 33.  
     in perinephric abscess, 1137.  
     infections due to, 33.  
   saprophyticus in eczema, 1219.  
     in infantile eczema, 1222.  
     in infective dermatitis, 1216.  
 Starch, digestion of, imperfect, 629.  
 Starling's principle in heart failure, 807.  
 Status asthmaticus, 980.  
   dysgraphicus, 1545.  
   epilepticus, 1502, 1506.  
   focal, 1502.  
   lacunatus, 1443.  
 Steapsin (lipase), 701.  
 Steatorrhœa, 612.  
   idiopathic, 620.  
   osteomalacia in, 621, 1178.  
 Steeple head, 1181.  
 Stegomyia fasciata, 184.  
 Stenosis, bronchial, 974.  
   hypertrophic pyloric, 596.  
 Stensen's duct in parotitis, 531, 532.  
   stone in, 531.  
 "Steppage" in alcoholic neuritis, 1589.  
   in beriberi, 470.  
 Stercobillin, 664, 701.  
 Stercolith, blocking appendix, 654.  
 Sterilisation in relation to mental deficiency, 1688.  
 Sterility, 522.  
   as result of X-rays, 410.  
 Sterno-mastoid paralysis, 1356.  
 Sternum, in emphysema, 999.  
 Stevens-Johnson syndrome, 1258.  
 Stibamine in filariasis, 328.  
 Stibophen in schistosomiasis, 321.  
 Stigmata of congenital syphilis, 227.  
   of degeneration, 1684.  
 Still's disease, 1163.  
 Sting-rays, 343.  
 Stitch in the side, 1063.  
 Stokes-Adams syndrome, 831.  
 Stomach, abscess of the, 572.  
   antiseptic barrier of, 556.  
   biochemical examination of, 559.  
   carcinoma of the, 589.  
   pernicious anemia in relation to, 736.  
   Stomach, chemical functions of the, 555.  
     dilation, acute, 597.  
     in congenital hypertrophy of the pylorus 596.  
   diseases of the, 553-599.  
   diverticula of, 598.  
   examination of the, 558.  
   functional disorders of the, 561-571.  
   functions of the, 556.  
   hour-glass, 593.  
   ileal, 599.  
   mothly, 555.  
   organic diseases of the, 571-599.  
   peristalsis in, 559.  
   protective rôle of, for small intestine, 556.  
   psychosomatic disorders of, 557.  
   rate of evacuation of, 555, 559.  
   sensation in, 556.  
   size, shape and position of, 558.  
   spasm of the, 593.  
   spasmodic stricture of, hour-glass, 593.  
   splashing, 558.  
   syphilis of the, 589.  
   thoracic, 550.  
   tone of, 556, 558.  
   tuberculosis of the, 588.  
   X-ray examination of the, 559.  
 Stomatitis, 525, 1325.  
   after arsphenamine remedies, 230.  
   angular, 474, 732, 1324.  
   aphthous, 526.  
   catarrhal, 525.  
   causes of, 1325.  
   chronic, 1326.  
   due to bismuth therapy, 217.  
   due to heavy metals, 1325.  
   epidemic, 182.  
   follicular, 526.  
   gangrenous, 527.  
     in benzene poisoning, 388.  
     in measles, 152, 155.  
     in pellagra, 473.  
     in pink disease, 309.  
   mercurial, 233, 382, 383.  
   recurrent ulcerative, in adults, 525.  
   ulcerative, 525.  
   ulcero-membranous, 526.  
   vesicular, 526.  
   Vincent's, 526.  
 Stone hewers' phthisis, 1009.  
   masons' disease, 1009.  
 Stools, blood in, 603.  
   examination of, 603.  
   in amœbic dysentery, 276.  
   in arsenical poisoning, acute, 374.  
   in bacillary dysentery, 114.  
   in blackwater fever, 262.  
   in cholera, 134.  
   in chronic pancreatitis, 705.  
   in ciliate dysentery, 283, 284.  
   in cœliac disease, 619.  
   in colon neurosis, 628.  
   in deficient pancreatic digestion, 701.  
   in diarrhœa, 611, 612.  
   in epidemic diarrhœa, 614.  
   in fibrosis of pancreas, 706.  
   in food poisoning, 121.  
   in gastro-intestinal allergy, 710, 711.

- Stools** *ingiardia intestinalis*, 284.  
 in hill diarrhoea, 627.  
 in idiopathic steatorrhoea, 620, 621.  
 in intestinal carbohydrate dyspepsia, 630.  
 plague, 128.  
 in jaundice, 663.  
 in kwashiorkor, 480.  
 in lead poisoning, acute, 363.  
 in leptospirosis icterohæmorrhagica, 240.  
 in leukaemia, 762.  
 in malaria, 251.  
 in rickets, 466.  
 in tropical sprue, 624.  
 in typhoid fever, 100.  
 in ulcerative colitis, 634.  
 in yellow fever, 187.  
 rice-water, 134.
- Strabismus**, diagnostic indications of, 1341.  
 in cerebral diplegia, 1489.  
 in disseminated sclerosis, 1475.  
 in encephalitis lethargica, 1416.  
 in hydrocephalus in children, 1402.  
 in third-nerve paralysis, 1341.  
 in tuberculous meningitis, 1396.
- Strawberry mark**, 1314.  
 tongue in scarlet fever, 38.
- Streptobacillus moniliformis**, sensitivity to penicillin, 7.
- Streptococcal infections from septic teeth**, 33.  
 peritonitis, 715.  
 septicæmia from insect bites, 337.
- Streptococci**, classification of, 33.
- Streptococcus faecalis**, 33, 34.  
 susceptibility to penicillin, 7, 8.  
 infection, 33, 34.  
 meningitis, 62.
- pyogenes**, 30, 33, 34, 35.  
 as causal organism of erysipelas, 34.  
 of scarlet fever, 36.  
 infections due to, 33, 34.  
 sensitivity to penicillin, 7, 8.
- septicæmia after mosquito bites**, 337.
- viridans**, 33, 34.  
 infections due to, 34.  
 sensitivity to penicillin, 7.
- Streptomyces aureofaciens**, 13.
- rimosus**, 14.
- venezuelæ**, 11.
- Streptomycin**, 10, 11.  
 acquired bacterial resistance to, 10.  
 as intestinal antiseptic, 11.  
 in abacterial urethritis, 312.  
 in acute infective enteritis, 121.  
 in bacillary dysentery, 118.  
 in chaneroid, 144.  
 in gonorrhoea, 66.  
 in granuloma venereum, 1250.  
 in diarrhoea, 613.  
 in lung abscess, 1004.  
 in meningitis, 1394, 1397.  
 in pericarditis, 880.  
 in plague, 129, 130.  
 in pulmonary actinomycosis, 1039.  
 in pulmonary tuberculosis, 1033.  
 in pyelitis, 1135.  
 in tuberculosis, 10, 89, 90.  
 in tuberculous laryngitis, 949.
- Streptomycin**, peritonitis, 720.  
 in tularæmia, 131.  
 in ulcerating granuloma, 1335.  
 in undulant fever, 127.  
 in whooping-cough, 10.  
 liver damage with, 11.  
 toxic effects, 11.  
 with isoniazid, 11.  
 with sodium aminosalicylate, 11.
- Striae cutis distensæ**, 1295.
- gravidarum**, 1295.
- Stridor**, congenital laryngeal, 946.
- Stripper's asthma**, 1015.
- Strongyloides stercoralis**, 325.
- Strongyloidiasis**, 325.
- Strophanthin** in cardiac disease, 814.
- Strychnine poisoning**, spasms in, differential diagnosis from tetanus, 83.
- Stupor**, catatonic, 1663, 1668.
- Sturge-Weber syndrome**, 1448.
- Stuttering**, 1374.
- Subacromial bursitis**, 1167.
- Sub-acute combined degeneration**, 1550.
- Subarachnoid hæmorrhage**, 1448.
- Sub-diaphragmatic abscess**, 579, 655.
- Subdural hæmorrhage (hæmatoma)**, 1450.
- Sublimation**, 1614.
- Submaxillary mumps**, 175.
- Subsultus tendinum**, 101, 1497.
- Succinylsulphathiazole** in amoebic dysentery, 279.  
 in bacillary dysentery, 117, 118.  
 in ulcerative colitis, 637.
- Succus entericus**, 599.
- Succussion splash**, 588.  
 in pneumothorax, 1083.
- Sucroseria**, 618.
- Sudamina** in rheumatic fever, 50, 1198.
- Sugar in urine**, tests for, 425.  
 loaf head, 1181.  
 metabolism, mechanism of, 423, 424.
- Suicide, risk of, in affective disorders**, 1650, 1655.  
 in anxiety states, 1651.  
 in hysteria, 1674.  
 in mental depression, 1650.
- Sulkowitch's urinary test**, 505.
- Sulphacetamide**, 17.  
 in pyelitis, 1135.
- Sulphadiazine**, 17.  
 in bacillary dysentery, 117.  
 in broncho-pneumonia, 1061.  
 in chronic cholecystitis, 693.  
 in lymphogranuloma inguinale, 192.  
 in meningitis, 1393.  
 in plague, 129, 130.  
 in undulant fever, 126, 127.
- Sulphadimidine**, 18.  
 in cerebrospinal fever, 63.  
 in measles, 155.  
 in pneumococcal pneumonia, 1055.  
 in urinary tract infections, 25.
- Sulphæmoglobinæmia**, 751.
- Sulphaguanidine**, 18.  
 in amoebic dysentery, 279.  
 in bacillary dysentery, 117.  
 in cholera, 136.

- Sulphaguanidine** in epidemic diarrhoea, 617.  
 in undulant fever, 127.  
**Sulphamerazine**, 17.  
 in plague, 129.  
**Sulphanilamide**, 17.  
**Sulphapyridine**, 17.  
 in dermatitis herpetiformis, 1287.  
**Sulpharsphenamine** in syphilis, 213.  
**Sulphates** in urine, 1099.  
**Sulphathiazole**, 17.  
 complications following use of, 27.  
 in cerebrospinal fever, 63.  
 in chancroid, 144.  
 in perinephritis, 1138.  
 in plague, 129.  
 in urinary tract infections, 24, 25, 312.  
**Sulphonal** causing enterogenous cyanosis, 751.  
**"Sulphonamide fever,"** 27.  
**Sulphonamides**, 17-29.  
 absorption of, 19.  
 acetylation of, 19.  
 action on bacteria compared with penicillin, 6, 7.  
 administration, methods of, 20.  
 antibacterial activity of, 19.  
 cautions in use of, 20, 21.  
 complications following use of, 25-28.  
 dosage of, 22, 23.  
 effect of, on colour of urine, 1106.  
 excretion of, 19.  
 in bacterial urethritis, 312.  
 in actinomycosis, 196.  
 in amœbic dysentery, 279.  
 in anthrax, 81.  
 in *B. coli* infections, 23.  
 in bacillary dysentery, 23, 117.  
 in blastomycosis, 198.  
 in broncho-pneumonia, 1061.  
 in cerebrospinal fever, 63.  
 in chancroid, 144.  
 in cholera, 136.  
 in epidemic diarrhoea, 617.  
 in food poisoning, 121.  
 in hæmorrhax, 1079.  
 in ill diarrhoea, 627.  
 in intestinal infections, 23.  
 in lobar pneumonia, 1055.  
 in lymphogranuloma inguinale, 192.  
 in measles, 155.  
 in meningitis, 63, 1393.  
 in meningococcal arthritis, 1155.  
 in mycetoma, 197.  
 in perinephritis, 1138.  
 in pharyngitis, acute septic, 539.  
 in plague, 129.  
 in pneumococcal meningitis, 1393.  
 in pneumonia, 1055.  
 in pyelitis, 1135.  
 in small-pox, 168.  
 in torulosis, 198.  
 in ulcerative colitis, 637.  
 in undulant fever, 126.  
 in urinary tract infections, 24, 25, 97, 312.  
 inhibition of action of, 19.  
 prophylaxis with, 28, 29.  
 solubility of, 18.  
 therapeutic use of, 20-22.
- Sulphonamides**, therapy, disseminated lupus erythematosus in, 933.  
 polyarteritis nodosa in, 931.  
 toxic effects of, 25-27.  
 urinary complications following use of, 26.
- Sulphones** in leprosy, 92-94.  
**"Sulphur granules,"** in pleural fluid, 108.  
 in pulmonary actinomycosis, 1038, 1039.
- Summer diarrhoea**, 614.  
**Sun-bathing**, risk of, in pulmonary tuberculosis, 1032.
- Sun-stroke**, 408.
- Suppuration**, 3.
- Suprarenal cortex**, 506.  
 adenomata of, 512.  
 in relation to sexual functions, 507.  
 glands, acute deficiency, 511.  
 diseases of the, 506-520.  
 in acromegaly, 484.  
 lesions of, in Addison's disease, 507.  
 tumours of, 512, 513, 516, 517.
- Medulla**, 506.  
 tumours of, 517.
- Supraspinatus tendinitis**, 1167.
- Suramin** in onchocerciasis, 329.  
 in trypanosomiasis, 273.
- Sutton's disease**, 1204.
- Swallowing**, mechanism of, 541.
- Sweating**, 1198, 1199.  
 after lesions of spinal cord, 1532.  
 in cardiac neurosis, 904.  
 in dinitrophenol poisoning, 391.  
 in exophthalmic goitre, 492.  
 in malaria, 253.  
 in methanol poisoning, 356.  
 in methyl bromide poisoning, 394.  
 in phæochromocytoma, 518.  
 in rickets, 465.  
 in suppurative pyelophlebitis, 689.  
 in typhus fever, 297.
- Sycosis barbæ**, 1227.
- seborrhœic**, 1218.
- Sydenham's chorea**, 1515.  
 mental changes in, 1634.
- Symbolism**, 1613.
- Sympathectomy** in angina pectoris, 842.  
 in malignant essential hypertension, 916.  
 in Raynaud's phenomenon, 924.  
 in superficial gangrene, 921.
- Sympathetic**, cervical, paralysis of, 1345.
- Sympathoblastoma**, 520.
- Syncope**, cardiogenic, 818.  
 in arsphenamine therapy, 230.  
 in heart disease, 794.  
 in heart failure, 817.  
 in postural hypotension, 917.  
 vasovagal, 817.
- Syndrome**, adreno-genital, 511.
- Albright's**, 502.  
 amnesic, 1627.  
 anterior cerebral artery, 1358.  
 apoplectic, 1449.  
 Avellis', 951.  
 Babinski-Fröhlich's, 488.  
 Banti's, 781.  
 Behcet's, 1326.  
 Benedikt's, 1342, 1362.

Syndrome, Bernheim's, 810, 874.

Brissaud's, 485.  
Brown-Séquard, 1529.  
carotid sinus, 818.  
carpal tunnel, 1572.  
cervico-brachial, 1167.  
crush, 1128.  
Cushing's, 516.  
Da Costa's, 904.  
effort, 904.  
Ehlers-Danlos, 1296.  
Fanconi, 468.  
Felty's, 1151.  
Foster Kennedy, 1358.  
Fröhlich's, 488.  
Froin's, 1379.  
frontal lobe tumour, 1358.  
Ganser, 1674.  
Gradenigo's, 1342.  
Hand-Schüller-Christian's, 783, 1186.  
Henoch-Schoenlein, 774.  
Horner's, 1345.  
Kelly-Paterson, 542.  
Korsakoff's, 1590, 1627.  
Laurence-Moon-Biedl, 489.  
Levi-Lorraine, 485.  
loculation, 1379.  
Loeffler's, 753.  
lumbago-sciatica, 1449.  
Lutembacher's, 896.  
mediastinal, 1090, 1094.  
Meigs', 1076.  
meningitic, 1449.  
Nothnagel's, 1362.  
of base of skull, 1366.  
of cavernous sinus, 1366.  
of Dejerine and Roussy, 1361.  
of frontal lobe tumour, 1358.  
of the anterior cerebral artery, 1358.  
of the sphenoidal fissure, 1341.  
ridge, 1366.  
Plummer-Vinson, 542.  
post-gastrectomy, 587.  
post-hepatitis, 669.  
Reiter's, 312.  
Seneear-Usher, 1289.  
shock, 725.  
Snapper-Witts, 487.  
Stevens-Johnson, 1258.  
Stokes-Adams, 831.  
Sturges-Weber, 1448.  
thalamic, 1361.  
Turner's, 486.  
von Gierke's, 452, 892.  
Waterhouse-Friderichsen, 511.  
Weber's, 1342, 1362.  
Weingarten's, 753.  
Wolff-Parkinson-White, 833.  
Synovitis, 1165.  
Syphilide, annular, 206.  
corymbose, 206.  
ecthymatous, 205.  
follicular, 206.  
frambesiform, 206.  
lichenoid, 206.  
maculo-roseolar, 205.  
nodular cutaneous, 207.  
papular, 205.

Syphilide, papulo-pustular, 205.

papulo-squamous, 205.  
psoriasiform tertiary, 208.  
pustular, 205.  
squamous, 205.  
tertiary, 208.  
Syphilis, 202-233.  
accidental infection in, 202, 203.  
aetiology of, 202.  
and cerebral thrombosis and hæmorrhage, 1435.  
and chancroid, 210.  
and mental disorder, 1632.  
cerebral, 1459.  
cardio-vascular, 858.  
congenital, 225-233, 1471.  
definition of, 202.  
diagnosis of primary stage of, 209.  
diagnosis of secondary eruptions in, 210.  
diagnosis of tertiary lesions of, 211.  
general management of, 221.  
in pregnancy, 225, 228.  
treatment of, 228.  
in relation to aneurysm, 858, 929.  
to angina pectoris, 859.  
to jaundice, 664.  
to marriage, 224, 225.  
incubation period of, 203.  
latent, 223.  
maternal transmission of, 202, 225, 228.  
meningeal, 1454, 1459.  
mental disorder and, 1632.  
of the aorta, 858.  
of bone, 203, 209.  
of the bronchi, 973.  
of the central nervous system, 1454-1472.  
of the heart and pericardium, 858.  
of the larynx, 206.  
of the liver, 681.  
of the lungs, 1040.  
of the pancreas, 707.  
of the pharynx, 206.  
of the stomach, 589.  
of the tongue, 206.  
of the trachea, 958.  
optic atrophy in, 1340.  
papulo-squamous lesions in, 205.  
parenchymatous or degenerative lesions of, 1454.  
pathology of, 203.  
pregnancy in relation to treatment of, 228.  
primary chancre of, 203.  
stage of, 203.  
prophylaxis of, 212.  
secondary stage of, 205.  
spinal, subacute and chronic, 1470.  
vascular, 1471.  
symptoms and signs of, 203.  
tertiary stage of, 207.  
transmission of, 202.  
by blood transfusion, 203.  
to fetus, 202.  
treatment of, 212-224.  
of early, 221.  
of late, 223.  
of neurosyphilis, asymptomatic, 224.  
Syphilitic alopecia, 225.  
aortitis, 858.

- Syphilitic arteritis, 858.  
 cerebral thrombosis, 1435.  
 dactylitis, 226.  
 eruptions, differential diagnosis of, 211.  
 infants, treatment of, 228.  
 jaundice, 681.  
 meningitis, 1398, 1461.  
 onychia, 225.  
 osteochondritis, 226.  
 pemphigus, 225.  
 phthisis, 1040.  
 pseudo-paralysis, 226.  
 snuffles, 226.  
 stigmata, 227.  
 wig, 225.  
 Syphiloma, intracranial, 1384.  
 Syringobulbia, 1545.  
 Syringocystadenoma papilliferum, 1309.  
 Syringomata, 1309.  
 Syringomyelia, 1545.  
 Systole, cardiac, 793.  
 premature, 821.  
 T.A.B. vaccine, 109, 127.  
 in undulant fever, 127.  
 Tabardillo, 296.  
 Tabes, conjugal, 1462.  
 dorsalis, 1461.  
 ataxia in, 1464.  
 cervical sympathetic paralysis in, 1345.  
 optic atrophy in, 1465, 1468.  
 visceral crises in, 1465, 1468.  
 juvenile, 1472.  
 mesenterica, 718.  
 Tabo-paresis, 1457.  
 Tâches cérébrales in cerebrospinal fever, 56.  
 in tuberculous meningitis, 1395.  
 Tachycardia, auricular paroxysmal, 823.  
 in cardiac infarction, 844.  
 in cor pulmonale, 853.  
 in exophthalmic gout, 492.  
 in heart failure, 810.  
 in hyperthyroidism, 901.  
 in pericarditis, 879.  
 in phæochromocytoma, 518.  
 in pink disease, 309.  
 paroxysmal, 823.  
 sinus, 820.  
 supraventricular, 823.  
 ventricular, 828.  
 Tænia africana, 322.  
 confusa, 322.  
*echinococcus* in relation to lung, 1046.  
 lata, 322.  
 multiceps, 324.  
 saginata, 322.  
 solium, 322, 323.  
 Tæniasis, 322.  
 intestinal, 322.  
 somatic, 323.  
 Talcosis, 1013.  
 Talipes calcaneo-valgus, 1575.  
 Tamponade, cardiac, 879.  
 Tape-worms, 322, 325.  
 Tarantula bites, 339.  
 Tartar emetic in clonorchiasis, 317.  
 in schistosomiasis, 321.  
 in ulcerating granuloma, 1335.  
 Taste, lesions of fifth nerve in relation to, 1345.  
 loss of, in Bell's paralysis, 1349.  
 in lesions of ninth nerve, 1354.  
 Tattooing, 1205.  
 Tay-Sachs disease, 1482.  
 Tea-factory cough, 1040.  
 -tasters' cough, 1040.  
 Teeth, care of the, 527, 528, 529.  
 in cadmium poisoning, 387.  
 shedding, in pink disease, 309.  
 Teichopsia in migraine, 1509.  
 Telangiectasia, familial hæmorrhagic (Osler), 1315.  
 hereditary hæmorrhagic, 775.  
 Telangiectasis in jaundice, 662.  
 multiple, 775, 938.  
 post-irradiation, 410.  
 Telegraphist's cramp, 1525.  
 Temperature, typus inversus of, in tuberculosis, 1023.  
 undulant, in Brucellosis, 125.  
 Temporal lobe, abscess of, 1408.  
 localising signs of lesions of, 1360.  
 Tendon reflexes in Friedreich's ataxia, 1480.  
 in tabes, 1462, 1463.  
 sheaths, fibrosis of, 1167.  
 Tendovaginitis, stenosing, 1167.  
 Tenesmus in amebic dysentery, 276.  
 in bacillary dysentery, 114.  
 "Tennis elbow," 1167.  
 Teratoma of mediastinum, 1094.  
 Terminal infection, 32, 33.  
 Tetramycin, see Oxytetracycline.  
 Testamentary capacity, 1629.  
 estimation of, in aphasia, 1372.  
 Test-meal for gastric diagnosis, 559.  
 in diagnosis of cancer of stomach, 591.  
 in diagnosis of duodenal ulcer, 577.  
 Testicle, amebiasis of, 277.  
 atrophy of, in dystrophia myotonica, 1602.  
 lesions of, in mumps, 175.  
 necrosis of, in small-pox, 160.  
 tertiary syphilis of, 209.  
 Testosterone, hypersecretion of, in acne vulgaris, 1282.  
 in acromegaly, 485.  
 in dwarfism, 487.  
 in eunuchoidism, 521.  
 in infantilism, 486.  
 in Simmonds's disease, 488.  
 Tetanoid chorea, 1484.  
 Tetanus, 81.  
 neonatorum, 81.  
 Tetany, 503.  
 blood calcium in, 503.  
 in celiac disease, 619.  
 in idiopathic steatorrhœa, 621.  
 in pyloric obstruction, 594.  
 in rickets, 466.  
 in scarlet fever, 43.  
 in sprue, 624.  
 mental disorders associated with, 1644.  
 parathyroid, 503.  
 Tete disease, 243.  
 Tetrachlorethane poisoning, 394, 670.  
 Tetrachlorethylene in ankylostomiasis, 333.  
 in ascariasis, 334.

- Tetracycline**, 14.  
**Tetra-ethyl lead poisoning**, 371.  
**"Thalamic syndrome" of Dejerine and Roussy**, 1361.  
**Thalamus**, *see* Optic thalamus.  
**Thalassemia**, 743.  
**Thiamine (Vitamin B<sub>1</sub>)**, 457.  
   in beriberi, 471.  
**Thiouracil** in exophthalmic goitre, 494, 495.  
   in toxic adenoma, 496.  
**Thomsen's disease**, 1602.  
**Thoracic duct**, diseases of, 787.  
**Thoracoplasty** in pulmonary tuberculosis, 1036.  
**Thorium compounds**, dangers of, 412.  
**Thornapple poisoning**, 344, 352.  
**Thought**, disorder of, in schizophrenia, 1659.  
   in anxiety states, 1648, 1649, 1651.  
**Thread-worms**, 335.  
**Three-day fever**, 188.  
**Throat**, septic, as cause of septicæmia, 31.  
   sore, in rheumatic fever, 49.  
   in scarlet fever, 38, 40.  
   in tonsillitis, acute, 533.  
   syphilitic lesions of, 206.  
**Thrombasthenia**, hereditary, 771.  
**Thrombin**, 765.  
**Thrombo-angiitis obliterans**, 921.  
**Thrombocytopenia** after arsphenamine therapy, 232.  
   essential, 771.  
   of infections, 771.  
**Thrombocythæmia**, idiopathic, 770.  
**Thrombocytosis**, essential, 770.  
**Thrombo-phlebitis**, 926.  
   migrans, 928.  
   non-suppurative, 927.  
   suppurative, 926.  
**Thromboplastin**, 765.  
**Thrombosis**, 925.  
   arterial, 926.  
   and hæmorrhage, 1435-1443.  
   atheroma a cause of, 1435.  
   calcarine, 1438.  
   cerebellar, 1440.  
   cerebral, 1435-1443.  
   coronary, 836, 842.  
   femoral, 927.  
   in infarction of the lungs, 990.  
   in typhoid fever, 103.  
   mural, 925.  
   of cerebral arteries, 1437.  
   sinuses, 1452.  
   veins, 1452.  
   of coronary arteries, 834.  
   of inferior vena cava, 927.  
   of internal carotid, 1437.  
   of renal vein, 1108.  
   of splenic vein, 781.  
   phlebitis in relation to, 926.  
   portal, 688.  
   sinus, 1366, 1453.  
   venous, 926.  
   in arsphenamine therapy, 229.  
   in heart failure, 812.  
**Thrombotic forms of pulmonary infarction**, 990.  
**Thorium X** in malignant reticulosos, 1316.  
   in nævus flammeus, 1314.  
**Thrush**, 527.  
**Thymic asthma**, 946.  
**Thymol turbidity test** in liver function, 660.  
**Thymus gland** 787.  
   and myasthenia gravis, 1606.  
**Thyroid extract** in cretinism, 499.  
   in myxœdema, 498.  
   in osteo-arthritis, 1159.  
   gland, diseases of the, 491-501.  
   in acromegaly, 484.  
   in relation to exophthalmic goitre, 493.  
   pressing on trachea, 500.  
**Thyroidectomy** in Graves's disease, 494.  
**Thyrototoxicosis**, in relation to heart disease, 900.  
   primary, 491.  
   secondary, 495.  
**Thyrotrophin**, 483.  
**Thyroxine**, 491.  
   excessive secretion of, in Graves's disease, 492.  
   in relation to blood formation, 731.  
**Tibia**, sabre-scarbard form of, 227.  
   in yaws, 234.  
**Tic**, convulsive, 1524.  
   douloureux, 1346.  
   psychical, 1524.  
   simple, 1523.  
**Tick** as transmitter of Rocky Mountain tick typhus, 294.  
   -bites, 336.  
   paralysis from, 336.  
   -borne relapsing fevers, symptoms of, 243.  
   fever, 243.  
   typhus, 293.  
**Tics**, the, 1522-1525.  
   post-encephalitic, 1418.  
**Tinea axillaris et cruris**, 1236.  
   barbæ, 1235.  
   capitis, 1233.  
   circinata, 1235.  
   cruris, 211, 1333.  
   flava, 1333.  
   glabrosa, 1235.  
   imbricata, 1333.  
   in the tropics, 1332.  
   nigra, 1333.  
   pedis, 1236.  
   tonsurans, 1233.  
   unguium, 1237, 1333.  
   versicolor, 1238.  
**Tinnitus**, 1351.  
**Titubation** in cerebellar lesions, 1364.  
   in Friedreich's ataxia, 1480.  
**Tityus bahiensis**, 340.  
**Tobacco**, effects of, 346.  
**Tobia fever**, 293.  
**Tocopherols**, 456.  
**Todd's paralysis**, 1441, 1497.  
**Toe-nail**, ingrowing, 1322.  
**Tolazoline hydrochloride** in Raynaud's phenomenon, 924.  
**Tongue**, affections of the, from hypoglossal nerve lesions, 1357.  
   black hairy, 1327.



- Tongue**, carcinoma of, neuralgia in, 1354.  
 hemiatrophy of the, 1357.  
 in acromegaly, 484.  
 in foot-and-mouth disease, 183.  
 in measles, 151.  
 in myasthenia gravis, 1605.  
 in nutritional macrocytic anæmia, 476.  
 in pellagra, 473.  
 in scarlet fever, 38, 39.  
 in tropical sprue, 624.  
 in typhus fever, 298.  
 in undulant fever, 125.  
 in yellow fever, 186, 187.  
 myositis of, in trichiniasis, 331.  
 paralysis of, 1357.  
 raspberry, 39.  
 scrotal, 1327.  
 strawberry, 38.  
 syphilitic lesions of, 206, 208, 209.  
 tremor of, in general paralysis, 1456.  
 worms, diseases due to, 336.
- Tongue-biting** in epilepsy, 1496.
- Tonsillectomy**, 536.  
 contraindicated during outbreaks of poliomyelitis, 1434.
- Tonsillitis**, acute, 533.  
 chronic, 535.  
 adenoids in relation to, 536.  
 in adults, 537.  
 in children, 536.
- Tonsils** as site of septic infection, 30, 533.  
 diseases of, 533-538.  
 in leucæmia, 761, 762.
- Tophi**, 446, 447.
- Torsion spasm**, 1484.
- Torticollis** after encephalitis lethargica, 1418.  
 congenital, 1522.  
 spasmodic, 1521.
- Torula histolytica**, 197, 198.
- Torulosis**, 197.
- Tower skull**, 1181.
- Toxæmia**, 30.  
 from endotoxin, 3.  
 from exotoxin, 3.  
 symptoms of, 30.
- Toxæmias**, infectious, mental disorders in, 1642.
- Toxic adenoma**, 495.
- Toxicosis**, hæmorrhagic capillary, 774.
- Toxins**, 3.  
 acting on the liver, 670.  
 in causation of acute catarrhal gastritis, 571.  
 present in food-poisoning, 121, 123.  
 varieties of, 3.
- Toxoid**, in prophylaxis of tetanus, 83.  
 -antitoxin floccules for immunising against diphtheria, 77.  
 test of susceptibility to diphtheria, 77.
- Toxoplasmosis**, *Appendix v*.
- Trachea**, aneurysm pressing on, 859, 860, 962.  
 carcinoma of, 957.  
 cysts of, 957.  
 diseases of the, 954-962.  
 foreign bodies in, 954, 959.  
 injury of, 962.  
 leprosy of, 959.  
 papilloma of, 957.  
 pressure on, in aortic aneurysm, 859, 860, 962.
- Trachea**, pressure on, in goitre, 500.  
 sarcoma of, 957.  
 scabbard, 962.  
 scleroma of, 959.  
 simple tumours of, 957.  
 syphilis of, 958.  
 tuberculosis of, 959.
- Tracheal obstruction**, 959.  
 from cicatrization, 961.  
 from external pressure, 962.  
 tugging in aortic aneurysm, 860.
- Tracheitis**, acute, 954.  
 chronic, 956.  
 in beryllium poisoning, 386.
- Tracheo-bronchitis**, acute, 963.
- Tracheocele**, 957.
- Tracheophony**, 1093.
- Tracheotomy** in acute laryngo-tracheo-bronchitis, 946.  
 in diphtheria, 78.  
 in oedema of larynx, 944.
- Trapezius**, paralysis of, 1356.
- Trauma** as cause of tracheal obstruction, 961.  
 in relation to arthritis, 1165.  
 to cerebral hæmorrhage, 1435.  
 to gout, 445.  
 to intracranial abscess, 1406.  
 to intracranial tumour, 1381.  
 to ischæmic heart disease, 835.  
 to mental disorders, 1635.  
 to progressive muscular atrophy, 1555.
- Travel sickness**, 401.
- Trematodes**, diseases due to, 316-321.
- Tremor** in cerebellar lesions, 1364.  
 in chronic mercurial poisoning, 382.  
 in disseminated sclerosis, 1474.  
 in exophthalmic goitre, 492.  
 in Friedreich's ataxia, 1480.  
 in general paralysis of the insane, 1456.  
 in hepato-lenticular degeneration, 1484.  
 in manganese poisoning, 385.  
 in paralysis agitans, 1512.  
 in pellagra, 474.
- Trench fever**, 300-302.  
 foot, 1209.
- Treponema berberum**, 241.  
 carateum, 1333.  
 carteri, 241.  
 duttoni, 241.  
 hispanicum, 241.  
 novyi, 241.  
 pallidum, 202.  
 sensitivity to penicillin, 7.  
 persicum, 241.  
 pertense, 233.  
 recurrentis, 241.  
 sogdianum, 241.  
 turicata, 241.  
 venezuelense, 241.  
 vincenti, sensitivity to penicillin, 7.
- Trichinella spiralis**, 331.
- Trichiniasis**, 331.  
 myositis in, 331, 1170.
- Trichlorethylene poisoning**, 395.
- Trichocephalus dispar**, 334.
- Tricho-epitheliomata**, 1309.
- Trichomonas hominis**, 284.

- Trichomonas vaginalis*, 66.  
*Trichomycosis axillaris*, 1238.  
*Trichophyton*, 1232, 1234, 1236, 1333.  
*Trichorrhexis nodosa*, 1319.  
*Trichosporon giganteum*, 1334.  
*Trichosporosis*, 1334.  
*Trichuriasis*, 334.  
*Trichuris trichiura*, 334.  
*Tricuspid atresia*, 893.  
     *incompetence*, 877.  
     *murmur in*, 877.  
     *stenosis*, 877.  
     *valve, congenital anomalies of*, 877.  
*Trigeminal neuralgia*, 1346.  
*Trinitrin in acute coronary insufficiency*, 850.  
     *in angina pectoris*, 840.  
*Trinitrotoluene poisoning*, 390.  
*Tri-ortho-cresyl phosphate, poisoning by*, 378.  
*Trismus in methyl bromide poisoning*, 394.  
     *in strychnine poisoning*, 83.  
     *in tetanus*, 82.  
*Trombicula akamushi*, 289.  
     *dellensis*, 289.  
     *fletcheri*, 289.  
*Trophozoites*, 247.  
*Tropical eosinophilia*, 313.  
     *skin diseases*, 1327-1335.  
     *ulcer*, 1331.  
*Trousseau's sign in hypoparathyroidism*, 504.  
     *in sprue*, 621, 624.  
*Truxidone in petit mal*, 1506.  
*Trypanosome brucei*, 270.  
     *cruzi*, 270, 274.  
     *equiperdum*, 270.  
     *evansi*, 270.  
     *gambiense*, 270, 271, 272.  
     *rhodesiense*, 270, 271, 272.  
*Trypanosome fever*, 271.  
*Trypanosomes in blood*, 271.  
     *in brain and cord*, 271.  
*Trypanosomiasis*, 270.  
     *African*, 270.  
     *South American*, 274, 275.  
*Tryparsamide in syphilis*, 217.  
     *in trypanosomiasis*, 273.  
     *toxic effects of*, 233.  
*Trypsin*, 701.  
*Trypsinogen*, 701.  
*Tsetse fly, the*, 270.  
*Tsutsugamushi disease*, 288.  
     *complications of*, 291.  
*Tubercle bacillus*, 1017.  
     *in milk*, 85, 86.  
     *in sputum*, 87, 1021.  
     *prognostic significance of*, 1030.  
     *in urine*, 85, 87.  
     *resistance to penicillin*, 7, 8.  
     *sensitivity to streptomycin*, 10.  
*Tubercles in choroid in tuberculous meningitis*, 1395.  
*Tuberculide, lupoid papular*, 1285.  
     *papulonecrotic*, 1245.  
     *rosaceous of Lewandowsky*, 1245.  
*Tuberculides of skin*, 1243.  
*Tuberculin tests for tuberculosis*, 88, 1028.  
*Tuberculoma, cerebral*, 1384.  
     *hypertrophic*, 1026.  
*Tuberculosis*, 84-90.  
     *acute caseous, pathology of*, 1019.  
         *temperature in*, 1022.  
         *miliary*, 89.  
         *pathology of*, 1019.  
         *temperature in*, 90, 1022.  
     *etiology of*, 85.  
     *avian*, 85, 1017.  
     *Bacille Calmette-Guérin in prophylaxis of*, 89, 1031.  
     *bovine*, 85, 1018.  
     *cerebrospinal fluid in*, 88.  
     *chronic miliary*, 1019.  
     *colliquativa*, 1243.  
     *congenital*, 85.  
     *cutis*, 1240.  
         *miliaris acuta*, 1241.  
         *officialis*, 1243.  
     *cytological evidence of*, 88.  
     *diagnosis of*, 87.  
     *droplet infection in*, 85.  
     *erythema nodosum and*, 307, 308, 1260.  
     *fibro-caseous, pathology of*, 1020.  
     *fibroid, pathology of*, 1020.  
         *temperature in*, 1023.  
     *general*, 89.  
     *incidence of*, 87.  
     *infection in, modes of*, 85.  
         *results of*, 87.  
     *intestinal*, 638.  
     *intracranial*, 1384.  
     *lymph gland*, 788.  
     *mental disorders in*, 1642.  
     *miliary*, 89, 1019.  
     *minimal*, 1037.  
     *mortality due to*, 87.  
     *of the cæcum, hyperplastic*, 639.  
     *of the epididymis*, 1026.  
     *of the kidneys*, 1139.  
     *of the larynx*, 948, 1021, 1022, 1023.  
     *of the pericardium*, 881.  
     *of the skin*, 1240.  
     *of the stomach*, 588.  
     *of the trachea*, 959.  
     *paths of entrance of bacilli in*, 85.  
     *predisposing factors to*, 86.  
     *prophylactic treatment of*, 88.  
     *prophylaxis of*, 1031.  
     *pulmonary*, 1017-1037.  
     *skin inoculation with*, 85.  
     *sources of infection in*, 85.  
     *tests for*, 88.  
     *treatment of*, 88.  
         *with streptomycin*, 10, 89, 90.  
     *verrucosa cutis*, 1243.  
     *vesical*, 1139.  
*Tuberculous arthritis*, 1156.  
     *colitis*, 638.  
     *enteritis*, 638.  
     *laryngitis*, 948.  
     *mediastinal glands*, 1092, 1093.  
     *meningitis*, 62, 1394.  
     *peritonitis*, 718.  
     *ulceration of ileum*, 639.  
*Tularæmia*, 130.  
*Tumbu disease*, 338.  
*Tumour, benign giant-celled*, 1175.  
     *glomus*, 1315.

- Tumours in acute leukaemia**, 763.  
   intracranial, 1380-1391.  
   urban, 1309.  
**Turbatrix aceti**, 326.  
**Turck cells in blood in Oroya fever**, 145.  
**Turner's syndrome**, 486.  
**Tussis hepatica**, 280.  
**"Twilight state,"** 1626.  
**Twitchings in eclampsia**, 1497.  
   in uraemia, 1497.  
**Tylosis**, 1297.  
**Tympanites in pneumonia**, 1053.  
   in typhoid fever, 102.  
**Typhoid fever**, 97-110.  
   abortive forms of, 101.  
   *aetiology of*, 98.  
   afebrile, 101.  
   age-incidence in, 98, 102.  
   alcoholism and, 102, 104.  
   bacteriemia in, 99.  
   "carriers," 98, 99, 108.  
   complications of, 102.  
   diet in, 109.  
   differential diagnosis of, 61, 106.  
   endemic occurrence of, 98, 99.  
   haemorrhagic type of, 102.  
   incubation period of, 100.  
   intestinal ulceration in, 99.  
   meningitis, 62, 101.  
   mortality rate of, 107.  
   nodules, 99.  
   pregnancy in relation to, 102.  
   prophylaxis in, 107.  
   provocation, 109.  
   pulmonary tuberculosis and, 102.  
   rash in, 100.  
   relapse in, 101.  
   seasonal incidence of, 98.  
   special symptoms and complications of, 102.  
   stools in, 100.  
   types of, 101.  
   Widal test in, 105.  
**spine**, 104.  
**"Typhoid state," the**, 100, 104.  
   in malaria, 251.  
   in malignant undulant fever, 126.  
   in small-pox, 162.  
**Typhus abdominalis**, 97.  
   blasting, 298.  
   differentiation from measles, 153.  
   endemic, 286.  
   epidemic, 295.  
   exanthematicus, 295.  
   flea, 286.  
   fleck-, 295.  
   icteroides, 184.  
   louse-borne, 295-300.  
   mite, 288.  
   murin, 286.  
   murine, 286.  
   Rocky Mountain tick, 293.  
   rural or scrub tropical, 288.  
   São Paulo, 293.  
   scrub, 288.  
   ship, 286.  
   shop, 286.  
   siderans, 298.  
   Typhus tick, 293.  
   urban tropical, 286.  
**Tyrothricin**, 6.  
**Tzanck test**, 1286.  
**Ulcer, chancreoid**, 143.  
   chrome, 384.  
   Curling's, 576.  
   gastric, 575.  
   intestinal, tubercular, 639.  
   of coronal sulcus in lymphogranuloma in-  
     guinale, 191.  
   of fauces, syphilitic, 206.  
   of larynx, syphilitic, 206.  
   tuberculous, 949.  
   of *oesophagus*, acute, 548.  
   phagedenic, 1331.  
   régime, 583.  
   rodent, 1303.  
   snail track in syphilis, 206.  
   sublingual, in whooping-cough, 139, 141.  
   tropical, 1331.  
**Ulcerating granuloma**, 1334.  
**Ulcerations**, Duguet's, 102.  
   in American dermal leishmaniasis, 268.  
   in Vincent's angina, 537.  
   in yaws, 234.  
   of larynx in typhoid fever, 103.  
   tuberculous, 949.  
   of legs in acholuric jaundice, 741, 742.  
   in sickle-celled anaemia, 743.  
   with hypostatic eczema, 1223.  
**Ulcerative stomatitis**, 525.  
**Ulcers of feet in diabetes**, 439.  
   in tabes, 1465.  
**Ulcus molle**, 143.  
   elevatum, 143.  
   terebans, 1304.  
   tropicum, 1331.  
**Ulerythema ophryogenes**, 1320.  
**Ulnar nerve**, lesions of, 1572.  
**"Ultimum moriens" of Duchenne**, 1556.  
**Umbilical abscess in tuberculous peri-  
 tonitis**, 719.  
   vein, thrombosed, causing peritonitis, 712.  
**Umbilicus**, diphtheritic infection of, 72.  
**Uncinariasis**, 332.  
**Uncinate lesions**, hallucinations in, 1360.  
**Undulant fever**, 125.  
   polyarthrits in, 1156.  
**Unguis incarnatus**, 1322.  
**Unverricht's myoclonus**, 1501.  
**Uræmia**, 1108.  
   acute, 1111.  
   chronic, 1110.  
   conditions associated with, 1441.  
   extra-renal, 1111.  
   ischaemic, 1128.  
   mental disorders associated with, 1645.  
**Uræmic asthma**, 979.  
**Urates in urine**, 1107.  
**Urea concentration test of renal efficiency**,  
   1101.  
   frost, 1110.  
   retention in relation to uræmia, 1110.  
**Ureteral catheterisation in determining  
 efficiency**, 1101.  
**Urethritis in abacterial infection**, 311.

- Urethritis** in coliform infections of urinary tract, 96.  
 in mumps, 175.  
 in Reiter's disease, 1156.  
 non-specific as cause of ankylosing spondylitis, 1160.
- Uric acid** in blood in gout, 445, 446.  
 in health, 445.  
 calculi, 1140.  
 crystals in urine, 1099, 1107, 1140.  
 excretion of, 445, 1098.
- Urinary** complications of sulphonamide therapy, 26.  
 culture for diagnosis of typhoid, 105.  
 secretion, abnormalities of, 1102.  
 test of Sulkowitch, 503.  
 tract, *B. coli* infections of, 95.  
 infections, treatment with sulphonamides, 22.
- Urine**, acidity of, 1098.  
 alcohol in, in alcoholic intoxication, 353.  
 appearances of, in bacilluria, 96, 1134.  
 Bence Jones protein in, 1103.  
 crystalline deposits in, 1099, 1107.  
 drugs which alter colour of, 1106.  
 formation, mechanism of, 1109.  
 in cirrhosis of the liver, 677.  
 in jaundice, 662.  
 in malaria, 249, 251.  
 in nephritis, 1116.  
 in porphyria, 453.  
 in pyelitis, 1134.  
 in the Fanconi syndrome, 1179.  
 incontinence of, in epileptic attack, 1496.  
 nitrogenous constituents of, 1098.  
 non-nitrogenous constituents of, 1099.  
 normal, 1098.  
 pancreatic ferments in, 701.  
 phosphates in, 1099.  
 pigments of, 1099.  
 port wine in blackwater fever, 262.  
 reaction of, 1098.  
 smoky, in dinitrobenzene poisoning, 390.  
 specific gravity of, 1098.  
 test of renal function, 1100.  
 suppression of, in blackwater fever, 262.  
 in cholera, 135.  
 in lead poisoning, 363.  
 in mercurial poisoning, 381.  
 tests for sugar in, 425.  
 tubercle bacilli in, 87.  
 typhoid bacilli in, 103.  
 uric acid crystals in, 1107.
- Urobilin**, 1099.
- Urobilinogen**, 1099.
- Urobilinogenuria**, 659.
- Urobilinuria**, 662.  
 in blackwater fever, 262.  
 in cirrhosis of liver, 677.  
 in malaria, 249.  
 in yellow fever, 187.
- Urochrome**, 1099.
- Uroerythrin**, 1099.
- Urorosein**, 1099.
- Urticaria**, 1255.  
 acute giant, 1255.  
 anaphylactic, 1255.  
 cholinergic, 1255.
- Urticaria**, factitious, 1255.  
 in arsphenamine therapy, 230.  
 in ascariasis, 334.  
 in penicillin therapy, 10.  
 in relation to asthma, 978.  
 papular, 1256.  
 pigmentosa, 1257.  
 psychogenic, 1256.
- Usure des ongles**, 1324.
- Uta**, 268.
- Uvula** in chronic pharyngitis, 540.
- Vaccination**, antirabic, 1423.  
 in small-pox, 167, 168-171.  
 protection afforded by, 171.  
 risks of, 170.  
 technique of, 169.
- Vaccine**, choleraic, 136.  
 therapy in rheumatoid arthritis, 1153.
- Vaccinia**, 168, 1249.
- Vaginal diphtheria**, 72.
- Vagotomy** in treatment of gastric and duodenal ulcer, 587.
- Vagus**, anatomy of, 1355.  
 involvement of, in cancer of œsophagus, 552.  
 in cerebellar apoplexy, 1440.  
 lesions of, 1355.
- Valleix**, the tender points of, 1347.
- Valvular disease** of heart, chronic, 862-878.  
 rupture, 904.
- Valvulitis**, chronic mitral, 862.
- Van den Bergh reaction**, 659.
- Varicella**, 171.  
 bullosa, 173.  
 gangrenosa, 173.  
 hæmorrhagica, 173.
- Variola**, 158.  
 hæmorrhagica pustulosa, 163.  
 major, 160.  
 minor, 163.  
 sine variolis, 163.
- Varioloid**, 163.  
 varicella, 163.
- Vascular disease**, peripheral, 917.
- Vasculitis nodular**, 1261.
- Vasomotor disturbances** in arsphenamine therapy, 230.
- Vasovagal attacks**, 1502.
- Vegetative neurosis**, 308.
- Veldt sore**, 1329.
- Venesection**, 816.  
 in beriberi, 471.  
 in hypertensive encephalopathy, 1445.  
 heart disease, 851.  
 in pulmonary œdema, 989.
- Venoms**, snake, 340.
- Venous pulse**, in chronic constrictive pericarditis, 882.  
 thrombosis, 812, 926.
- Ventricles**, radiographic appearances in diseases of the, 804.
- Ventricular ectopic beats**, 822.  
 septal defect, 896.  
 tachycardia, 828.
- Ventriculography** in intracranial tumours, 1390.
- Ver du Cayer**, 338.
- Ver macaque**, 338.

- Verbigeration, in schizophrenia, 1663.  
 Verruca, 1301.  
 Verruga peruviana, 145.  
 Vertebral tumours in relation to compression of cord, 1539.  
 Vertigo, aural, 1352.  
   in cerebellar lesions, 1440.  
   in decompression sickness, 398.  
   in paroxysmal tachycardia, 824.  
   in streptomycin therapy, 11.  
   labyrinthine, 1352, 1353.  
   nystagmus in, 1352.  
   positional, 1354.  
   recurrent, 1352.  
 Vesical crises in tabes, 1462, 1465.  
   tuberculosis, 1139.  
 Vestibular irritation in sea-sickness, 402.  
   lesions, tests for, 1352.  
   neuritis, 1354.  
 "Vi" agglutinin in typhoid fever, 105.  
 Vibrio cholerae, 133.  
 Vincent's angina, 537.  
   organisms in ulcero-membranous stomatitis, 526.  
   spirilla in measles, 152.  
   in throat, 69, 74.  
   stomatitis, 526.  
 Viperidae, 341.  
 Virilism, 511.  
   in acromegaly, 484.  
 Virulence, bacterial, 1.  
 Virus diseases, 146-193.  
   of lymphopathia venereum, 191.  
   of measles, 150.  
   of nervous system, 1414-1434.  
   of skin, 1246-1250.  
   of yellow fever, 185.  
   pantropic, 185.  
   pneumonia, 1056.  
 Viruses, filtrable, 146.  
   diseases due to, 146-193.  
   neurotropic, 1414.  
   resistance to penicillin, 7.  
 Visceral crises of tabes, 1462-1465.  
 Visceroptosis, 710.  
 Vision, disorders of, in acromegaly, 484.  
   in disseminated sclerosis, 1474, 1475.  
   in hydrocephalus in children, 1402.  
   in hypoparathyroidism, 504.  
   in encephalitis lethargica, 1416.  
   in jaundice, 663.  
   in migraine, 1509.  
 Visual word centre, 1368.  
 Vitamin values of foods, 455-461.  
 Vitamin A, 454, 455.  
   daily requirement of, 454.  
   effects of lack of, 455.  
   sources of, 454.  
 B<sub>1</sub> (aneurine, thiamine), 457.  
   daily requirement of, 457.  
   deficiency, effects of, 457.  
   in beriberi, 468.  
   in chronic alcoholism, 355, 356.  
   in treatment of beriberi, 471, 472.  
   of neuritis, 1586, 1589.  
 B<sub>2</sub> (riboflavin), 457, 458.  
   complex, 457-461.  
   in treatment of pellagra, 474.  
 Vitamin B<sub>6</sub> (pyridoxine), 459.  
   B<sub>1</sub> (nicotinamide), 458, 459.  
   daily requirement of, 458.  
   deficiency, effects of, 459.  
   B<sub>12</sub> (cyanocobalamin), 460.  
   deficiency, results of, 460.  
   in subacute combined degeneration of spinal cord, 1554.  
 C, 461.  
   daily requirement of, 461.  
   deficiency, relation to scurvy, 462.  
   sources of, 461.  
 D, 455.  
   daily requirement of, 455.  
   deficiency, relation to rickets, 465.  
   effects of overdosage of, 455.  
   in idiopathic steatorrhea, 622.  
   in the Fanconi syndrome, 468.  
   in treatment of osteitis deformans, 1174.  
   of osteomalacia, 1178.  
   of rickets, 467.  
   of tetany, 505.  
 D<sub>2</sub> (calciferol), 455.  
 D<sub>3</sub>, 455.  
 E, 456.  
 K, 456.  
   in relation to coagulation of blood, 766, 769.  
   in treatment of jaundice, 664.  
   sources of, 456.  
 K<sub>1</sub>, 456.  
 K<sub>2</sub>, 456.  
 Vitamins, 454.  
   fat-soluble, 454-456.  
   in pink disease, 310.  
   international standards for, 454.  
   water-soluble, 457-461.  
 Vitiligo, 1203.  
 Vocal cords, abductor paralysis of, 950, 1356.  
   complete, 951.  
   functional, 952.  
   in chronic laryngitis, 947.  
   in tuberculous laryngitis, 949.  
   organic, 950.  
   paralysis of, 950-953.  
 Voice, change in, in paralysis agitans, 1512.  
   in acute laryngitis, 943.  
   in beriberi, 469, 470.  
   in chronic laryngitis, 947.  
   in goitre, 500.  
   in progressive muscular atrophy, 1558.  
   in tetany, 504.  
   in tonsillitis, 536.  
   in tuberculous laryngitis, 949.  
   production, faulty, 948.  
 Vole bacillus in tuberculosis prophylaxis, 89.  
 Volhynia fever, 300.  
 Vollmer patch test of tuberculosis, 88, 1028.  
 Voluntary movement, disorders impairing, 1376.  
 Volvulus as cause of acute intestinal obstruction, 650.  
   complicating megacolon, 648.  
 Vomiting, 561.  
   after arsphenamine therapy, 230.  
   as cause of alkalosis and uræmia, 1110.  
   black, post-operative, 597.  
   central, 561.

- Vomiting, cyclic, 561.  
     emotional, 561  
     fecal, 651.  
     following deep X-ray therapy, 410.  
     from local gastric irritation, 562.  
     habit, 561.  
     hysterical, 561.  
     in acute appendicitis, 651.  
     in acute hepatic necrosis, 671.  
     in acute intestinal obstruction, 651.  
     in acute necrosis of pancreas, 702.  
     in ackee poisoning, 351.  
     in bacillary dysentery, 114.  
     in blackwater fever, 262.  
     in cancer of the stomach, 590.  
     in cardiac infarction, 844.  
     in cerebellar apoplexy, 1440.  
     in cerebrospinal fever, 55.  
     in cholera, 134.  
     in chronic duodenal ulcer, 579.  
     gastric ulcer, 577.  
     in cirrhosis of the liver, 676.  
     in diphtheria, 73.  
     in duodenal ileus, 598.  
     in epilepsy, 1500.  
     in epidemic diarrhoea, 615.  
     in food poisoning, 121, 122, 124.  
     in gastritis, 571, 572, 574.  
     in hypochromic idiopathic anaemia, 732.  
     in intracranial tumour, 1386.  
     in melioidosis, 133.  
     in mercury poisoning, acute, 381.  
     in migraine, 1509.  
     in peritonitis, 713, 714.  
     in plague, 128.  
     in pregnancy, 562.  
     in pyloric obstruction, 594.  
     in sulphonamide therapy, 25.  
     in syphilis of the stomach, 589.  
     in travel sickness, 402.  
     in tuberculous meningitis, 1395.  
     in uraemia, 1110.  
     in whooping-cough, 138, 139, 140.  
     in yellow fever, 186, 187.  
     morning, in alcoholics, 356, 563.  
     obstructive, 562.  
     post-anæsthetic, 562.  
     post-operative, causing peptic œsophagitis  
         and ulcer, 548.  
     projectile, 596.  
     reflex, 561.  
     sickness of Jamaica, 350.  
     stercoral, 651.  
     toxic, 562.  
 von Bechterew's disease, 1160.  
 von Gierke's syndrome, 452, 892.  
 von Jaksch's disease, 748.  
 von Recklinghausen's disease, 1485.  
     skin lesions in, 1312.  
 von Willebrand's disease, 776.  
 Vrolik, prenatal fracture of, 1180.  
 Vulva, granuloma of, in schistosomiasis, 320.  
 Vulval diphtheria, 72.  
     lesions in lymphopathia venereum, 192.  
 Vulvitis in typhoid, 104.  
     senile atrophic, 1295.  
 Warbles in myiasis, 338.  
 Warren Tay-Sachs' disease, 1482.  
 Warts, infective, 1301.  
     juvenile, 1301.  
     plantar, 1302.  
     seborrhæic, 1301.  
     senile, 1301.  
 Wasp sting, anaphylactic symptoms after,  
     337.  
 Wassermann reaction, first appearance of  
     positive, 204, 205.  
     in cerebrospinal fluid, 1380.  
     in diagnosis of syphilis, 204, 205.  
     in syphilis of the nervous system, 1455.  
     in typhus fever, 296.  
     in Vincent's angina, 537.  
 Wasting, chronic, 617.  
     in coeliac disease, 619.  
     in nutritional mactocytic anaemia, 475.  
     in pellagra, 473.  
 Water and electrolytes, disturbances of, 415-  
     422.  
     as vehicle of cholera infection, 133.  
     of typhoid infection, 98.  
     dehydration, 417.  
     drinking, contamination of, 365.  
     intoxication, 417.  
     lead contamination of, 365.  
     supply in relation to goitre and cretinism,  
         498, 499.  
 Waterbrash, 563.  
 Water gas, 358.  
 Waterhouse-Friderichsen syndrome, 511.  
 Water-pock, 171.  
 Watsonius watsoni, 316.  
 Waxy kidney, 1131.  
 Weaver's cough, 1015.  
 Weber's compass test, 1359.  
     syndrome, 1342, 1362.  
     test for nerve deafness, 1351.  
 Weigl's anti-typhus vaccine, 300.  
 Weigl reaction, 296.  
 Weil's disease, 238.  
 Weil-Felix reaction in rickettsial diseases, 285,  
     287, 291, 293, 294, 296, 298, 303, 304.  
 Weil strain of leptospira, 238.  
 Weingarten's syndrome, 753.  
 Welders' siderosis, 1014.  
 Wens, 1303.  
 Werdnig-Hoffmann disease, 1565.  
 Werlhof's disease, 771.  
 Wernicke's hemianopic pupil phenom-  
     enon, 1360.  
 "Wet brain," 354.  
 Whipple's disease, 632.  
 Whitfield, erythema induratum of, 1261.  
 Whitlow, 1321.  
     diphtheritic, 72.  
     Hutchinson's melanotic, 1311, 1322.  
     in syringomyelia, 1547.  
 Whooping-cough, 137.  
     eclampsia, 140.  
 Widal test, 105.  
 Wig, syphilitic, 225.  
 Wilson's disease, 1484.  
 "Winged scapula," 1568.  
 Winterbottom's sign in African trypanoso-  
     miasis, 271.  
 Witzelsucht, 1358.

- Wohlfartia magnifica*, 337.  
*Woillez*, maladie de, 987.  
*Wolff-Parkinson-White syndrome*, 833.  
*Wood's light* for diagnosis of ringworm, 1233.  
*Wool-sorter's disease*, 79.  
*Word-blindness*, 1369.  
     in lesions of occipital lobe, 1360.  
     pure, 1368.  
     -deafness, 1368, 1369.  
*Wounds*, diphtheria of, 72.  
     scarlet fever after, 41.  
*Wrist-drop* in lead palsy, 367, 1593.  
*Writer's cramp*, 1525.  
*Wuchereria bancrofti*, 326.  
*Xanthelasma palpebrarum*, 1299.  
     malayi, 326.  
*Xanthelasmaoidea*, 1257.  
*Xanthine* in urine, 1098.  
*Xanthochromia*, of cerebrospinal fluid,  
     1379, 1535.  
*Xanthoerythroderma perstans*, 1275.  
*Xanthoma diabeticorum*, 1293.  
     disseminata, 784.  
     juvenile, 784, 1299.  
     planum, 1298.  
     tuberosum, 1298.  
*Xanthomatosis*, hypercholesterolaemic, 784.  
     hyperlipaemic, 784.  
     normocholesterolaemic, 783.  
     secondary, 1298.  
*Xanthomatosis* of skin, 1298.  
*Xanthopsia*, 663.  
*Xenopsylla cheopis*, the rat-flea of plague  
     and typhus, 127, 287.  
*Xeroderma*, 1200.  
     pigmentosum, 1210.  
*Xerophthalmia*, in idiopathic steatorrhea,  
     620.  
     in vitamin deficiency, 455.  
*Xerosis bacillus*, 69.  
*Xerostomia*, 530.  
*X-irradiation* in leukaemia, 760.  
     in pruritus ani, 1191.  
*X-rays*, injuries from, 409.  
     uses of, in industry, 409.  
     dermatitis from, 410.  
*Yaws*, 233.  
*Yeasts*, resistance to penicillin, 7.  
*Yellow fever*, 184.  
     Jack, 184.  
*Zenker's degeneration* of muscle, 1169.  
     in typhoid, 99.  
     in typhus, 296.  
*Ziehl-Neelsen staining* of tuberculous sputa,  
     87.  
*Ziemann's stippling* in malaria parasite,  
     248.  
*Zona*, 1247.  
*Zoster*, 1247, 1419.  
*Zygote* of malarial parasite, 247.